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Regulated En Route Care – A Scoping Review

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14. ABSTRACT

The goal of the Joint En Route Care (J-ERC) Consortium is to expand the operationally relevant ERC research, consistent with the research priorities identified by the J-ERC Steering Committee. One key aspect of this work is to identify research gaps specific to ERC. The purpose of this scoping study is to conduct a systematic, integrative review of the literature and survey to develop a state of the science summary and identify research gaps specific to regulated en route care. A scoping study was conducted including 1) a systematic review of the unclassified literature/documents specific to regulated ERC, 2) identification of research gaps, and 3) presentation of a gap analysis to the Committee on En Route Care (key stakeholders). A systematic review of relevant literature (e.g., PubMed, DTIC, military libraries, AMEDD website) and a hand search of military-specific conference proceedings (e.g., ATACC, MHSRS, ASMA, AMSUS, etc.) and clinical practice guidelines has been conducted. Over 1000 source documents were screened for appropriateness to the topic area and output organized to address current and future research gaps (e.g., time to transport, safe handoffs). Additional topics used for organization included aeromedical evacuation (AE) specific topics such as transport of a patient with entrapped air, hypobaria and hypoxia, and the association between these stresses of flight on morbidity (e.g., wound infections), as well as consideration of other stresses of flight. En route care including pain management and infection prevention and the use of technologies for the detection of hypoxia and compartment syndrome were also addressed. In addition to trauma patients, research gaps were identified for patients with cardiac or pulmonary dysfunction. Considerations of all theaters of operation and operational events (e.g., wartime, disaster) were also included. The analysis led to the generation of a gap list. Additionally, an evidence table summarizing included/excluded documents and a reference library containing all resource documents were created. This scoping study represents the first systematic integration of evidence to inform current knowledge and research gaps for regulated aeromedical evacuation and will serve to create a repository of evidence for this unique care environment.

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En route care, research gaps, aeromedical evacuation

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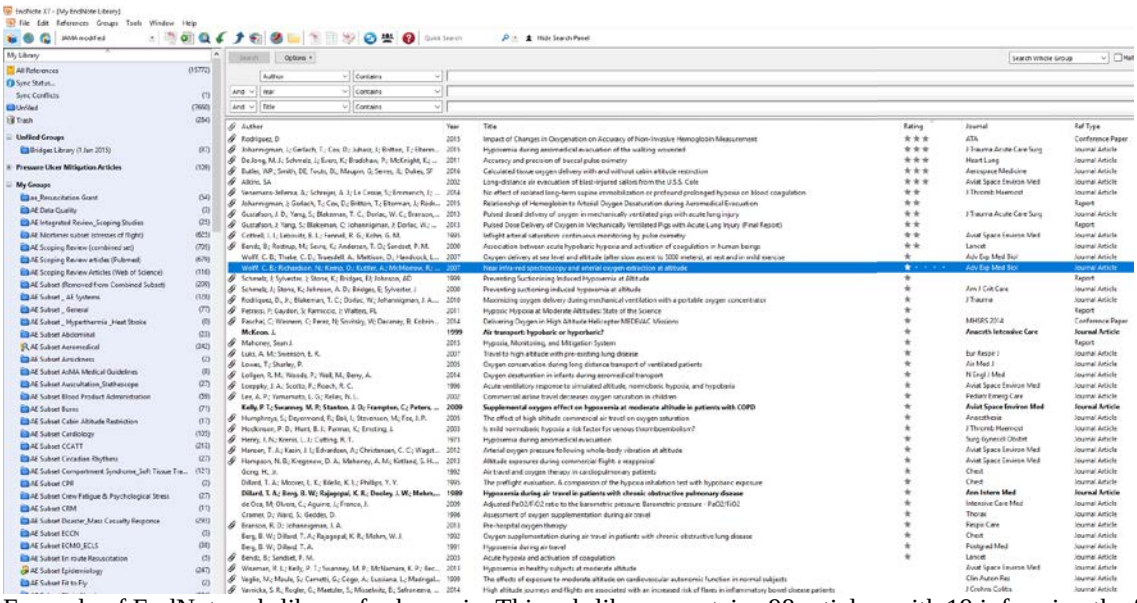
EXECUTIVE SUMMARY

The goal of the Joint En Route Care (J-ERC) Consortium is to expand the operationally relevant ERC research, consistent with the research priorities identified by the J-ERC Steering Committee. One key aspect of this work is to identify research gaps specific to ERC. The purpose of this scoping study is to conduct a systematic, integrative review of the literature and survey to develop a state of the science summary and identify research gaps specific to regulated en route care. A scoping study was conducted including 1) a systematic review of the unclassified literature/documents specific to regulated ERC, 2) identification of research gaps.

A systematic review of relevant literature (e.g., PubMed, DTIC, military libraries, AMEDD website) and a hand search of military-specific conference proceedings (e.g., ATACC, MHSRS, ASMA, AMSUS, etc.) and clinical practice guidelines was conducted. Approximately 2,285 documents were included after the initial screen for appropriateness to the topic area. These documents were further reviewed, with the output organized to address current and future research gaps (e.g., time to transport). Additional topics used for organization included aeromedical evacuation (AE) specific topics such as transport of a patient with entrapped air (cabin altitude restriction), hypobaria and hypoxia, and the association between the stresses of flight on morbidity (e.g., wound infections). En route care including pain management and infection prevention and the use of technologies for the detection of hypoxia and compartment syndrome were also addressed. In addition to trauma patients, research gaps were identified for patients with cardiac and pulmonary dysfunction. Considerations of all theaters of operation and operational events (e.g., wartime, disaster) were also included. The decision on the major sections was informed by the literature in addition to the a priori search criteria:.

Major Sections of Report		
• Epidemiology • Time to Transport • Care Across the Continuum	• Neurological • Spinal Cord Injury • Pulmonary • Cabin Altitude Restriction (Pneumothorax, Pneumocephalus, Ocular Air) • Abdominal Disease, Injury/Surgery • Cardiology • Infection Prevention • Highly Contagious Infections • Venous Thromboembolism (VTE) • Soft Tissue Trauma • Renal • Thermal Stress • Fever	• Pressure Injury Prevention • Pain/Pain Management • Anemia • En Route Monitoring • En Route Nutrition • Noncompressible Junctional/ Torso Hemorrhage – REBOA/ Junctional Tourniquets • ECMO

The articles were sorted in an EndNote reference library (see below) and coded for relevance. The EndNote file contains all the original source material for the cited documents, and thus represents the first systematic collation of documents specific to en route care.



Example of EndNote sub-library for hypoxia. This sub-library contains 98 articles, with 19 informing the final gap analysis. Stars: ***Highly relevant (data specific to AE/CCATT), **Moderately relevant (research/documents with direct application to gap analysis – may include bench research); *Relevant (review articles, background – may be drawn from civilian literature).

Evidence tables were created to collate and summarize the documents screened based on title and abstract review. Documents related to pre-hospital care, MEDEVAC and general reviews were not included unless they informed the identification of research gaps specific to regulated en route care. Information included in the summary tables includes: Primary topic, secondary topic, author, title, year, source (e.g., journal or conference title), include, reason excluded, source availability, purpose, methods, independent/dependent variables, sample size, sample characteristics, category (e.g., BI, NBI, Disease), body area, phase of en route care, results, conclusions, gaps. Separate tables were included.

The summary document provides pertinent data to inform the development of the gap list. The gap list is not prioritized. The results can be used to create a new research focus and/or address status on addressing gaps identified by previous working groups.

Summary: This scoping study represents the first systematic integration of evidence to inform current knowledge and research gaps for regulated aeromedical evacuation. The summary paper and accompanying evidence table and library have create a repository of evidence for this unique care environment. Consideration should be given to creating a living systematic review to facilitate on-line up-to-date summaries of research in a targeted topical area. Integration of the findings of the gap analysis with HPT documents should inform research priorities.

1.0 SUMMARY

The goal of the Joint En Route Care (J-ERC) Consortium is to expand the operationally relevant ERC research, consistent with the research priorities identified by the J-ERC Steering Committee. One key aspect of this work is to identify research gaps specific to ERC. The purpose of this scoping study is to conduct a systematic, integrative review of the literature and survey to develop a state of the science summary and identify research gaps specific to regulated en route care. A scoping study was conducted including 1) a systematic review of the unclassified literature/documents specific to regulated ERC, 2) identification of research gaps, and 3) presentation of a gap analysis to the Committee on En Route Care (key stakeholders). A systematic review of relevant literature (e.g., PubMed, DTIC, military libraries, AMEDD website) and a hand search of military-specific conference proceedings (e.g., ATACC, MHSRS, ASMA, AMSUS, etc.) and clinical practice guidelines has been conducted. Over 1000 source documents were screened for appropriateness to the topic area and output organized to address current and future research gaps (e.g., time to transport, safe handoffs). Additional topics used for organization included aeromedical evacuation (AE) specific topics such as transport of a patient with entrapped air, hypobaria and hypoxia, and the association between these stresses of flight on morbidity (e.g., wound infections), as well as consideration of other stresses of flight. En route care including pain management and infection prevention and the use of technologies for the detection of hypoxia and compartment syndrome were also addressed. In addition to trauma patients, research gaps were identified for patients with cardiac or pulmonary dysfunction. Considerations of all theaters of operation and operational events (e.g., wartime, disaster) were also included. The analysis led to the generation of a gap list. Additionally, an evidence table summarizing included/excluded documents and a reference library containing all resource documents were created. This scoping study represents the first systematic integration of evidence to inform current knowledge and research gaps for regulated aeromedical evacuation and will serve to create a repository of evidence for this unique care environment.

2.0 BACKGROUND

The goal of the Joint En Route Care (J-ERC) Consortium is to expand operationally relevant en route care (ERC) research, consistent with the research priorities identified by the J-ERC Steering Committee. One key aspect of this work is to identify research gaps specific to ERC. Historically, research proposals submitted to J-ERC Program Announcements have not fully addressed the programmatic research strategy identified by the J-ERC Steering Committee (SC). Proposals submitted by extramural sites (both Industry and Academia) have not always been operationally relevant, as there is limited en route care research in civilian institutions and limited exposure to military operations. Conversely, intramural (military research) sites have submitted operationally relevant proposals, but have logistical challenges with contracting and continuity of personnel with research expertise for short-term projects. In addition, there have been uncoordinated research efforts between Services and military labs, with minimal cross-talk between ERC researchers and a limited ability to rapidly respond to future operational questions within the ERC setting. The goal of the J-ERC Consortium is to expand the operationally-relevant ERC research, consistent with the research priorities identified by the J-ERC SC. This effort will also integrate and coordinate ERC research efforts and provide input on the transition of research findings into fielded products, clinical guidance, or policies. One key aspect of this work is to identify research gaps specific to en route care.

Most the studies regarding military en route care, are descriptive or observational (i.e., cross-sectional, case series, or cohort design) or technical reports. The integration of these studies and reports poses a challenge as the data are not appropriate for statistical meta-analysis. Given that the **primary aim of this study is to integrate the literature to identify research gaps related to en route care**, a scoping study is an appropriate strategy. A scoping study is conducted to synthesize research and non-research material to

provide clarity in a topical area, and/or to identify gaps in existing literature to inform a focused area or research or policy development.[1-3]

The purpose of this scoping study was to conduct a systematic, integrative review of the literature and survey to develop a state of the science summary and identify research gaps specific to regulated en route care.

3.0 METHODS

A scoping review was conducted to synthesize research and non-research materials to provide clarity in a topical area, and/or to identify gaps in existing literature to inform a focused area or research or policy development.[1-3] A limitation of a scoping study, as it was originally conceptualized by Arksey, is that it does not include an evaluation of the quality of evidence. For purposes of this study, we are including an evaluation of study/document quality, which is consistent with current recommendations.[2,4] The scoping study was performed using the framework originally described by Arksey and O'Malley[1] with the enhancements proposed by Levac.[2]

The primary aim of this study was to identify research gaps related to en route care. For purposes of this study, we focused on regulated Aeromedical Evacuation, to include pre-post flight.

3.1 Stage 1. Identification of Research Questions

Stage 1 involved the identification of research questions or priority areas outlined by various High Performance Teams and Command specific teams (e.g., Air Mobility Command, HPT – Optimal Time to Transport).[5] (See Appendix 1). These source documents are being used in lieu of additional stakeholder consultation (note – stakeholders will be consulted after the initial summary of research/research questions is collated). The research questions/priority areas identified will be used to refine the search.

3.2 Stage 2. Identification of Relevant Studies

Search Method: A search of unclassified literature was conducted (Appendix 2). Because of the special nature of the topic; we drew on traditional and non-traditional resources from a variety of sources, including the use the services and resources of military libraries. We searched bibliographic, report, and research databases covering biomedical, nursing, psychological, military, and governmental scopes. We used the bibliography from a previous research study on operational nursing competencies and an annotated bibliography created by the PI for the TriService Nursing Research Program En route Care Research Interest Group (TSNRP ERC-RIG). The search focused on military en route care, to identify the main concepts and initial subject heading terms when possible. For bibliographic database searching, search results were tested against the 'gold standard' of the original bibliography. The literature search process also involved hand searching, citation tracking, and informal networking. Military specific journals, such as Military Medicine, were hand searched for articles that either describe the characteristics of the en route care environment, care requirements and/or outcomes of the target population. Ongoing research was also included, with information obtained from sources such as abstracts presented at Aerospace Medicine Association (ASMA) or Military Health System Research Symposium (MHSRS) and lists of military funded protocols from the J-ERC or service specific sites. Validation of the completeness of the dataset were ascertained using citation tracking from seminal articles identified by the study PI. The data sources that were initially searched include the following:

- Databases: PubMed (NLM), EMBASE, CINAHL, PsychInfo, Web of Science, Dissertation Abstracts, FEDRIP, DTIC, NIH RePORT, NTIS, Knowledge Exchange, Military libraries, AMEDD website. Journal hand search, reference lists, Borden Institute, TriService Nursing Research (TSNRP) portfolio
- Conference Proceedings: PJ Verhonick Abstracts (US Army sponsored nursing research conference), Karen Rieder Abstracts (US Navy sponsored nursing research conference), Critical Care Medicine/Trauma, Aerospace Medicine (ASMA), ATACC/MHSRS, Uniformed Services University of the Health Sciences (USUHS) Annual Conference, AMSUS (Association of Military Surgeons of the United States)
- Operational Clinical Practice Guidelines (Joint Theater Trauma System CPGs)
- Military operations/events: Operation NEW DAWN, Operation ENDURING FREEDOM/IRAQI FREEDOM, Operation DESERT SHIELD/DESERT STORM, Battle of the Black Sea (Mogadishu, Somalia), Operation JUST CAUSE (Panama). Acts against the US military and other US facilities: USS Cole, USS Stark, USS Franklin, US embassies (Kenya/Tanzania), Marine Corps Barracks – Beirut. Aeromedical Evacuation (to include non-operational missions – Asia/Pacific) and military response to disasters.
- Disaster response: Hurricane Katrina, Hurricane Alison, Haiti, Tsunami (2004)

We also conducted targeted literature reviews to identify evidence to further identify gaps (data may be drawn from civilian literature) and to address targeted areas, such as those identified by related to Headquarters, Air Mobility Command identified en route care research areas of interest. For example:

- Lack evidence-based criteria to determine optimal time for patient transport
- Lack capability to adequately resuscitate and transport casualties requiring prolonged evacuations from or near the point of injury in an A2/AD or similar environment.
- Lack knowledge of the impact of cumulative effects from stress of flight (e.g., TBI, abdominal injuries, burns, vascular grafts, and compartment syndrome) on patient outcomes.
- Lack consistent standard of care from MTF to aeromedical staging facility to include patient transfers/handoffs.

We started with the original annotated bibliography developed for the TSRNP En route Care Research Interest Group (ERC-RIG). This bibliography contained articles specific to all aspects of aeromedical evacuation, including CCATT and MEDEVAC. We then added additional articles and documents that had been identified by members of the ERC-RIG.

3.3 Screening

Abstracts were included for full review if they directly mentioned en route care. Non-research documents (e.g., review articles, reports) were also included to provide context. Articles that specifically addressed prehospital transport (from point of injury to first hospitalization) were excluded as the purpose of this scoping study was focused on regulated AE; however, these references were retained in a separate EndNote library. The inclusion/exclusion criteria were refined as the literature review was completed. The excluded files were re-reviewed using the final criteria to ensure consistency of inclusion/exclusion criteria.[1] No specific time frame was established for article/document abstraction, but priority was given to articles from 1990 -2014 to capture the major recent military operations. After completion of the title and abstract review, the full text documents were further reviewed for inclusion/exclusion. Finally, the articles were organized and reviewed based on the pre-established research priorities. A quality review of the articles/documents and abstraction of key study/document related information was conducted. Critical to this abstraction was the identification of study results and research gaps. The intent of the review process was to focus on the epoch of regulated en route care (pre-flight/in-flight/post-flight care, events

and outcomes), thus research related to the phenomenon of interest but not related to en route care were not included in the final data set. The original scope was limited to non-CCATT transports, but expanded after initiation of the project. Additionally, this search limited the scope to regulated (fixed-wing) en route care (aeromedical evacuation), but did not include pre-hospital MEDEVAC transports.

A first level scan was performed based on title, followed by abstract and full document review. Approximately 2285 documents were initially screened as relevant to en route care. Evidence tables were created for the following major sections, with further delineation of documents related to the identification of gaps for regulated en route care. The number of documents and levels of evidence for the documents included in the final gap analysis (see Appendix 3) are summarized in Table 1.

Table 1. Topic Area for Evidence Tables

Topic Area	Articles From 1st Level Screen (title/abstract)	Included	Evidence Levels
Abdominal	13	6	Prospective Observational (1), Review (5)
Blood Transfusion	18	3	Retrospective Medical Record Review (3)
Burns	5	2	Retrospective Medical Record Review (1), Review (1)
Cabin altitude restriction – pneumothorax, pneumocephalus, ocular air	92	20	Bench/Model (4), Case Series (2), Prospective Observational (3), Quasi-experimental (1), RCT-Animal (1), Retrospective Medical Record Review (5), Single Case (3), Presentation (1)
Cardiac (ACS, hemodynamics)	47	23	Bench (2), Case Series (1), Presentation – Non-research (1), Prospective Observational (5), RCT (2), Retrospective Medical Record Review (5), Single Case (6),
CCATT	30	17	Bench/Model (1), Prospective Observational (1), Qualitative (1), Retrospective Medical Record Review (11), Review (1), Single Case (2)
ECMO	25	13	Case Series (1), Manufacturer's Guidelines (1), Prospective Observational (1), Report (1), Retrospective Medical Record Review (5), Review (2), Single Case (2)
Endotracheal Tube Cuff	16	10	Bench/Model (7), Letter (1), Prospective Observational (1), Review (1)
Epidemiology	51	35	Case Series (1), Epidemiologic (10), Prospective Observational (1), Report (2), Retrospective Medical Record Review (14), Review (6), Single Case (1)
Fever	13	5	Retrospective Medical Record Review (4), Review (1)
Hemoglobin	7	6	Prospective Observational (1), Retrospective Medical Record Review (5)
Hypoxia	42	25	Bench/Model (2), Cross-Over (4), Prospective Observational (10), RCT (1), RCT-Animal (4), Repeated Measures (1), Retrospective Medical Record Review (2), Single Case (1)
Infection Prevention	40	9	Case Series (1), Clinical Practice Guideline (1), Prospective Observational (1), RCT (1), RCT-Animal (2), Retrospective Medical Record Review (1), Review

Table 1. Topic Area for Evidence Tables (concluded)

Topic Area	Articles From 1st Level Screen (title/abstract)	Included	Evidence Levels
Infectious Disease (Ebola, SARS)	36	14	Case-Control (1), Epidemiologic (1), Presentation – Non-Research (1), Prospective Observational (1), Retrospective Medical Record Review (1), Review (5), Single Case (3), Systematic Review (1)
Mental Health	6	3	Retrospective Medical Record Review (3)
Monitoring (blood pressure, shock index, SpO2, buccal oximetry, NIRS – StO2/SmO2, functional hemodynamics, bioreactance, continuous hemoglobin, ultrasound)	67	14	Bench (2), Prospective Observational (7), RCT (2), RCT-Animal (1), Retrospective Medical Record Review (1), Single Case (1)
Neurological	109	40 + 6	Case Series (1), Letter (1), Prospective Observational (9), RCT-Animal (11), Retrospective Medical Record Review (11), Review (3), Single Case (2), No Report Available (6)
Nutrition	4	1	Review (1)
Orthopedic			
Pain	51	25	Prospective observational (9), Qualitative (1), Report (1), Retrospective Medical Record Review (10), Review (1), Single Case (1), Survey (2), Model (1)
Pressure Injury (ulcers)	6	5	Bench (1), QI Audit (1), RCT (2), Retrospective Medical Record Review (1)
REBOA/Junctional Hemorrhage	10	1	Prospective observational (1)
Renal	10	1	Prospective observational (1)
Reviews	28	14	Presentation – non-research (4), Report (3), Retrospective medical record review (1), Review article (4), National Academy of Medicine Report (1)
Soft tissue trauma	53	21	Presentation (1), Prospective observational (2), RCT-Animal (14), Retrospective Medical Record Review (3), Review (1)
Spinal cord injury/stabilization	30	9	Bench (1), Prospective observational (1), RCT Animal (3), Retrospective Medical Record Review (4)
Stethoscope	25	6	Bench (2), Prospective observational (2), RCT (2)
Time to transport	6	2	1 Report/1 Review (see other sections for indirect discussion)
Thermal stress (onboard aircraft), hypothermia)	19	9	Animal RCT (5), Bench (1), Prospective observational (2)
Ventilator	24	13	Retrospective medical record review (5), bench (7), RCT (1)
VTE	47	19	Cross-Over (2), Epidemiologic (2), Letter (1), Prospective observational (5), meta-analysis (1), Review (1), Retrospective medical record review (4), RCT (3)

Throughout this paper the following terminology is used to differentiate patients based on outcomes:[6-9]

- Casualty: individuals lost to the combat theater for any medical reason including illness and injuries not related to combat.
- Combat Injury: any casualty [resulting from] hostile action sustained in combat or [en route] to or from a combat mission.
- Killed in action: Individuals who die of wounds before receiving treatment at a military facility
- Wounded in action: Individuals who survive their injury until arrival at a military treatment facility
  - Died of wounds (DOW): individuals who died of wounds (DOW) from combat injuries after reaching a military treatment facility,
  - Return to duty: individuals treated and returned to duty (RTD) within 72 hours and those treated and medically evacuated

4.0 RESULTS

The results are divided into three sections. The first section provides a summary of previous articles and documents summarizing gaps. The second section summarizes epidemiological reports, with a subset summary for CCATT and Navy transports. The third section presents a review of extant literature and identifies potential gaps based on injury types (e.g., neurological injury, soft tissue trauma, spinal cord injuries, etc.) and en route care (e.g., pain management, pressure injury prevention, cabin altitude restriction for injuries with entrapped air/hypoxemia, en route monitoring, etc.).

4.1 Review Articles/Previous Research Priority Documents

Review articles specific to en route or trauma care research were studied for research gaps related to en route care.[10-31] The reference lists were also used to continue to validate the completeness of the literature review conducted for this study.

Although most of the review articles were related to combat casualty care, several review papers summarized the current state of research and practice specific to en route care and are useful for informing this gap analysis (Table 2). Hatzfeld's review[15] summarized research specific to the epidemiology of CCATT, en route pain management, spinal cord injuries and the vacuum spine board, and en route monitoring. Johanigmann's[28] 2008 paper summarizing CCATT and Mason's[24] 2012 presentation identified numerous potential gaps. Santullo's[20] 2012 presentation on the J-ERC portfolio identified priority areas for research (Appendix 4). The final report from the 2010 Research Development Document (RDD) for En Route Clinical Research (ECCR)[32] also informed the organization of literature review. The 2010 document identified 124 questions related to en route care, and may inform the creation of a master list of questions. Within each area (e.g., head injury, patient safety), the top five questions were identified. The 2010 report is useful as it provides specific questions to focus future research efforts. The most current areas of research are summarized in the PB 2015 and 2016 RDT&E Budget Item Justification: Defense Health Program request. The major sub-areas for Air Force En Route Care included: 1) physiological effects of aeromedical evacuation on patients and crew, 2) impact of transport times on en route trauma and resuscitative care, and 3) en route patient safety, including handoffs. Accomplishments cited included 1) assessing how the transport of psychiatric patients impacts AE crew protocols, 2) initial research on identifying optimal time to transport patients, 3) AE material solutions (portable electrical power source, negative pressure multi-channel negative pressure wound therapy device; automation of the CCATT patient record (Form 3899L) onto portable physiologic monitoring device; and supported Air Mobility Command (AMC) in prototype development for a replacement aircraft patient loading system). The ongoing research initiatives for 2014/2015 are outlined in Table 2. A 2016 presentation "Joint En Route Care" summarized research gaps across the triservice en route

continuum.[33] Relevant gaps identified by the Navy included the need for modeling for patient flow, use of alternate platforms (e.g., Osprey) and the development of an autonomous critical care platform. Finally, the 2016 Joint En-Route Care Research Portfolio Update[34] summarized research priorities in prolonged field care (prolonged damage control resuscitation) addressed by other program, presented an updated en route care portfolio scope and purpose, and identified priorities related to 1) impact of transport, 2) system of care, 3) en route interventions and treatment, 4) provider currency/skill levels, and 5) autonomous en route care. Matsumoto's[35] thesis summarizes the work of a Capabilities Based Assessment (CBA) on the CCAT system. As a part of the CBA process, four scenarios, based on the 2005 National Defense Strategy,[36] were developed to cover *traditional* (i.e., states employing recognized military capabilities/forces in well-understood forms of military competition /conflict), *irregular* (i.e., come from those employing "unconventional" methods to counter traditional advantages of stronger opponents), *catastrophic* (i.e., acquisition, possession, and use of WMD or methods producing WMD-like effects , and *disruptive* (i.e., may come from adversaries who develop and use breakthrough technologies to negate current US advantages in key operational domains) situations. **The finalized scenarios were included in this document and may be useful in informing research gaps.** (NB: these terms were not used in the 2015 National Military Defense Strategy document). Key strategic source documents also informed this work. The project used a Human Systems Interface approach to identify gaps; thus, the major topical areas include safety, occupational health, environment, along with the creation of a hierarchical task analysis (HTA) summary and a concept map. Aspects of the final HTA relevant to this document are summarized in Table 2. This report also included an assessment of the operational risk associated with each capability gap. Thirty two tasks were identified as high risk (requiring immediate materiel or non-materiel solutions), with nine listed as highest priority: 1) maintain critical care proficiency, 2) select suitable CCAT physician, 3) provide appropriate manpower, 4) CCAT representation in acquisition process, 5) select suitable CCAT respiratory therapist, 6/7) determine requirements, 8) create curriculum to facilitate the effects of altitude on patient outcomes, 9) Equipment to monitor patient status locally. A review of this prioritized risk list and task-level recommendations may inform decisions regarding research priorities and doctrine. Note – the official CCATT CBA report could not be located, thus the summary from Matsumoto's thesis should be reviewed against the final report. Nix[37] presented a report from 2005 from Naval Health Research that crosslinked supplies and clinical requirements for CCATT. In this model, there were 111 patient conditions identified from the DSMB lists. These 111 conditions were further compressed into 12 categories: post-surgical thoracic, post- surgical staged exploratory lap, post-surgical craniotomy, Burns > 20% BSA. Class III/IV hemorrhagic shock, crush/blunt injury, head injury, environmental emergency, medical, anaphylaxis/asthma, medical, cardiac event medical). For each category, a task profile was created - with subcategories for clinical care tasks, change in patient status en route, administrative and equipment support). Further iterations combining categories were also created. Using these categories and with input from CCATT SMEs, revisions were recommended for CCATT supplies. This study was presented in 2005, indicating a need for an update. The categories and identified tasks are also useful in informing areas for further research. Of note, the organization of these categories is similar to the outline of this report based on body area of injury, with the addition of status (e.g., crush injury with hemorrhagic shock).

Table 2. Gaps Identified in Reviews Related to En Route Care

Author	Identified Gaps
Johannigman (2008)[28]	• Monitoring under red light condition (monitors, detection of skin color changes, bleeding) • Noise - alarms, voice amplification, noise reduction • Vibration/gravitational stresses - especially during combat maneuvers • Hypobaria (trapped gas; air inflated balloons), effect of hypobaria on tissue edema, effect on performance of mechanical ventilators) • Variations in flight duration (45 minutes - 10 hours) • Equipment limitations, lack of coordinated data retrieval, the potential uses for wireless technologies (feasibility, security) • Autonomous controllers (mechanical ventilation, oxygen, target controlled infusions)
Mason (2012)[24]	• Need for en route imaging (ultrasound, vital signs waveforms, ventilator waveforms, bronchoscopy) • Need for en route expertise (improved training and experience of CCATT personnel, high fidelity simulation, smart monitoring with decision assist algorithms, robust telemedicine capability) • Alarms (better alarms with 360-degree visibility, auditory alarms in headset) • The ability to maintain normothermia in TBI patients, automated collection of all patient medical data and population of the medical record • Perceived gaps (patient warming, advanced hemodynamic monitoring)
Santullo (2012)[20]	• Impact of movement environment on patient physiology • Life-saving interventions for ERC and preparation/transition for movement across all levels of evacuation • Non-Invasive methods for patient monitoring during patient transport • Skill level/training of ERC medical personnel • Patient safety • Patient immobilization during transport • Joint documentation ERC • Medical personnel human factors • Standard equipment/supplies for ERC • Medical equipment test standards • Autonomous control equipment/remote monitoring

Table 2. Gaps Identified in Reviews Related to En Route Care (continued)

Author	Identified Gaps
RDT&E Budget Item Justification: PB 2015 Defense Health Program[38,39]	USAF AE Research and Development FY 2014 Plans: • Finalize FDA requirements and plan for transition of the miniaturized ECMO device to AMC for AE and CCATT use. • Make recommendations regarding way-ahead on closed loop ventilation and oxygenation. • Complete research assessing the clinical effect of prolonged hypobaria during AE, how AE affects blood volume responsiveness, pain assessment during AE, and factors impacting patient safety during AE. • Apply the results of the effectiveness of life saving interventions study to modifying clinical practice guidelines. FY 2015 Plans: • Plan and test for transition of miniaturized Extra Corporal Membrane Oxygenation device to Air Mobility Command (AMC) for Aeromedical Evacuation (AE) and Combat Casualty Air Transport Team (CCATT) and lung team use on long flight missions. • Monitor technology readiness level of closed loop ventilation and oxygenation. • Analyze final results of research assessing the clinical effect of prolonged hypobaria during AE, how AE affects blood volume responsiveness, improving pain management during AE, and factors impacting patient safety during AE, and determine translational elements of completed research or need for further studies. • Complete and transition automated CCATT patient record and multi-channel negative pressure wound therapy device to acquisition process. • Analyze results of cabin altitude restriction retrospective study, which should lead to better evidence-based decision-making for when to fly low. • Continue swine study to investigate post AE effects on coagulation and inflammation.
RDT&E Budget Item Justification: PB 2016 Defense Health Program[39]	<u>En Route Care R & D</u> 2014 Accomplishments • Continued research to enhance the care of acutely injured AE trauma patients through projects assessing closed loop technology for autonomous control of oxygenation and ventilation. • Continued research to improve AE trauma patient care through the development and assessment of continuous, real-time vital sign monitoring system. • Continued research assessing the clinical effect of prolonged hypobaria during AE on TBI, how AE affects blood volume responsiveness, improve pain management during AE, and identify/mitigate factors impacting patient safety during AE. • Continued study of optimal time to transport patients. • Continued development of the multi-channel negative pressure wound treatment device and monitor FDA 510K process. • Began swine study to investigate post AE effects on coagulation and inflammation. • Began a retrospective study of the efficacy of cabin altitude restrictions on AE patients. • Continued automation of CCATT patient record, perform operational test. • Began development of en route care retrospective research database. • Completed Air Worthiness certification for simulator mannequin and initiated use on Aeromedical Evacuation (AE) and Critical Care Transport Team (CCATT) training flights – transitioned to the CCATT Pilot Unit.

Table 2. Gaps Identified in Reviews Related to En Route Care (continued)

Author	Identified Gaps
RDT&E Budget Item Justification: PB 2016 Defense Health Program[39]	<u>En Route Care R & D</u> 2014 Accomplishments (continued) • Continued research to enhance the care of acutely injured AE trauma patients though projects assessing closed loop technology for autonomous control of oxygenation and ventilation. • Completed and archived miniaturized Extra Corporal Membrane Oxygenation (ECMO) device bovine study. • Analyzed initial results of research assessing the clinical effect of prolonged hypobaria during AE on Traumatic Brain Injury (TBI), how AE affects blood volume responsiveness, pain assessment during AE, and factors impacting patient safety during AE. • Began assessing how the transport of psychiatric patients impacts AE crew protocols. • Continued research examining medical records of traumatically injured patients transported by Critical Care Air Transport Teams (CCATT). • Conducted research prospectively characterizing the incidence and success of Life Saving Interventions (LSI) performed by combat medics during pre-hospital and en route care. • Began research for identifying optimal time to transport patients to ensure best outcomes. • Began investigations into advanced development options for AE material solutions: began testing for a portable electrical power source; began development of a negative pressure multi-channel negative pressure wound therapy device; awarded and initiated automation of the CCATT patient record (Form 3899L) onto a widely-accepted portable physiologic monitoring device; and supported Air Mobility Command (AMC) in prototype development for a replacement aircraft patient loading system. • Spear-headed DoD Information Assurance Certification and Accreditation Program (DIACAP) for telemedicine capability of a physiologic monitoring device in support of AMC requirements, which will allow for transmission of aeromedical electronic medical information across DoD information platforms. • Completed study on the following: o Effects of AE on the injury response, including potential worsening of the systemic inflammatory response, increased susceptibility to infection, and secondary brain injury after traumatic brain injury; o The effects of hypobaric hypoxia exposure on a crush muscle crush injury during air transport. • Continue research to enhance the care of acutely injured AE trauma patients through projects assessing closed loop technology for autonomous control of oxygenation and ventilation. • Continue research assessing the clinical effect of prolonged hypobaria during AE on TBI, how AE affects blood volume responsiveness, • Improve pain management during AE • Identify/mitigate factors impacting patient safety during AE • Optimal time to transport patients • Continue development of the multi-channel negative pressure wound treatment device and monitor FDA 510K process. Begin Began swine study to investigate post AE effects on coagulation and inflammation • Efficacy of cabin altitude restrictions on AE patients. • Effects of altitude on patients requiring ECMO system for respiratory support during transport.

Table 2. Gaps Identified in Reviews Related to En Route Care (continued)

Author	Identified Gaps
RDT&E Budget Item Justification: PB 2016 Defense Health Program[39]	<u>En Route Care R & D</u> 2014 Accomplishments (continued) • Automation of CCATT patient record, perform operational test. • En route care retrospective research database. • Plan and test for transition of miniaturized Extra Corporal Membrane Oxygenation device to Air Mobility Command (AMC) for Aeromedical Evacuation (AE) and Combat Casualty Air Transport Team (CCATT) and lung team use on long flight missions. • Monitor technology readiness level of closed loop ventilation and oxygenation. Analyze final results of research describing blood administration, analgesics used, and burn care provided during Critical Care Air Transport. • Development of new clinical practice guidelines and validation of existing guidelines for CCATT. • Evaluate and describe current en route care practices from point of injury to in-theatre military treatment facilities. • Provide descriptive analysis of non-traumatically injured patients and the clinical care provided during transport out of theatre on CCATT. • Analyze final results of research assessing the clinical effect of prolonged hypobaria during AE, how AE affects blood volume responsiveness, improving pain management during AE, and factors impacting patient safety during AE, and determine translational elements of completed research or need for further studies. • Complete and transition automated CCATT patient record and multi-channel negative pressure wound therapy device to acquisition process. • Analyze results of cabin altitude restriction retrospective study, which should lead to better evidence-based decision-making for when to fly low. • Continue swine study to investigate post AE effects on coagulation and inflammation. FY 2016 Plans: • Analyze final results of swine study investigating post AE effects on coagulation and inflammation, which will lead to a knowledge platform to develop guidelines for evacuation strategies during transport of combat casualties. • Pursuant system build, and demonstration of the closed loop ventilation and oxygen delivery system, the data from the pre-hospital use of capnometry and the ventilator registry will be used to define the requirements of a system to perform closed loop ventilation. • Continue pursuing the AFMS strategic goal A1 to "Transform the En-route Care System" based on war fighter identified gaps and validated requirements. • Begin and/or continue work that will improve mission effectiveness in the A2AD environment such as closed loop technologies and enabling capabilities leading to autonomous patient transport.
Joint En Route Care Research Summary[33]	Transport telemedicine (briefing specific to MEDEVAC) Osprey transport (CASEVAC) – CDR Goforth • Evaluating existing PMI for adaptation to V22 environment, including potential electrical and oxygen requirements • Inflight visibility of patient status • Evaluate for A2/AD conditions • Casualty modeling o Rates for ashore casualties (WIA & DNBI) o Possible V-22 event en route with casualties (mean # WIA 28) o Timing of mass casualty events ashore and mean number expected

Table 2. Gaps Identified in Reviews Related to En Route Care (continued)

Author	Identified Gaps

Joint En Route Care Research Summary[33]	Automated Critical Care System (Navy – Dr Tim Bentley)
	• Outline of required monitoring capabilities and therapeutics (open, semi-closed, closed loop)
	  o Mechanical ventilation
	  o Drug infusions (closed loop vasopressors – blood pressure)
	  o Closed loop sedation
	  o Maintenance of body temperature
	  o Medication administration (antibiotics)
	  o Patient data transmission

Joint En Route Care Research Portfolio[34]	Impact of transport • Baseline measures (stress/transport response) • Impact of transport on patient physiology; time to transport • Mitigate physiologic responses Systems of care • Interoperability/standardization; teleconsultation; patient safety • Intelligent tasking; teleconsultation; integrated systems of support – safe patient care/handoffs • Integration/interoperability between services/countries En route interventions and treatment • Resuscitation/surgical care during transport & impact on outcomes; space requirements • Transporting patients with invasive procedures at point of injury • Prospective clinical trials to revolutionize en route care Provider currency/skill levels • Define skill sets (patient-provider ratio) • Competencies & impact on patient outcome • Individualized, evidence-based training plans; telerobotics Autonomous en route care • Decision assist (ventilation, sedation, resuscitation) • Closed loop devices (ventilation/sedation/resuscitation) • Closed loop system of systems for ICU level patient
CBA - CCATT[35]	Care for patients • Neonatal, pediatric, burned, geriatric, critically ill/injured Communicate with essential personnel • Non-English-speaking personnel, ASF, strategic communication, CCAT personnel on non-standard platform, MTF, AE team Document patient information Enable Immediate access to information • Electronic document transfer, access medical information (reference database) at all times Function as a High Performing Team • Team communication, Crew Resource Management skills Transport patients on any platform • Safely load/offload patients into non-standard platform (personnel focus) • Safely load/offload patients into standard platform • Secure patients for movement

Table 2. Gaps Identified in Reviews Related to En Route Care (concluded)

Author	Identified Gaps
CBA - CCATT[35]	Sustain CCATT capabilities Provide qualified CCATT teams Provide equipment to CCAT teams • Provide state-of-the-art lightweight portable, durable medical equipment Establish interoperability with DoD and allied partners Provide equipment that is compatible with all (air, land, sea) platforms including international partners (NATO, ASIC, DoD)
CoERCC Research Subcommittee (2017)[40,41]	Documentation • Identify minimal documentation elements • Simple, iterative "what", "when", "why" supports handoff, ongoing care and research Handoffs – optimal handoff methods Monitoring – individualized, miniaturized Maintenance of normothermia during en route care • Blood warmers • Body warmers • TBI, fever TBI Transport • Motion effects • Hypoxia/altitude effects Optimizing timing of DCR and DCS around transport • Decision support tools to integrate mode of transport, duration, resources • Decision support for staffing transport missions ('Intelligent Tasking") Transportation Risk Stratification • Resource-adjusted "clinical stability" risk scoring Physiology of cardiopulmonary decompensation in transport • Pulmonary complications, oxygenation • ECMO as a risk mitigatory Decision rules for intubation/extubation and transport • Outcomes associated with transport adverse events, delayed extubation (VAP rates, etc.) Commander's risk assessment tool • Mortality effects of staffing and capability decisions En route pain management • Assessment, monitoring, dosing Top product development priorities • "Wand" – wireless scanning documentation device (record type/timing of interventions (e.g., grocery store scanner, RFID) • Tele-documentation (voice to text, from ground medic to evac team) • Effective blood warmers (rapid, maintain blood functionality) • Individual patient monitors (goes with patient, collects continuous data throughout the continuum) • Autonomous intervention systems (ventilation, resuscitation, etc) • Oxygen concentrators (optimized for transport) • REBOA for transport (linked to monitors, autonomous systems, decision support)

Orman[23] conducted a review of the literature to identify the 50 most frequently cited articles related to combat casualty care. The search strategy used the following terms: combat, war, military, OEF, OIF, Operation Enduring Freedom, Operation Iraqi Freedom, Overseas Contingency Operations, operation New Dawn, Global War on Terrorism in combination with one or more terms related to trauma (wound, injury casualty). The search was further restricted to subject areas related to combat casualty care:

surgery, orthopedics, critical care medicine, emergency medicine, infectious diseases or hematology. Given these narrow search parameters, none of the studies were related to en route care. A similar search strategy could be conducted from the sources used for this scoping review.

Each year the supplements related to research presented at MHSRS identify areas for future research. The introduction[42] to the supplement summarizing the 2016 MHSRS conference outlines a future program of research based on the principles of "No Drift" and "Ahead of the Curve" within a multi-dimensional battlefield that may be devoid of traditional en route care capabilities. This environment may require prolonged field care. A similar strategy for analyzing gaps to include prolonged transport without the benefit of field resuscitation may inform gaps for future research.

4.2 Epidemiology

There are a series of studies summarizing the epidemiology of AE transports, with seven of these papers reflecting the annual summary published in the Medical Surveillance Monthly Report (MSMR).[43-48] There is redundancy in these data, as they are drawn from three primary data sources: Joint Theater Trauma Registry, TRAC^{2}ES and Armed Forces Health Surveillance database.

The first epidemiologic study[43] reflected evacuations from Central Command during 2003. This study, which used data from TRAC^{2}ES, is important as it provided insight into AE during the early stages of military operations. During 2003, there were 28,404 patient movement requests, reflecting 11,183 military patients. Among these patients, 85% were evacuated for disease/non-battle injuries (DNBI). These TRAC^{2}ES data were linked to the DMSS database. Among these patients 86% had one or more outpatient encounters and 33% were hospitalized before or after their deployment (*not clear if the pre-deployment hospitalization was for the same condition*). No information on specifics of the post-evacuation care was presented.

Among the studies reported in the MSMR, one used medical records as a source to describe the primary diagnosis for 23,719 patients evacuated from Afghanistan between 7 Oct 2001 and 31 December 2012.[46] The major diagnostic categories were musculoskeletal (primarily back and knees), non-battle injuries (sprains and fractures), mental health disorders (e.g., adjustment reactions, mood disorders, anxiety disorders, and post-traumatic stress disorders), and general "signs and symptoms" (primarily respiratory). A second study reported in MSMR analyzed Operation Iraqi Freedom/New Dawn, with 50,634 evacuations of military personnel. A similar distribution of injury/illness reason for evacuation was noted compared to the Afghanistan theater.[48]

In a study, which used data from the Landstuhl Deployed Warrior Medical Management Center of evacuations between January 2004 and December 2007, there were 34,006 personnel evacuated.[49] Similar to the MSMR reports, the most common reasons for evacuation were connective tissue disorders (24%), combat injuries (14%), neurological disorders (10%), psychiatric disorders (9%) and spinal pain (7%). During this same period, there were 2155 nonmilitary (e.g., DoD personnel, private contractors and diplomats) personnel evacuated. The most common evacuation reasons were non-war related injuries. Among the war-related injuries (25%), 55% of the injuries were related to combat and 23% musculoskeletal. Compared to military personnel evacuated during this same period, the nonmilitary evacuees had a lower incidence of psychiatric diagnoses (2.1% vs 9.1%, $p < .001$) and non-war related musculoskeletal/spine disorders (13.3% vs. 24.4%, $p < .001$) and a higher incidence of circulatory conditions (12.6% vs. 4.4%; $p < .001$) and noncardiac chest pain or abdominal pain (11.2% vs. 3.7%, $p < .001$). Similar results were found in a review of 21,477 British casualties (86.5% military) who underwent evacuation between 2004 and 2011.[50] The most common reasons for evacuation in the military members were musculoskeletal/connective tissue disorders (50%), trauma (7%) and mental health disorders (6.3%). Among the nonmilitary members, the most common reasons for evacuation were

musculoskeletal/connective tissue disorders (24%), genitourinary disorders (10.5%) and circulatory disorders (8.3%). From 2001-2006[51] there were 31,728 soldiers evacuated from Iraq and Afghanistan (NBI: 11,045; battle injury: 5401; diseases: 15,282). In Iraq, there were 27,563 evacuations (9530 NBI, 4968 BI, 13,065 disease). Among these patients, the largest percentage evacuated were for NBI ~35%, BI ~15%. Most common disease diagnoses were ill defined (~15%), digestive (10%), Mental 9%, GU 6%, Nervous system 4%, and circulatory 3%. In Afghanistan, there were 4165 evacuations (NBI 1515 (40%), BI 433 (10%), Disease 2217). The most common disease diagnoses were digestive (~10%), GU (~8%), Mental (5%), Circulatory (5%), and nervous system (4%). On average evacuations for NBIs occurred at a rate of 18.4/1000 person-years for both Iraq and Afghanistan. Butler[52] reported on practices of two Theater Validating Flight Surgeons as related to the evacuation of 1389 patients in 2007. This study is important as it describes physiological parameters for the patients and TVS recommendations for disposition (e.g., Remain Overnight, no stops), backrest, cabin altitude restriction, CCATT requirement, and supplemental O2. A limitation of the study was to link the preflight orders with en route care requirements and to develop criteria to standardize decision making linked to en route and post-flight outcomes (e.g., did the patient have preflight O2 ordered – did they require supplemental O2 during flight – characteristics of patient).

Two recent studies provide epidemiologic data on US[53] and UK[54] patients requiring evacuation from 2013-2015. During this period there were 3912 evacuations of US military personnel from the AOR. The most common diagnosis was mental health disorders (n = 750), with adjustment disorder the most common psychiatric diagnosis. Non-battle injuries, primarily musculoskeletal accounted for approximately 33% of evacuations. Battle injuries accounted for 13% of evacuation. No data were provided on the number of patients requiring CCATT. During this period, there were 133 patients evacuated to Great Britain, with 95 suffering a non-battle injury. Of note, a majority of the patients evacuated to the UK were not from combat areas, but no data were provided for this time period on casualties with battle injuries

In a longitudinal study[55] of 3846 severely/critically injured combat casualties there was an association between injury severity and the development of chronic disease in the period approximately one to three years after the injury. These rates were higher than non-injured military cohorts.[56-58] After adjusting for age, race, MAP, HR, burn injury, and acute kidney injury, for every 5-point increase in the ISS, there was a relative increase in hypertension (6%), coronary artery disease (13%), diabetes mellitus (13%) and chronic kidney disease (15%). Acute kidney injury was also associated with an increase in the rate of hypertension (66%) and chronic kidney disease (479%). There was no specific analysis of type of care or any aspects of en route care included in this analysis. Putative mechanisms included post-injury inflammation and PTSD. ***Gap: There is a need to integrate evidence related to the effect/timing of AE on inflammation for a given injury type and possible association with long-term outcomes***.

A gap identified by JPC-6 was the absence of information on en route care in the DoDTR. Several modules related to en route care are being created under the general name Project MERCury. These modules will interface with the DoDTR (Figure 1).

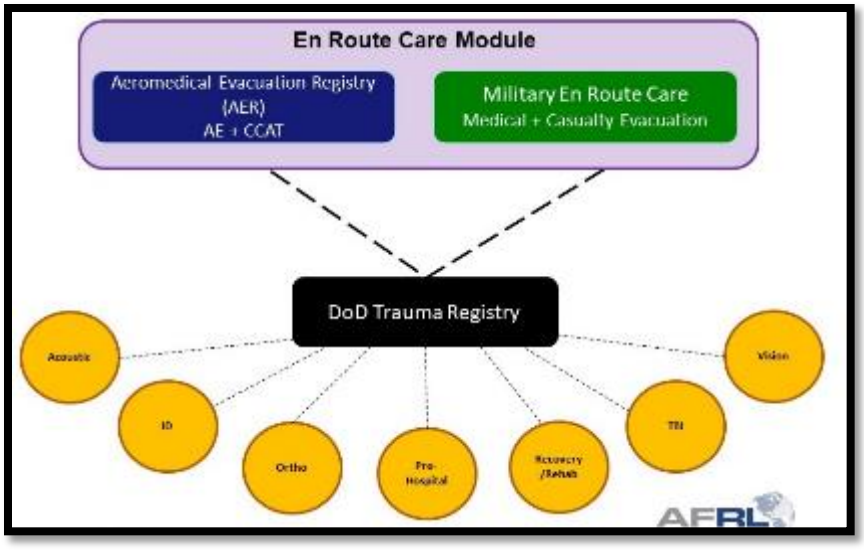


Figure 1. En route care modules linking to DoDTR.

Specific to this gap analysis is the Aeromedical Evacuation Registry (AER), which is a quality improvement registry. The AER collates mission and medical data specific to en route care for both acute/critical and non-critical patients, starting at the Role 2 (military field hospital) through transport to the continental United States (CONUS). Data for the AER are being obtained from multiple sources, including TRAC2ES, en route medical records (Air Force Form 3899) and existing CCATT data. Information on the number of Flight Nurses and Aeromedical Evacuation Technicians and specialty teams on each mission is also being entered. The first phase of the creation of the AER is to integrate all data from TRAC2ES. Between 2001 and 2014, there were 210,863 patient movement requests (PMRs), reflecting the transport of 137,433 individual patients (Figure 2). These patients were transported on 36,845 missions, reflecting 81,869 flights (a mission may have more than one take-off/landing or flight). The highest year for transports was 2003, when over 19,000 patients were evacuated worldwide, with 14,737 requests for evacuation from Central Command (CENTCOM) in support of military operations in Iraq and Afghanistan. In 2005 there were 14,666 patients evacuated, including 1169 patients transported in a single day in response to Hurricane Rita.

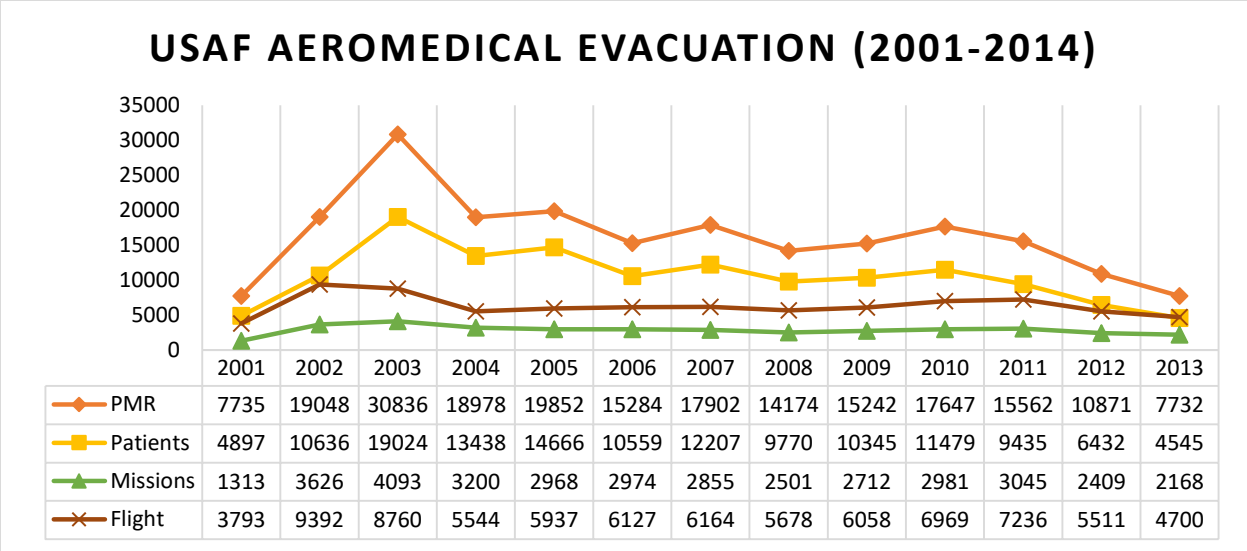


Figure 2. Number of patient movement requests (PMR), patients, missions and flights for regulated aeromedical evacuation from September 2001 through December 2014.

As a part of the development of the registry, data are being entered year by year. 2009 was associated with a high operational tempo associated with the shifting of the primary theater from Iraq to Afghanistan. To exemplify the potential of the registry, in 2009, there were 15,242 PMRs, representing 10,345 unique patients on 2,712 missions. Among these patients, there were 1007 CCATT transports, representing 660 patients. In addition, 10 working dogs were evacuated (Table 3). Care unique to transport is the requirement for a cabin altitude restriction (i.e., cabin altitude maintained at less than 8000 feet), to mitigate the effects of gas expansion (ocular, pneumothorax) or hypoxia at altitude.[59] In 2009, less than 1% of patients had a CAR ordered.

Table 3. Demographics (2009 AER)

# Patient Movement Requests	15,242
# Patients	10,345
# Patients with usable SSN	10,091
# Missions	2,712
# Flights	5,186
# Flights per patient	3.3 ± 2.3 (Range 1-17)
Patients/Mission • All missions • Within theater (520 missions) • AOR – EUCOM (545 missions) • EUCOM – CONUS (166 missions) • PACOM – CONUS (79 missions)	 • 8.8 ± 9.9 (Range 1-57) • 8.1 ± 6.8 (1-39) • 15.6 ± 11.1 (1-55) • 27.6 ± 11.7 (1-57) • 1.9 ± 1.1 (1-6)
Injury Type • Battle Injury • Nonbattle Injury • Disease • Missing	 • 1267 (12.3%) • 7683 (74.3%) • 977 (9.4%) • 417 (4.0%)
Cabin Altitude Restriction	140 (< 1%)
# transports by CCATT (n = 660 patients)	1007 (6.6%)

AOR – area of responsibility (i.e., Iraq, Afghanistan); CONUS – continental US, EUCOM – European Command (Germany); PACOM – Pacific Command

As summarized in Figure 3, the primary medical specialties required for 42% of the patients were orthopedics, neurosurgery and general surgery, while psychiatry was the primary medical specialty for 15% of the patients. However, there were an array of specialties, including obstetrics and pediatrics, highlighting the breadth of expertise required for Flight Nurses and AE Technicians. Annual data allow for analysis of temporal changes in diagnosis over time. For example, in 2004, orthopedics, neurosurgery and general surgery accounted for 48% of the patients, but psychiatric diagnoses accounted for only 6.4%.

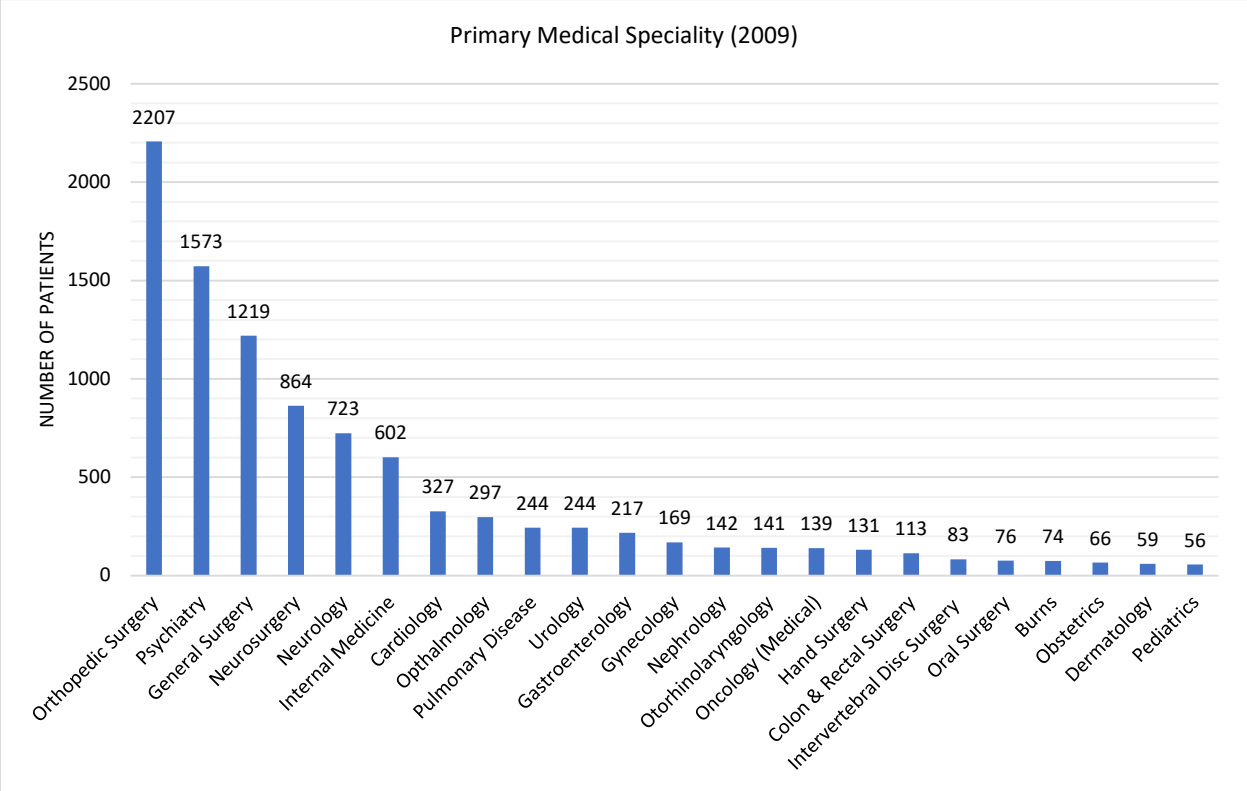


Figure 3. Summary of patients by primary medical diagnosis transported in USAF aeromedical evacuation system in 2009.

4.2.1 Mission/Flight Level. The AER will also allow analysis of mission/flight level data. As an example, in August 2009 there were 264 missions (47 missions from the AOR-Germany; 15 from Germany to the US). On the AOR to Germany missions, there was a median of 13 (IQR 13) patients per flight. On the Germany to US, there were a median of 32 (IQR 15) patients per flight. For both routes, approximately 50% of patients were on litters. A typical medical crew consists of two Flight Nurses and three AE Technicians, but the medical crew complement may be adjusted based on patient numbers and acuity. An important point when considering patient care requirements is that all the patients onload simultaneously, thus, strategies to ensure safe handoffs are essential. Table 4 provides an example of 13 patients (two cared for by CCATT) on a single AOR-Germany mission. Most of the patients suffered acute trauma; however, on other flights, the preponderance of patients had medical diagnoses.

Table 4. Summary of 13 Patients Transported on a Single Mission (AOR – Germany)

1	Spontaneously resolving palpitations
2	Continuous headache
3	Day 3. MVA – back "popped" -lumbar disc injury (NOS)
4	Day 1. Landmine blast. Traumatic BKA. s/p washout. RUE laceration, R gluteal laceration, soft tissue injury to LLE. PAN CT no traumatic abnormality identified within the head, face, neck, chest, abdomen, pelvis, cervical, thoracic or spinal fracture. Pain 8/10 w/out meds, 4/10 with meds.
5	Day 1. Sustained shrapnel injury to neck. DX: Right zone II Injury, s/p removal of retained frag, neck exploration. No airway or esophageal injury identified fragment removed. Initial GCS 15, current GCS 15.
6 CCATT	Day 2. IED blast. Injuries included open lower extremity fracture, right tibial plateau fracture, right distal tibia/fibula fracture, right midfoot fracture, right metatarsal fracture x 4, left distal fibula fracture, left calcaneal fracture, fractures to both distal upper extremities, including left ulnar fracture. L5 burst fracture (unstable) per CT scan. Pt has external-fixators to bilateral lower extremities. GCS on arrival 15. No MACE; respiratory status: intubated/sedated w/Propofol, Fentanyl). Appears comfortable.
7	Day 2. Gunshot wound to right forearm, fractured radius: soft tissue derangement, no other trauma. Radial nerve damage
8	Day 11. MVA vs IED blast. Blast came through gunner hatch. No LOC. Originally presented with low back pain only, then developed persistent headache with decreasing MACE 20/30 and persistent tinnitus in left ear.
9	Day 0. Right Hemothorax. Pt suffered injury from suicide bomber (vest) with shrapnel wound to the right chest with right hemothorax. Injury occurred at 0555 (Day 0), GCS 15. Lacerations to posterior thighs. Pain 5/10 premed, 2-3/10 post meds.
10	Male with fatigue during past few months. Pt sent to medical officer for positive HIV screen on blood drive in country. Autoimmune infectious disease suspected.
11 CCATT	Day 0. Evacuated to Role 3 IED blast at 0730Z. Pt arrived here at Role 3 at 1230Z. Pt presents with penetrating injury to left neck, right thigh, chest, piece of metal in right ventricle presently okay. Piece of metal entered the heart through venous system. patient needs immediate flight to Germany for possible cardiac intervention.
12	Day 0. Transferred to Role 3 with right upper extremity (RUE) distal humerus fracture and multiple shrapnel wounds to right upper extremity and bilateral lower extremities s/p suicide bomber explosion. Arrived in stable condition. RUE 9/10 pain with movement, 6/10 after meds. Went to OR for external fixator of right humerus. Radial nerve intact, Ulnar nerve possible dysfunction. Good sensation & movement. Compartment syndrome considered. GCS 15/15. Current VS: 137/78, 87, 16, 98% on RA. Pain 7/10 before meds, now 3/10 after meds. CT not functioning. C-spine cleared clinically.
13	History of maxillofacial dental symptoms prior to deployment. Dentist recommends evacuation to home base secondary to pain, bone loss, periodontal disease, erosion. Pain 7/10 w/out meds, 4/10 w/meds.

The AER is currently under development. All data have been abstracted from TRAC2ES and are undergoing cleaning. Data abstraction is pending for the 3899 using an interface similar to the DoDTR. Data from the CCATT pilot unit will also be integrated. Areas identified as challenges include a lack of consistent information on medical crew complement and the loss of a large number of the en route care documents for the AE patients. Characterization of all diagnoses requiring consideration during AE is required.

4.2.2 Preexisting Conditions. Three British descriptive studies discussed the presence of preexisting disease as a reason for aeromedical evacuation. In 74 British personnel evacuated from Yugoslavia in 1996-1997, 41% were evacuated for exacerbation of a previous medical condition, and of these patients 78% were considered outside medical qualification.[60] However, a more recent study of 270 patients admitted to Camp Bastion over a nine-month period in 2011, found only 14 (5.2%) with conditions requiring a downgrade of deployment status.[61] Of note, only two of these patients were considered avoidable. An area for future research would be to describe the incidence of preexisting conditions as the reason for evacuation with consideration for pre-deployment screening. There are no published reports on the incidence of evacuations due to exacerbation of a preexisting medical condition among US personnel.

The 2010 MSMR epidemiologic report (October 2001-September 2009)[44] found that among patients evacuated for a non-battle injury or disease, there was a strong association between the primary cause of the evacuation and having a medical encounter for the same reason within 90-days of deployment (Figure 4). The highest risk categories were musculoskeletal, respiratory, nervous system, mental health disorders and genitourinary. A limitation of the report is the lack of detail of the specific diagnoses.

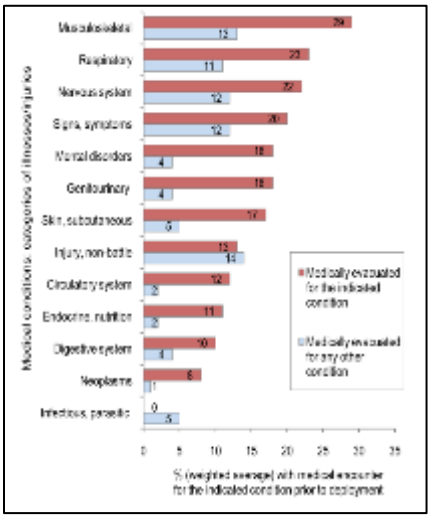


Figure 4. Among deployers who were medically evacuated from OIF/OEF, percentages with medical encounters for various conditions within 90 days prior to deployment, US Armed Forces, October 2001 - September 2009. From MSMR 2010.

4.2.3 Preexisting Conditions – Mental Health. Between 2001-2004 there were 1264 patients medically evacuated from OEF/OIF for a primary psychiatric reason.[62] During this same period, the primary mental health cause for evacuation among British troops was adjustment disorder.[63] In American troops, the severity of the mental illness increased from 2004 to 2006.[64] Between 2004 and 2010 there were 5,087 US patients who required a psychiatric evacuation, with a progressive increase in incidence each year.[65] A limitation of these studies is the lack of control of mental health state before deployment as well as other risk factors, specifically multiple deployments, although as demonstrated in Figure 4, 18% of patients evacuated for mental disorders had a medical encounter related to the same issue within 90 days of deployment.[44]

4.2.4 Navy En Route Care. Only two studies were found regarding Navy en route care. A recent study by Walrath[66] reported on 428 Navy transports, with a median transport time of 54 (30-78) minutes. A majority of the missions were supported by Search and Rescue Medical Technicians (76%); 48% of the missions were trauma related, and 54% met advanced life support criteria. Welsh[67] reported on MEDEVAC transports (2012-2104) from submarines. During this period, 323 patients were evacuated (180 (56%) medical, 76 (23%) trauma, and 67 (21%) psychiatric, with approximately 22-45 MEDEVACs per quarter. No data were provided on en route care requirements. There are no reports on Navy transports in the AOR.

4.2.5 Coalition AE. Four papers provide epidemiologic data for patients evacuated by Great Britain, Spain and Poland.[50,68-70] The AE database for the Royal Air Force was used to provide epidemiologic data on evacuations from Apr 2003 to March 2010. During this period, the RAF evacuated 28,116 patients, with clinical data available on 21,477 (average evacuations 4.9/month). A majority of these evacuations were within the United Kingdom, with only 16.5% from Iraq, 15.3% from Afghanistan, 9.1% from Cyprus, 5.6% from Germany, and 5.6% from the Falkland Islands. Fifty percent of the evacuations were for musculoskeletal/connective tissue disorders, trauma (7.1%) and mental health disorders (6.3%). Nontraumatic disorders accounted for a majority of the military (92.9%) and nonmilitary (95.1%) patients, with a majority of the patients with low acuity (Dependency 3 – 11.4%; Dependency 4 – 83.2%) in contrast to severely or critically injured/ill (Dependency 1 1.95; Dependency 2 – 3.4%). Overall 13.6% of evacuations from Iraq and Afghanistan were for trauma (specific diagnoses not described – no delineation of BI vs NBI; 14% of US evacuated with BI). Similar to Harman's study,[71] these data reflect only the first ICD diagnosis, thus do not capture the complexity of patients condition. These data are important in demonstrating the need to capture all AE transports, not solely those from the current AOR (Iraq/Afghanistan). There were 232 Spanish patients evacuated to the Role 4 Spanish military hospital in Madrid (2008-2013), with 110 (47%) from Afghanistan, 45 (19.3% from Lebanon, 22 (9.4%) from Djibouti and Seychelles, 5 (2.1%) from Kosovo, 6 (3%) Libya, 2 (0.8%) from Haiti, and 32 (13.7%) from sea navigations. Annually between 20-49 patients were evacuated, with only 33 (14.2%) in a medicalized plane with an AE team. A majority (91%) of the patients were noncombat casualties, with 21 (9%) with combat injuries. The primary medical causes for evacuation were psychiatric (12.3%), cardiovascular (9%), and gynecological (7.1%). Among Polish military members medically evacuated from Iraq,[70] the primary reason was psychiatric (acute stress disorders) requiring pharmacological treatment, followed by battle injuries (GSW and shrapnel wounds) and non-battle injuries (sports injuries, traffic accidents). There were also 47 self-requested evacuations for non-medical adaptation disorders and family-related problems. In contrast, in Afghanistan (2007-20113), there were 485 evacuations (1.9% of total Polish troops), with the largest percentage (40.6% - compared to 23.8% for US) due to battle injuries and non-battle injuries (32.4% compared to 14.3% for US).[69]The remaining 27% (compared to 61.9% for US) were due to disease, with gastrointestinal (4.6%), psychiatric (4.5%), neurological (4.3%) and musculoskeletal (2.7%) as the most common causes.

4.2.6 Disaster/Humanitarian Response. There is limited research related to AE disaster/humanitarian responses. Lezama[72] provided an overview of USAF disaster evacuations (Hurricane Katrina – 2600 patients via AE, Hurricanes Gustav and Ike – 833 transports from three aeromedical staging facilities in Texas and Louisiana, AFSOC response to earthquake in Haiti until MASF was in place for AE and a medical support hospital to assist in transfers to/from USNS Comfort). Several presentations summarize the role of AE in the patient movement action in response to Hurricane Katrina and Rita including a timeline of activities (Figure 5).[73-75] The numbers/dates of the major aspects of the evacuations coincide with the data abstracted from TRAC2ES as a part of the AER (see Figure 6).[76]

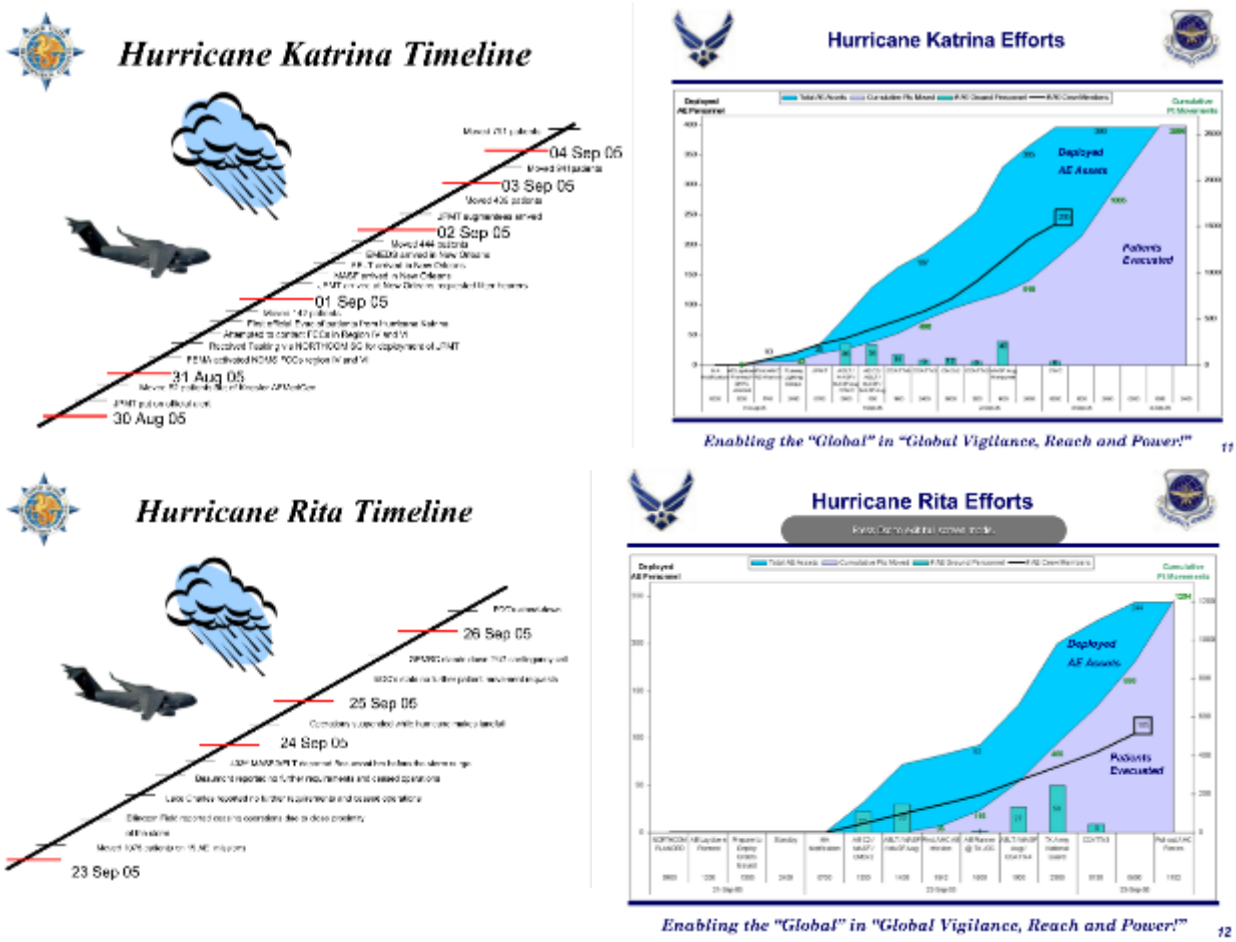


Figure 5. Hurricane Katrina and Hurricane Rita timeline. From NDMS Patient Movement After Action Report.[73]

Lezama also presented the GPMRC National Disaster Medical System Patient Movement Clinical Guidelines were presented and outlines the ABCs of evacuation (Table 5). The original source cited for these guidelines is no longer active, thus it is unclear if these guidelines are still recommended. No other guidelines specific to disaster evacuation were identified. A Clinical Practice Guideline available through the JTS may be appropriate.

Table 5. GPMRC NDMS Patient Movement Clinical Guidelines (from Lezama[72])

Airway protected	CCATTs are trained to manage ventilated patients and can monitor endotracheal tube cuff pressure. Patients who have been recently extubated should be monitored for at least 4 hours before evacuation.
Breathing adequately supported	Normally, oxygenation at altitude is impaired. Do not move vented patients with high oxygen requirements (FiO2 greater than 60%).
Circulation acceptable?	Do not transport patients with hemoglobin levels <7 g/dL. Hemoglobin of 9 g/dL is the lowest that is safe without either significant supplemental oxygen or transfusion.
Disability	Brain injuries swell and seizure thresholds lower at altitude. Take precautions and premedicate to prevent seizures, if needed. Ensure the aeromedical evacuation crews have the tools they need to address seizures if they develop (i.e., IV Ativan and IV access).
Expansion, as in trapped air	Specifically consider intra-abdominal (i.e., postop ileus, postop laparoscopic procedures), intracranial, intrathoracic, and trapped air within the sinuses, ears, or eyes.
Fixation	Ensure careful fixation and stabilization of all lines and tubes, plaster casts should be at least 48-hours old to allow for possible soft tissue expansion after an acute injury or should be bivalved if swelling is expected. There can be no hanging weights for traction in flight; other traction devices must be used if required.
Other considerations – equipment and supplies	If the patient is dependent on continuous treatment, the transferring facility should send additional medications and supplies with the patient. Only authorized medical equipment is allowed on aeromedical evacuation missions. Patients will be switched over to approved medical equipment before flight. There is a waiver process for unapproved medical equipment; call GPMRC
Psychiatric patients	Psychiatric patients are likely to need attendants, they must not be disruptive, and they must be able to follow directions.

National Disaster Medical System Aeromedical Evacuation: A Guide for Healthcare Providers. Available at http://www.transcom.mil/tcsg_public/files/ndms_aeromedical_evacuation_clinical_guidelines.pdf

Other reports and documents were generally reviews or first-person accounts with limited details regarding en route care in humanitarian and disaster response.[77-80] Cancio's[69] report on the evacuation of casualties with burns after an airplane crash in Guam summarizes lessons learned and recommendations for future operations. It is not known if these recommendations have been maintained. Frykberg[81,82] summarized the injury patterns and care provided to the 112 survivors of the Beirut bombing. These reports are important as they describe the characteristics of casualties requiring evacuation shortly after injury. A majority of the casualties received care onboard the USS Iwo Jima, and with 12 hours all had been evacuated by air to Germany or Naples or by ground to Cyprus. No information is available on the en route care of these patients. A unique report[83] summarized the en route care of 14 critically ill/injured tsunami victims to Finland. Two patients were intubated, two patients had severe head injuries and one patient was in septic shock – necrotizing fasciitis, one severe wound infection and pulmonary dysfunction. The remaining patients were in stable condition. A surgeon evaluated all wounds to determine if they could wait the 12-15 hours of the flight. In flight, two patients had wound debridement. and one patient had a cast removed followed by external fixator stabilization and a fasciotomy. The authors note that cavitary surgery (except decompressive laparotomy) would not be recommended. They summarized their findings that standard treatment is not dependent upon the location, but rather the expertise of the team. Roedig[84] provided a general overview of AE and CCATT, and summarized the response of the German Air Force to the December 2004 tsunami that struck Thailand (Table 6).

Table 6. German Military Aeromedical Evacuation Response – 29 Dec 2004 to 4 Jan 2005 Tsunami

3 STRATAIRMEDEVAC Missions (GAF Airbus A 310) - Locations: Phuket (2), Bangkok (1) 113 patients from 8 nations • Intubated (ICU) = 11 • Non-intubated (ICU) = 17 • Polytrauma (litter) = 14 • Severely/moderately/slightly injured litter kit = 71 • Sitting patients = 20

A review[85] of September 2005 TRAC^{2}ES data provides a general overview of the number of individuals evacuated in response to Hurricane Katrina and Hurricane Rita. The response to Hurricane Rita preceded arrival of the hurricane, with 1169 individuals evacuated on 17 missions on 23 September 2005. On these missions, there were on average 61 ± 27 patients/flight (range 42-123), with missions flown to destinations across the southeastern US (e.g., North Carolina, Tennessee, Kentucky, Arkansas, Oklahoma, Dallas/San Antonio TX). Most of the patients were 2A (Immobile litter patient, non-psychiatric, who are not able to move about on own volition) or 3A (Ambulatory patient, non-psychiatric and nonsubstance abuse, going for treatment or evaluation), with a smaller number of non-medical attendants (Figure 6B). There were 68 patients coded as CCATT for Hurricane Katrina, but none for Hurricane Rita.

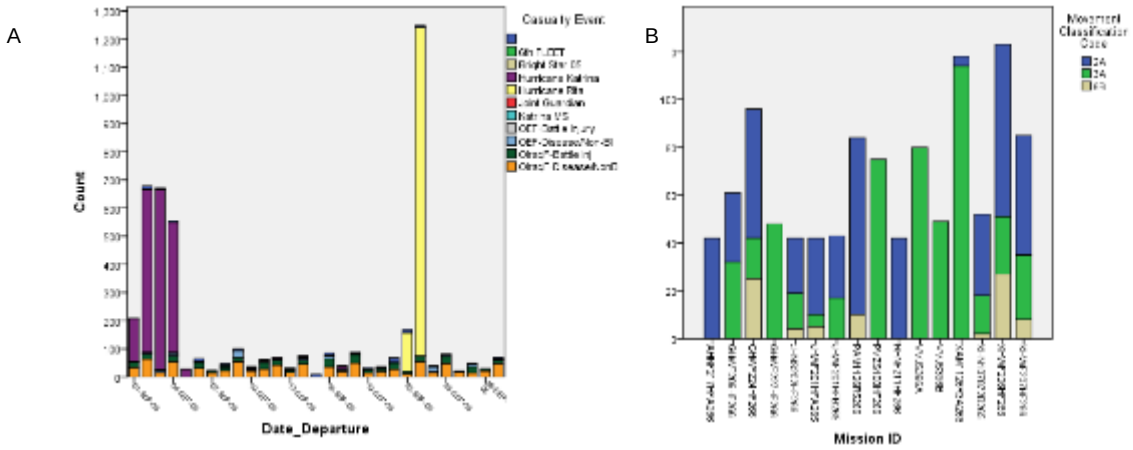


Figure 6. Statistics from USAF AE evacuations in September 2005. A. Patients evacuated. B. Classification of 1169 patients/non-medical attendants on missions on 23 September 2005 in support of Hurricane Rita evacuation.

A limitation of the TRAC^{2}ES data specific to the hurricane response is the lack of any patient specific information, which restricts its use for planning. The identification of readiness databases that may include more specific patient information, will enhance the use of these data for planning. **A gap is the ability to rapidly collect required data during a large-scale humanitarian response. Consideration of module in TRAC2ES or an appropriate registry that could be used to facilitate standardized data collection for disaster response). Another limitation is the lack of a central repository for after action reports. Consistent with the principles of a learning health care system,[86] a central repository for after action reports and a systematic and rapid process for the integration of lessons learned (as appropriate) is needed.**

4.2.7 Working Dogs. A unique population are military working dogs.[87] The newly created Aeromedical Evacuation Registry (AER) includes a code to quickly identify records for the military working dogs, which may inform refinements to include en route care in the JTS CPG related to the care of military working dogs.

Gaps:

- ***Inclusion of information on en route care, including days since event, and outcomes (beyond return to duty rates).***
- ***Inclusion of all diagnosis, not just primary diagnosis.***
- ***Inclusion of information on pre-existing condition.***
- ***Integration of data on AE during high-operational tempo actions (e.g., Battle of Fallujah, Somalia) is needed to develop flight profiles.***
- ***Any future epidemiologic studies specific to this patient population should be designed to link en route care medical records with existing databases to explore contemporaneous outcomes (e.g., within the first seven days post-evacuation) or longer-term outcomes.***
- ***Integrate epidemiologic data (see AER) and patient flow data in models for planning (see recommendation from Rand Corporation on STEP approach to planning.[88,89]***

4.2.8 CCATT. Several studies have reported on the epidemiology of CCATT patients (Table 7). Rasmussen reviewed the records of 2899 patients transported by CCATT from 11 Sept 2001 to 31 Dec 2010. Among the patients, only 975 had complete records (1560 with missing time of injury or time of arrival at LRMC). The patients arrived at LRMC a median of 38-hours post-injury, with 93% of all casualties arriving at LRMC within 72 hours. The 30-day mortality rate was 2.1% and en route mortality was 0.02% (no information if patients were DNR/comfort care only). In a multivariate analysis, ISS, units of whole blood transfused and worst international normalize ratio (INR) were the only factors associated with mortality. Time to transport/arrival at LRMC was not associated with mortality. No information was provided on the timing of the variables included in the analysis (obtained from JTTR). The study did not assess the relationship between time to transport and morbidity or complications, and except for the en route mortality, the study does not provide any information regarding the in-flight phase of care.

Bridges[90] conducted a retrospective medical record review (TRAC2ES and medical records) for patients transported by CCATT from October 2001 to 2006. During this period, there were 2,439 patients (3,492 patient moves) in support of military operations in Iraq and Afghanistan. Data on flight times were available for a subset of patients: Flight times (AOR-AOR 2 ± 1 hour, n = 134), AOR-LRMC (6.5 ± 1.5 hours, n = 727, LRMC-CONUS (9.4 ± 1.5 hours, n = 399). In a sub-analysis of the 1,995 patients evacuated from the AOR, 1491 patients had injuries (1280 -battle injuries, 156 -non-battle injuries, 55-injury type not specified) and 504 (25%) had a disease diagnosis. Sixty five percent of the injured casualties suffered polytrauma. Among the patients with an injury, the most common type was soft tissue trauma (64%, n = 948), orthopedic/extremity (43%, n = 636), pulmonary/thoracic (29%), neurological (28%), skull/facial fracture (27%), vascular (35%), abdominal/GI (24%), ocular (18%), amputations (15%), burns (10%). Overall, 69% of these patients suffered polytrauma. The most common medical diagnoses were cardiac (n = 275) and pulmonary (n = 121). A major challenge for this study was the large number of missing in-flight records, with the anecdotal report that because the forms were not standardized they were not retained in the medical records. The most common inflight care provided was mechanical ventilation (1265/1995; 63%). Among the 475 patients with a primary neurological injury, 38% had documentation of ICP monitoring. This study did not analyze the data for adverse events**. Areas for future research identified in this study are summarized in Table 8 (note – data in this set, may allow for exploration of these questions).**

Table 7. Summary of CCATT Epidemiologic Studies

Author	Transport Date	n	Results
Rasmussen[91]	11 Sep 2001-31 Dec 2010	975 (1560 with missing time of injury or time of arrival LRMC)	Analysis of time to transport • Arrival LRMC median 38 hours' post-injury; 93% arrived within 72 hours • 30-day mortality 2.1% • En route mortality (0.02%)
Bridges[90]	Oct 2001-Dec 2006	2439 (3,492 patient moves). Sub analysis 1995 AOR-LRMC transports. Large number of en route care records not retained in medical record	• 1491 injuries (1280 BI/156 NBI, 55 unknown); 504 disease • Flight times (AOR-AOR 2 ± 1 hr, n = 134), AOR-LRMC (6.5 ± 1.5 hrs, n = 727, LRMC-CONUS (9.4 ± 1.5 hrs, n = 399). • Most common injuries (soft tissue – 64%; orthopedic -43%). 69% with polytrauma • Primary neurological injury (n= 475); 38% with ICP monitoring documents • MOI: Explosion (53%), fragmentation (28% - may be secondary to explosion), GSW (16%), motor vehicle crash (16%) • Most common medical diagnoses: cardiac (275/504), pulmonary (121/504), vascular (12%), neurological (11%), infectious disease (8%) • Mechanical ventilation (63%); monitor (ECG)> 95%, arterial line (21%), ICP (9%)
Mason[92]	2005-2006	133	• ISS 20 • BI 78 (59%) • Most prevalent injuries – extremity trauma (amputations, vascular, fractures, soft tissue) • Medical: cardiac (68%), pneumonia (9%), cerebrovascular accident (9%) • Mechanical ventilation (57%) • En route adverse event: hypotension (17%) • Ventilator failure (2/76); iStat failure (4) • Aline placement (3); central line (1)
Renz[93]	2003-2007	540 (burn casualties)	• Mean burn size was 16.7% total body surface area (range, <1%-95%) • Injury Severity Score of 12.2 +±- 13.7. • Mechanical ventilation (n = 108; 33.5%) • Inhalation injury (n = 69; 12.7%) • 206 (38.1%) transported by the Burn Flight Team; 174 (32.2%) CCATT; 106 (Routine AE) • Mean transit time: 4 days after injury. • In-flight deaths (0); 30 (5.6%) patients died of their wounds at burn center. • Associated injuries: ISS > 16 for 169 (31.3%). 275 with multiple traumatic injuries with fractures - lower extremities most common. • 109 (21%) required escharotomies
Beninati[94]	2007-2008	656	• Trauma (n = 425; 65%); 269/425 with polytrauma • Most common injuries: extremity amputations (80; 19%), TBI (90; 21%), intraabdominal (121; 28%), intrathoracic (93; 22%), burns (73, 17%) • Medical (n = 231; 35%) • Most common medical diagnoses: cardiac (125; 55%) with 29 STEMI or NSTEMI • Pulse oximetry (100%), invasive BP monitoring (51%), mechanical ventilation (318; 49%), vasoactive medications (68; 10%) • En route blood (9%) • Adverse en route events: desaturation < 90% (19; 2.8%), hypotension (29; 4%), decreased neurological status (3, < 1%), anuria/oliguria (23, 3.5%). • No en route deaths, accidental extubations, or loss of chest tube

Table 7. Summary of CCATT Epidemiologic Studies (concluded)

Author	Transport Date	n	Results
Galvagno[95]	2011		• Median age (25; IQR 22-33). Male (97.6%). • Most common ICD-9 diagnoses (bilateral; lower extremity amputation 897.6 = 40; injury from bomb fragments E991.3 = 29; myocardial infarction/ACS 410.9 = 19; open wound to groin/testes/penis 878.0-8 =17; lumbar fracture 805.4 = 16; foot amputation unilateral 805.4 = 16; lower extremity amputation 897 = 13; hand amputation 887 = 10; femur fracture 821 = 9; cervical fracture 805 = 7; pneumothorax 860 = 7; liver injury 864 = 5; foot amputation - bilateral 896.2 = 5; femur fracture (open) 821.1 = 5; pneumothorax - open 860.1 = 4). • Comparison with 2001-2006 vs 2011 MOI: Explosion (58% vs 45.5%), fragmentation (28% vs 5.5%), gunshot wounds (17% vs 15%), motor vehicle crashes (8% vs 4.1%), blunt trauma (2% vs 2.8%), toxic exposure (2% vs 0.7%), other (2% vs. 2.5%). • BI (90.3% vs 75.2%)/NBI 9.7% vs 24.8%). • TBI 15.9% (reporting not consistent). • Burns (0.7%); ACS/MI (6.6%), • Stroke (3.1%). • Pulmonary explosion injuries (n = 6; 2.1%)/ALI or ARDS (3.1%).
Bebarta & Ervin[96]	2007-2013	1128	• En route procedures: fluid bolus (267; 24%), blood (179; 16%), vasopressors (35; 3%), chest tube (12; 1%), intubation (5; 1%), analgesia – parenteral (1044; 93%), sedation (730; 65%), ketamine (51; 5%), PCA (236; 21%), epidural (90; 8%), regional block (5; 1%), paralytic (50; 4%) • En route adverse events: Hyperthermia (532; 47%), respiratory (460; 41%), hemodynamic (209; 19%), hemoglobin $\leq$ 8 g/dl (200; 18%), heart rate (161; 14%), decreased UOP (87; 8%); increased ICP (52; 5%), bleeding (9; 1%), neurologic (8; 1%), medication reaction (2, < 1%), cardiac arrest (0; 0%).
Medellin[97]	2007-2015	657 non-trauma patients	• Most common diagnosis: cardiac (52%), neurological (16%), pulmonary (13%); neurological (16%). • En route interventions: supplemental oxygen (62%), anti-coagulant/anti-platelet medications (46%), analgesia (30%), cardiac medications (20%), and ventilation (21%), sedatives (24%) • Inflight events – pain (20%), respiratory (9%), cardiac (71%), temperature (11%), renal/urinary (4%), equipment failure (2%), abnormal labs (16%)

Table 8. Research Questions Based on 2001-2006 CCATT Analysis[90]

1. Incidence of hypothermia or hyperthermia during the acute phase of care and transport
2. Relationship between en route complications (decreased blood pressure or oxygen saturation or need for supplemental oxygen above what is predicted) and preflight hemoglobin
3. Neurological Casualties
   a. Physiological profile (BP, ICP, CPP, temperature, oxygen saturation) during flight
   b. Incidence of events associated with secondary brain injury (hypotension, hypoxia, hyperglycemia, hyperthermia or hypothermia, hypocapnia, or acidosis)
4. Blast Injury Casualties – Blast lung injury
   a. Review the preflight medical records for indications of pulmonary blast injury (PaO2/FiO2, chest radiograph characteristics and the presence of bronchopleural fistula) and other factors strongly associated with pulmonary blast injury (skull fracture, burns > 10% body surface area or penetrating injuries to the head or torso)
   b. En route cardiopulmonary status and care requirements (e.g., increase in supplemental oxygen or changes in ventilator parameters)
   c. Acute outcomes en route or post-transport indicative of worsening pulmonary status (e.g., pneumothorax, desaturation, or increased supplemental oxygen)
5. Soft Tissue Trauma
   a. Relationship between altitude induced hypoxemia, hypothermia, and wound complications
6. Acute Coronary Syndrome
   a. Demographic characteristics to include status (Active Duty, Guard, Reserve, civilian) and prevalence of risk factors
   b. Incidence of inflight complications and the relationship between the occurrence of en route complications and the time since the initial event and stabilization of signs and symptoms

Mason[92] provided an in-depth description of 133 severely injured (ISS 20) CCATT patients transported from Iraq to Germany in 2005-2006. Among these patients, 78 (59%) were combat trauma. The most prevalent injuries were lower extremity trauma (i.e., amputations, fractures, vascular injuries, soft tissue trauma). The most common medical diagnoses were cardiac (68%), pneumonia (9%) and cerebrovascular accident (9%). Fifty seven percent of the patients were ventilated, and the most common en route adverse event was hypotension (17%). A unique aspect of this study was the incidence of equipment failures (ventilator 2/76 ventilated patients and iStat failure due to ambient temperature (4 occurrences). En route procedures included arterial line placement (n = 3) and one central line placement for monitoring in a hypotensive patient. Tobin[98] summarized critical care procedures performed during 1198 transports patients with ISS > 15 for POI-Role 2/3 (n = 634; 53%) or Role 2-3 transports (n = 564; 47%). Although this study summarized the procedures performed during 147 (12.3%) of transports (e.g., intubation, cricothyrotomy, central venous access, cardiopulmonary resuscitation), it did not delineate when the procedure was performed (phase of transport) or by whom (CCATT, DUSTOFF). Further delineation of these data would inform requirements (personnel, equipment) and analysis of pre-post flight outcomes for seriously/critically injured casualties. Analysis of patients transported by CCATT in 2007-2008 were summarized in a several papers.[94,99] In this subset of patients, 65% were trauma (n = 425), with 269/425 (63%) suffering polytrauma. The most common injuries were extremity amputations (80; 19%), TBI (90; 21%), intraabdominal injuries (121; 28%), intrathoracic injuries (93; 22%), and burns (73; 17%). Nine percent of the trauma patients received an en route blood transfusion, although no information on the indications for the transfusion were presented. Among the 231 (35%) medical subset, the most common diagnosis was cardiac (125; 55%), with 29 patients suffering a STEMI or NSTEMI. The most common en route interventions were pulse oximetry (100%), invasive BP monitoring (51%), mechanical ventilation (318; 49%), vasoactive medications (68; 10%), and blood products (43; 7%). This study is important as it describes the most common en route adverse events were desaturation < 90% (19; 2.8%), hypotension (29; 4%), decrease in neurological status (3, < 1%), which were most likely related to sedation, and anuria/oliguria (23; 3.5%). There were no deaths, accidental extubation or loss of a chest tube en route. **Gaps in this analysis included information on the number of flights for the patient, time from**

injury/event, timing (which flight) of adverse events, adverse events by injury/disease type, preflight/post flight vital signs, no short term (post-transport) outcomes. The characterization of the en route adverse events may allow for standardization of definitions for the analysis of other populations.

Galvagno[95] summarized the epidemiology of 290 CCATT patients transported in 2011. A strength of this study was a comparison of 2011 data with those reported from earlier phases of the war. For example, the MOI from this study was compared to the 2001-2006 period.[90]. Explosion (58% vs 45.5%), fragmentation (28% vs 5.5%), gunshot wounds (17% vs 15%), motor vehicle crashes (8% vs 4.1%), blunt trauma (2% vs 2.8%), toxic exposure (2% vs 0.7%), other (2% vs. 2.5%). Note the differences in explosion and fragmentation wounds may reflect variations in coding. Additionally, the study reports differences between the 2001-2006 and 2011 BI rates (90.3% vs 75.2%) and NBI rates (9.7% vs 24.8%). The study also compared the incidence of possible pulmonary explosion injury (2.1%) compared to the rate in Dorlac's report (2005-2007),[100] which had a documented diagnosis of ALI/ARDS in 3%. Information on the use of the Lung Team were not available. **This study is important as it provides a comparison with previous periods, which may reflect changes in the operational setting, but also emphasize the need to standardize coding.**

Bebarta and colleagues analyzed data from the CCATT registry for 1128 patients evacuated from 2007-2013. Procedures in flight: Fluid bolus (267; 24%), Blood (179; 16%), Vasopressors (35; 3%), chest tube (12; 1%), intubation (5; 1%). analgesics/sedation/paralytics: parenteral (1044; 93%), oral opioid analgesia (39; 3%), sedation (730; 65%), ketamine (51; 5%), PCA (236; 21%), epidural (90; 8%), regional block (5; 1%), paralytic (50; 4%). Complications during flight: Hyperthermia (532; 47%), respiratory (460; 41%), hemodynamic (209; 19%), hemoglobin $\leq$ 8 g/dl (200; 18%), heart rate (161; 14%), decreased UOP (87; 8%); increased ICP (52; 5%), bleeding (9; 1%), Neurologic (8; 1%), medication reaction (2, < 1%), cardiac arrest (0; 0%). This complete data set has been presented only in abstract form. Additional questions to address include: patient demographics, time to flight; en route O2 requirements, complications by injury type; en route pain management (scores). Per the abstract, most patients were hemodynamically stable, but no discussion was presented for the unstable subset. Other gaps include lack of information on en route blood transfusions, timing of hyperthermia (by patient population subset). Number of flights/flight route (AOR-AOR/AOR-LRMC/LRMC-CONUS). It was unclear if there were 1128 patients or patient movement requests (i.e., patient may have been transported by CCATT more than once).

A limitation of most studies related to CCATT is the focus on trauma patients only. As described in previous epidemiologic studies, over 35% of all CCATT transports are for patients with a medical diagnosis. Medellin[97] reported on the analysis of CCATT patients with a non-trauma diagnosis transported from 2007 to 2015, using data from the CCATT pilot unit. Similar to previous reports, among the 657 patients studied, the most common medical diagnoses were cardiac (52%), neurological (16%) and pulmonary (13%). En route interventions included supplemental oxygen (62%), anti-coagulant/anti-platelet medications (46%), analgesia (30%), cardiac medications (20%), and ventilation. **This preliminary report did not address specific demographics (e.g., ACS vs. cardiac arrhythmia as diagnosis), time to transport since stabilization (see Cardiology section for further discussion), en route adverse events, post-flight diagnostics (i.e., MI vs rule-out MI), preflight state (vital signs/labs) predictive of en route adverse events or post-flight status.**

Research was also available for unique patient transport requirements, including 540 patients with burns who required CCATT/Burn Team transport or routine AE,[93] and 24 patients who were transported from the AOR to Landstuhl by the Acute Lung Rescue Team.[101] Other relevant reports may include those related to Role II-III transport.[102] Although these missions are generally flown by Army MEDEVAC, the evacuations can also be performed by CCATT**. These reports may identify gaps related to the en route**

care requirements/effect of en route care on patients who are stabilizing/stabilized acutely post-injury and inform gap identification for potential A2/AD scenarios.

Gaps:

- ***Create profiles of casualty flow from different disaster response scenarios (based on disaster type, location, military, military-civilian response) – start with summary of extant literature. Modeling.***
- ***TRACE^{2}ES – for AE disaster response***
- ***Reanalyze composite data sets (confirm coding) for trends across time – See Galvagno[95]***
- ***Identification of patients with occult pulmonary blast injury***

4.3 Time to Transport

There is limited focused evidence on the time to transport. In 2014, a summary paper developed by the 59th Medical Wing, addressed time to transport. This paper included 35 documents. As summarized in Table 9, except for two studies related to the transport of patient with TBI, no information was provided to inform recommendations on time to transport.

Table 9. Optimal Time to Transport[103]

Topic Area	Papers Reviewed	Findings Specific to En Route Care
Correlation between transport time and outcomes ins trauma patients	4	Civilian – prehospital. No studies specific to regulated en route care
Patient Transfer	6	No studies addressed optimal time to transport for regulated en route care. One military specific study addressed flight time (2.5 hours), but did not address time to transport
Optimal time to transport for patients with TBI	6	Only two of the studies provided data on time to transport. No specific recommendations were identified. Goodman[104] addressed time to transport related to inflammatory response. Dukes[105] summarized transport times and the timing of adverse events (hyperthermia, hypotension, hypoxemia) for each leg of the transport. Three military studies addressed the incidence of adverse events, ICP patterns during pre-transport and en route care phases. The final civilian study addressed transport times, but not time to transport.
Optimal time to transport for patients with burns	7	Five of the studies were related to US military population. None of the studies addressed time to transport
Optimal time to transport for trauma patients with hemorrhagic shock	5	None of the human or animal studies addressed optimal time to transport
Optimal time to transport for psychiatric patients and patients with various organ injuries	6	This section summarized literature related to the transport of patients with lung, vascular, renal, or blast injuries or a mental health diagnosis. None of the studies addressed time to transport.

Stevens[106] presented a summary of patients cared for by the US Navy Forward Surgical System in 2003 in Iraq. While this study focused on pre-hospital care, an important finding was the time to evacuation from the FRSS to a higher level of care, with times ranging from 45 minutes to 37 hours. A further analysis of this population is warranted for prolonged field care under austere conditions, implications for in-theater en route critical care for patients with delayed evacuation, and long-term outcomes based on time to transport. Ingalls[107] analyzed differences in mortality for975 patients undergoing early and rapid

evacuation from the AOR by CCATT from September 2001 to 31 December 2010. The overall mortality for this group was 2.1%., with a 0.02% en route mortality. Most of the en route deaths were in individuals with severe or lethal neurological injuries. Ninety three percent of the patients arrived at LRMC within 72 hours of wounding, and 98.5% arrived at LRMC within 96 hours. The only factors associated with mortality in these patients was ISS (OR 1.06; 95% CI 1.04—1.08), whole blood transfused (OR 1.09; 95% CI 1.03-1.16) and INR (OR 2.81; 95% CI 1.48-5.34). Evacuation time in hours was not significantly associated with mortality (OR 0.99; 95% CI 0.87-1.01). This study was the first to provide a large-scale review of the CCATT transports, and demonstrates the safety of rapid CCATT evacuation as related to mortality. However, the study does not address morbidity and long-term outcomes or provide insight into the transport of less critically ill/injured patients. **A recent review[108] of military medical doctrine noted that beyond MEDEVAC there is a lack of guidance on time to transport to a specified level of care. The report also noted inconsistencies in allied joint medical planning documents.** Throughout this gap analysis, each document was reviewed relative to time to transport, with findings (or lack of findings) included in each specific section.

Gap

- **Limited findings related to time to transport – need to integrate data into all registries and documentation records**
- **Expand research from pre-hospital/Role I to transport times Role 2-3 and 3-5**
- **Use data to explore en route care requirements for casualties who have undergone prolonged field care**
- **Provision of prolonged field care in en route setting**
- **Include in doctrine**
- **Effects of time to transport on morbidity, mortality and long-term outcomes**
- **Describe transport times for entire population (CCATT and AE)**

4.4 Neurological Injuries

The gap analysis from the High Performance Team: Optimal Time to Transport[5] specific to neurological injuries is summarized in Appendix 1. Several review papers summarize issues related to en route care of patients with TBI.[109-112] These documents were used to identify areas for further literature search (i.e., effect of AE on systemic and intracranial inflammation, continuous intracranial pressure monitoring across the different phases of transport – pre/in-flight/post-flight, time to transport, cabin altitude restriction). The reference lists were also queried to ensure completeness of the literature review.

Goodman's review[104] provides an excellent summary of the function and timing of the release of inflammatory and anti-inflammatory mediators in TBI and consideration for the effects of exposure on hypobaria and hypoxia. A study summarized in a report by Pritts[113] in which a murine model of TBI was exposed to simulated AE, identified IL-6 and MIP-1α as key inflammatory mediators associated with worse motor coordination after a mild TBI. The blockade of IL-6 decreased hypoxia-induced neuroinflammation and motor coordination deficits in this TBI model. A limitation was that is report did not provide specific details of this experiment, but suggests an area for future research.

In 2010, the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury published a report: "Traumatic Brain Injury (TBI) and Effects of Altitude: An Analysis of the Literature."[114] The literature search identified 16 articles published between 2000-2010 that describe human clinical studies of factors that can threaten the outcome or survival of patients with moderate-severe TBI: altitude-related brain damage, aeromedical evacuation, hypoxia, ICP/blood pressure, hydration and temperature. These 16 articles were reviewed for this current summary to identify those specific to AE. Studies were excluded if

the focus was on high altitude exposure (exceeding 10,000 feet), such as the neurological decompression sickness in a high-altitude pilot or extreme hypoxemia. Articles specific to pre-hospital evacuation were included for background, but considered outside the scope of this review. The reference list from the DCoE report was also used to confirm the completeness of the articles selected for this review. In contrast to the 2010 DCoE review, which characterized two articles[115,116] as specific to AE. This synthesis reflects the growing body of research in this area.

4.4.1 TBI Epidemiology. Based on data from Defense Medical Surveillance System (DMSS) and Theater Medical Data Store (TMDS) there have been 347,962 service members diagnosed with TBI since 2000 (Figure 7).[117] Among these patients, 5000 were penetrating, 3653 were severe, 31,202 were moderate, 286,255 were mild, and 21,852 were not classifiable. A limitation of these epidemiologic data is that number of patients who required AE cannot be quantified.

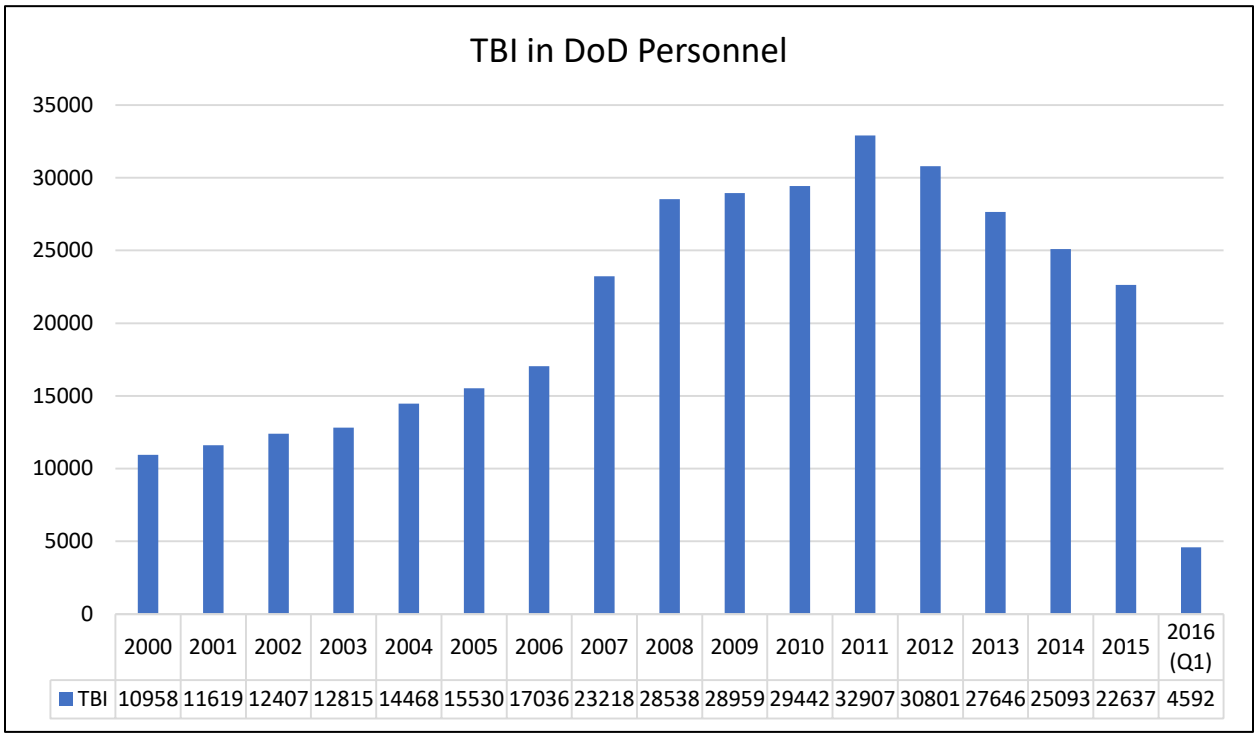


Figure 7. TBI in DoD personnel based on data from DVBIC.
(http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi)
https://health.mil/Military-Health-Topics/Conditions-and-Treatments/Physical-Disability/Traumatic-Brain-Injury

For example, the 2009 DVBIC report identified 28,958 cases of TBI. For the same period, there were 15,292 patient movement requests in TRAC2ES, there were 605 Patient Movement Requests for 302 patients with a primary and/or secondary diagnosis consistent with a TBI (Table 10). For example, the 78 patients with an intracranial injury (854.0-854.1) were transported on 157 flights.

Table 10. Patient Movement Requests (TRAC2ES 2009) for Patients with Primary/Secondary TBI

ICD-9	Definition	PMRs (% PMRs)	N (% Patients)
310.2	Post-concussion syndrome	143 (0.94)	49 (0.48)
800-800.9	Fracture of vault of skull	8 (0.5)	4 (0.04)
801.0-801.9	Fracture of base of skull	13 (0.9)	3 (0.03)
803.0-803.9	Other and unqualified skull fracture	17 (0.11)	6 (0.06)
804.0-804.9	Multiple fractures involving skull or face with other bones	1 (0.01)	1 (0.01)
850.x	Concussion	167 (1.09)	93 (0.92)
851.0-851.9	Cerebral laceration and contusion	7 (.05)	4 (0.04)
852.0-852.5	Subarachnoid, subdural, & extradural hemorrhage, following injury	18 (.12)	8 (0.08)
853.0-853.1	Other and unspecified intracranial hemorrhage following injury	16 (.1)	11 (0.11)
854.0-854.1	Intracranial injury of other and unspecified nature	157 (1.03)	78 (0.77)
959.01	Head injury, unspecified	58 (.0.38)	45 (0.44)
Total		605 (4.0)	302 (2.98)

*Patients may have more than one PMR.

Beginning in 2006, a screening program was initiated at LRMC to identify casualties with mild or moderate TBI. From 2006 to 2008, 18,000 patients were screened for risk for TBI (68% outpatient/32% inpatient).[116] Among the outpatients, 16% screened at risk for mild or moderate TBI and 31% of inpatients screened positive. A more recent study[117] extended the period of analysis (2006-2011). During this period, 43,852 were screened for mild TBI, with 6954 patients admitted to LRMC. Among these patients, 2805 (42.6%) screened positive for a mild TBI and 2393 (85.3%) were clinically diagnosed with TBI. These studies provide baseline data with confirmed TBI diagnosis to compare with pre-transport diagnosis (incidence of occult TBI - not identified as diagnosis in TRAC2ES). The screening tool used at LRMC had an 85% sensitivity for identifying patients who ultimately had a TBI. A gap is whether this tool could be used pre-transport to identify at risk patients.

As noted above, the data from the LRMC screening program provide a diagnostic outcome for patients at risk for TBI. As a part of the creation of the AER, an in-depth analysis of data from TRAC2ES indicated a high incidence of TBI not captured solely by the primary and secondary ICD codes. As summarized in Table 11, these data support the need to expand epidemiologic analysis beyond primary/secondary ICD codes for this population.

Table 11. TBI Based on ICD or History (2009)

TBI	Frequency (%)
Negative (ruled out)	3052 (20%)
Positive	1418 (9.3%)
Unable to assess	135 (0.9%)
Pending diagnosis	84 (0.6%)
Post-Concussion Syndrome (TBI not confirmed)	13 (0.1%)
No TBI (no documentation)	10,420 (68%)
Not applicable	130 (0.9%)

Similarly, Harman[71] used TRAC^{2}ES to analyze evacuations in 2003. In this study, data from TRAC^{2}ES (single line per patient) were linked to DMSS, with data cleaning to identify 11,183 patients deployed in support of operational efforts. Among these individuals 765 had a neurosurgical diagnosis, and 529 had a neurology (medical) diagnosis. In contrast, the DVBIC data set identified 12,815 individuals who suffered a TBI during the same period.

Bridges summarized data from TRAC^{2}ES and Mission reports to characterize patient transported by CCATT (2001-2006).[90,118] Of note, these data pre-date the creation of the CCATT Pilot Unit. The final integrated database reflected 3,492 CCATT patient moves, representing 2439 patients. Among casualties with a Battle Injury (n = 418), 28% had a neurological injury, 27% had a skull/facial fracture, and among Non-Battle Injuries (n = 76), 34% had a neurological injury. The second phase of the study involved a medical record review, with record searches at Walter Reed Army Medical Center, Bethesda National Naval Medical Center, Landstuhl and the JTTR. A challenge in this study was the lack of documents, with only 824/3,492 (24%) of the patient moves with both TRAC^{2}ES and Mission Report Data. Specific gaps that were identified in the initial analysis of these data specific to patients with neurological injury were to describe the en route physiological profile (BP, ICP, CPP, temperature, SaO2) and the incidence of secondary brain injury (hypotension, hypoxia, hyperglycemia, hyperthermia or hypothermia, hypocapnia or acidosis).

In a preliminary analysis[119] of the 2001-2006 CCATT data, among 36 patients (63 flights) with isolated TBI (ISS 14.3 ± 6.8) there were adverse events on 7/63 flights (decreased SaO_2, increased ICP or decreased CPP) and 33% of patients had a temperature > 38°C in the first 72 hours. En route care requirements: ICP monitoring 36%/ventilator 88%. A review of post-flight medical records described patient disposition (still in ICU n = 8, average 14 ± 7 days), transfer to medical-surgical unit (n = 14), transferred out of hospital/lost to follow-up (n =11), deaths (n = 3). Other documentation:

- CPP -LRMC (5/7 CPP < 60 mm Hg) 45 ±23 mm Hg
- CPP -CONUS (0/7 CPP < 60 mm Hg) 88 ±17 mm Hg
- Hgb (LRMC /CONUS admission) 11 ±2 gm/dl
- Patients transported with Hgb < 8 6%
- P/F ratio (LRMC admission) 339 ±106
- P/F ratio (CONUS admission) 283 ±158
- Pain documentation (en route/admit) 20%
- Pressure ulcer on admit LRMC (3/18) 17%
- Pressure ulcer on admit –CONUS (7/17) 41%

Dukes[105,120,121] expanded Bridges study and described the incidence and timing of secondary injuries in 63 combat casualties with severe TBI ISS 17 ± 8). Among these casualties 53% experienced at least one secondary injury during transport: hyperthermia 47%, hypoxia 25%, hypotension 17%, hyperglycemia 13%, hypothermia 8%. Additionally, patients experienced combinations of secondary injuries: hyperthermia + hypoxia (25%), hyperthermia + hypotension (25%), hyperthermia + hyperglycemia (15%). The ISS was a significant predictor of hyperthermia (OR 1.16; 95% CI 1.06-1.27). The timing of transport was not associated with the occurrence of a secondary injury. This study was limited by the missing data in the 2001-2006 database, and focused only on patients with isolated TBI.

O'Connell[122] conducted a study to evaluate the utility of the JTTR to establish mortality benchmarks for patients with severe TBI. A subset of 281 patients (2004-2010) with a blunt TBI and an AIS > 2 were studied. The incidence of secondary insults in the first 24 hours and their association with 24-hour mortality were study. Hyperthermia (> 38°C) was present in 13.9% of the sample; hypothermia (< 35°C) was documented in 3.9% of the cases. Hypotension (SBP < 90 mm Hg) was recorded in 11% of casualties. Regression analysis indicated that hypoxemia (SpO2 < 90%), hypotension (SBP < 90% or MAP < 60 mm Hg), hypothermia (< 35°C) were associated with increased mortality. A limitation of this study is that it used data from the JTTR, and did not specify when these secondary insults occurred. Re-analysis of this data set with the integration of en route care variables would enhance the understanding of the effect of these adverse events on mortality.

A review of the DVBIC research database in May 2017 (http://dvbic.dcoe.mil/research) failed to identify any research specific to aeromedical evacuation, with the exception of Xydakis' post-transport epidemiologic study. However, this repository of research and literature should be explored for post-transport outcomes.

Other epidemiology studies report on the incidence of mild TBI[123-129] or moderate-severe TBI. [130-132] None of these studies include information on any AE considerations; however, they do inform gaps in the literature. For example, Galarneau's[133] study of TBI describes the in-theater characteristics of 115 casualties with battle/non-battle injury TBI, and describes factors associated with in-theater transport to a Role 3 hospital (severity of injury, battle injury). The study also reports longer-term outcomes (return to duty, discharge from service), but does not include any information on en route care. These results (and information from the Navy Trauma Registry) could be integrated with information from the JTTR, in addition to en route care information to provide a complete description of these patients. Armonda's study[134] reports on the incidence and factors contributing to traumatic cerebral vasospasm (TCV) in casualties with TBI reported a CONUS arrival 2 to 18 day after injury. **No data were provided on the time from injury to detection of the vasospasm or information about the timing of the evacuation flights or en route care considerations. These data could be reanalyzed to add in the en route phase of care (AOR-LRMC) and LRMC-CONUS to explore any relationship between outcomes (including TCV) and GOS at discharge.**

Several of these studies report the prevalence of TBI diagnosed as LRMC, which is important as many of these individuals have undergone AE transport. Zonies[128] conducted a study of mTBI screening of 6,594 inpatients at LRMC (2006-2011). Among these patients (86% battle injury), 2805 (42.6%) screened positive for concussion/mTBI, and among these patients 83.5% were clinically diagnosed with a TBI. It would be important to know how many of these patients had a TBI diagnosis prior to transport and the time of transport relative to the causal event and diagnosis. Similar to the other research cited here, this study does not provide any information on en route care. Montgomery[135] evaluated 119 inpatients admitted within eight days of injury. Upon admission, there was no report of any neurological sequelae among the 29 patients with head/neck injuries. There were no deaths within 30 days; however, one casualty with a head injury complicated by an empyema died after 30 days. Xydakis[129] explored the relationship between loss of consciousness (LOC) and confirmed mTBI. Among 460 trauma patients evacuated to WRAMC within a median of 4 days (IQR 3-6) from injury there was an unexpected inverse relationship between reported LOC and confirmed TBI. These results suggest the need for additional diagnostic criteria to confirm mTBI when attributing en route care to mTBI outcomes. Finally, Orman's study,[131] which described the epidemiology of closed and penetrating TBI, suggests **the need for both isolated and polytrauma models of TBI reflecting these mechanisms of injury, in addition to current blast-related injuries.**

4.4.1.1 TBI-Time to Transport. A synthesis report on time to transport was developed by the 59th MDW.[103] The section of the report on time to transport for patients with TBI was limited to six papers - a civilian ground based cohort study,[136] two retrospective reviews related to CCATT transport of patients with TBI,[105,137,138] two observational studies[139,140] and a literature review.[104] The overall conclusion from this analysis, which primarily included studies relevant to pre-hospital transport was that patients with TBI can undergo air transport after initial treatment. However, as evidenced by the limited research on the topic, further studies are needed.

4.4.1.2 TBI – Inflammation – AE. Goodman studied a murine model of blunt TBI, with the mice exposed to a five-hour hypobaric flight (8000 feet). TBI alone was associated with increased inflammatory mediators (IL-6 and keratinocyte-derived chemokine [KC]) 6-hours post-injury. The exposure to hypobaric hypoxia at 3-hours post-injury further increased cerebral levels of IL-6 and macrophage inflammatory protein-1α (MIP-1 α). In contrast, there was no effect from the simulated flight

(24 hours post-injury). Pritts[113,141] summarized research on the timing of neuroinflammation in a murine TBI model (see Goodman). Pritts noted that an additional finding was that as little as 30 minutes of hypobaric hypoxia alone was associated with worse outcomes This study recommended that to avoid the early exposure to hypobaric hypoxia, transport should be delayed until after the period of initial neuroinflammation. No studies were reported on the effects of supplemental oxygen mitigating these adverse effects. These results are similar to Goodman's[142] research, where hypobaric hypoxia exacerbates neuroinflammation. However, these findings contrast with the results of murine model of hemorrhagic shock, where simulated AE did not affect systemic inflammation or organ injury -lungs, ileum, colon,[143] demonstrating the limitations of generalizations regarding time to transport. A study on the effects of time to transport for patients with TBI or compartment syndrome on patient outcomes is ongoing.[144].

4.4.1.3 Patient Outcomes – TBI. There is limited research on outcomes in patients with TBI directly associated with AE. Mac Donald[145-147] evaluated four cohorts of patients, with outcomes evaluated a median of 7-14 days post-injury. Three cohorts were evacuated to LRMC along with a control group (TBI – no AE). The patients underwent additional neurobehavioral and neuropsychological testing at 6-12 months post-injury. There were no differences based on AE; however, the study does not provide any AE specific data. Barnard developed models to predict prolonged mechanical ventilation in patients transported by CCATT, but there were no data specific to diagnostic categories.[148] Larres[149] reported on the natural recovery of patients with mTBI who were not evacuated from the AOR. The results demonstrated a pattern similar to a sports concussion and provide control data for comparison against subjects who required evacuation. Additionally, these results could be integrated with MacDonald's research [145,147] to capture the acute post-injury phase.

Bell [150] studied outcomes for 408 patients with severe TBI and spinal injury admitted to NNMC/WRAMC from 2003-2008. The study provided data differentiated by type of injury (penetrating vs. CHI) including field and admission GCS, presence of ventriculostomy/ICP monitor on arrival, concomitant spinal cord injury and time to arrival (7.4 ± 9 days). Outcomes included short and long-term neurological status (GCS/GOS) and complications. Of note, the discussion conjectures that the increased incidence of PE and performance of craniectomy may be associated with the long-distance transport; however, no data were provided regarding pre-transport treatment decisions nor en route care. The period of the study was before systematic implementation of the JTS CPG for severe TBI; thus, a pre-post evaluation of care and outcomes associated with implementation of the guidelines and adherence with the guidelines during the en route phase of care controlling for time from injury to transport may be warranted. The study did not capture any descriptions of en route secondary injuries to explore the relationship with outcomes.

4.4.2 Adherence to TBI Guidelines and Outcomes. An area for exploration is the adherence with the JTS Guidelines for mild and severe TBI.[151-155] No studies were found that analyzed adherence with the TBI guidelines (for mild or severe TBI) during en route care, nor the association between en route care and acute or long-term outcomes.

Civilian studies have explored adherence with the 2007 Brain Trauma Foundation (BTF) guidelines[153,156] for severe TBI. Lee found that a decreased odds of mortality with > 55% adherence to the guidelines. In a study by Piper,[157] which is part of a larger study[158] assessing the military-civilian translation of battlefield innovations into surgical trauma care, a survey was completed by trauma directors from approximately 40% of trauma centers across the US. Results indicated that 83.3% of the trauma centers reported having severe TBI guidelines in place, but the guidelines are used in less than 75% of cases. Of note, there was an increased use of depressive craniectomies after publication of the military experience with this procedure. This study is limited by use of survey data and a limited number of general questions and the lack of information on patient outcomes. A recent study[153,159] from US and Indian civilian trauma centers used retrospective and prospective methods to explore the association between early (first 72-hours) ICU adherence to the BTF guidelines for severe TBI and hospital mortality. The study identified 17 indicators

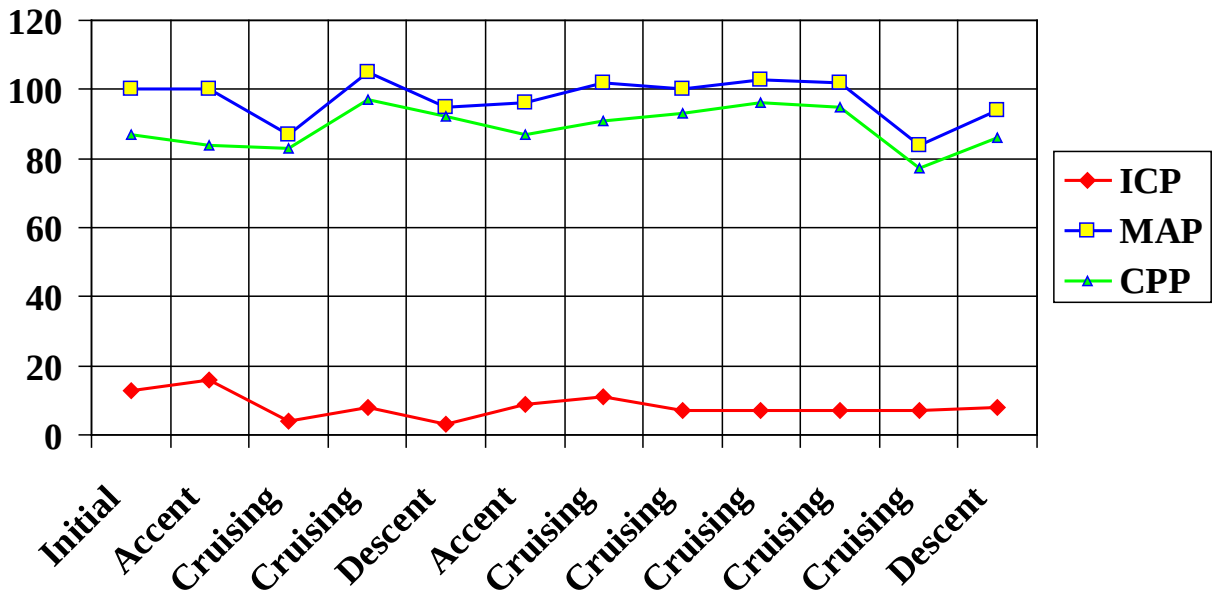
of ICU management. At the Indian facility, an increase in guideline adherence rate by1% was associated with a 3% decrease in in-patient mortality (aRR = 0.97, 95% CI 0.95-0.99). A less than 65% adherence was associated with a 2-fold increase in mortality. There was no association between guideline adherence and outcomes at the US hospital (Level 1 trauma center). This study provides specific indicators of adherence and provides baseline data for analysis of care under resource restricted conditions, which may be relevant to the austere conditions on the battlefield and during en route care. A recent systematic review, which is part of the Living Systematic Review program conducted by the European Center-TBI (https://www.center-tbi.eu) examined adherence to three different TBI guidelines using 13 indicators. In general, there was a large amount of variability in adherence with different components of the guidelines, but overall there was a trend towards lower mortality with increased adherence (OR 0.15 to 0.96). However, no military relevant studies were included. An ongoing meta-analysis[160] is exploring the association between guideline adherence and outcomes; however, all military-related TBI studies are being excluded. These studies demonstrate a possible relationship between guideline adherence and outcomes; however, no studies have been conducted in any phase of the military care continuum. The need to focus on outcomes is supported by recent research that found no association between adherence and risk adjusted outcomes; supporting the need to not solely focus on adherence, but also include functional outcomes.[161,162]

There is also no research on prognostic models to evaluate observed versus expected outcomes for the military population. McHugh[163] developed a model for the relationship between secondary insults (hypoxia, hypotension, and hypothermia) and 6-month outcomes for patients with TBI as part of the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT). A recent civilian study[151] used data from IMPACT to evaluate the effect of implementation of evidence-based guidelines for patients with severe TBI. These models may inform future research, but validation of the IMPACT[164] prognostic model, to include en route care, would be needed.

4.4.3 En Route Care for Casualties with TBI. Two studies have been presented that specifically address en route care for casualties with TBI. Boyd [137,138] presented a study at MHSRS (2014), which summarized the short-term outcomes of 121 patients (192 patients moves) with severe TBI who were managed by CCATT (Jun 2007-Aug 2010). The study is important in that it reports en route adverse events (ICP > 20 mm Hg n = 10; CPP outside 60-80 mm Hg n = 16; hemodynamically unstable n =45; hypoxia – SaO2 < 93% n = 11; seizures n = 4/seizure prophylaxis n = 92). Of interest, only 34 patient moves (18%) had a cabin altitude restriction. The study also reports that 50 patients received blood products, but it is not clear if these products were administered during flight. Complications inflight occurred during 21 patient moves (no information at patient level or route when adverse event occurred – AOR-LRMC/LRMC-CONUS). Of note, it will be important to delineate events as adverse events consistent with the disease/injury (e.g., central diabetes insipidus with sodium > 170 mEq/L or temperature 105°F) versus potentially preventable occurrences (hypoxia with FiO2 80-100% n = 4 patient moves). A limitation of the study is the lack of analysis of the relationships between events and long-term outcomes. Also, no data are presented regarding time to transport.

4.4.4 Effect of Transport on ICP. A series of case and observational studies explored changes in ICP associated with transport. A case report[165] of a patient with fresh water near drowning, pneumothorax, and fractured femur demonstrates the effect on the ICP with the patient flown with feet forward on the tactical mission and head forward on the strategic mission. The patient was ventilated with a ventriculostomy and chest tube. In both cases the ICP increased slightly with ascent to altitude, but did not increase > 20 mm Hg, but stabilized during flight.

Phase of Flight	SBP	MAP	ICP	CPP	$ETCO_2$	FiO_2	SaO_2
Initial	157	100	13	87	N/A	50%	100%
Ascent	162	100	11 (16*)	84	N/A	50%	100%
Cruising	161	87	4	83	N/A	50%	100%
Cruising	174	105	8	97	N/A	50%	99%
Descent	146	95	3	92	N/A	50%	99%
Ascent	136	96	9	87	36	50%	98%
Cruising	157	102	11	91	35	50%	100%
Cruising	160	100	7	93	34	50%	100%
Cruising	165	103	7	96	36	50%	99%
Cruising	167	102	7	95	34	40%	99%
Cruising	163	84	7	77	35	40%	99%
Descent	150	94	8	86	34	40%	99%



Limitations of this study were the intermittent collection of the vital signs data and inability to measure gravitational forces, particularly during take-off/ascent/descent/landing phases of transport.

A published paper, report and two abstracts summarized continuous monitoring of ICP during transport using an innovative monitor that provides ICP, MAP and motion (three-axis accelerometer) every 5 seconds.[139,140,166 167] This observational study reported on in-hospital and in-theater (en route) fluctuations in ICP in 11 critically injured combat casualties. The study found increased variability in ICP during the in-hospital phase (moving patient on/off CT scanner) in contrast to the AE phase of transport (Figure 8).

In the preliminary analysis of the first six cases, the ICP increased during take-off or at some point in the flight, with the increases described relative to baseline. For example, an increase > 50% of baseline and sustained for > 1 hour. There were no patients with an ICP >20 mm Hg. This characterization of the changes in the ICP and absolute values provides important insight into the potential stresses of flight. Further analysis of the effects of surgical procedures (hemicraniectomy, craniotomy) and type of TBI (e.g., blunt, penetrating) and outcomes associated with increase variability and time above ICP of 20 mm Hg or a CPP < 60 mm Hg is needed. The studies presented the motion data graphically, but did not summarize these data numerically, which would be useful for future model development. Additional information that could be extracted from this study would be to quantify the gravitational forces during take-off and landing, and calculation of the CPP. This small study was limited by the inability to use identifiable data, thus there was an inability to collect any demographics or the interventions used to control the ICP or MAP. Additionally, there were no linkages to short or long-term outcomes.

These two studies are important as they systematically report on continuous physiologic state during en route care and demonstrate the relatively small number of adverse events or complications recorded during flight. The major gap identified by both studies is to explore the relationship between en route events and outcomes.

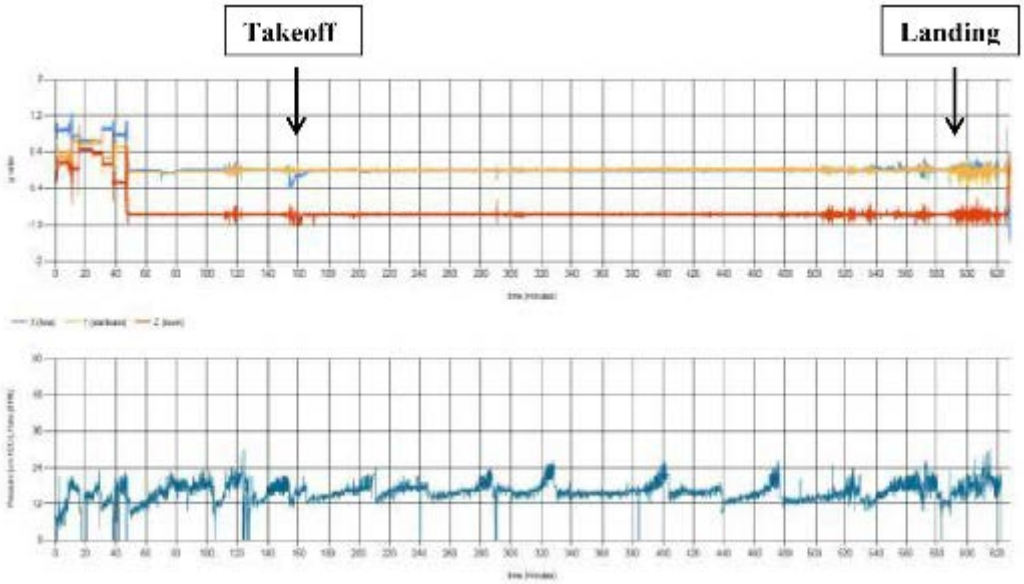


Figure 8. Example of aircraft movement and ICP variability.

4.4.5 Civilian Transport Studies – TBI. Studies conducted in the civilian setting focus on short distance pre-hospital transport and provide background for comparison. For example, Davis' study[115] on civilian pre-hospital transport of patients with moderate to severe head injury may serve as a useful comparison to Fang's study[168] of early in-theater management and the description of the patients physiologic state upon admission.

4.4.6 Preflight Identification for Occult TBI/En Route Risk. Several papers have discussed factors to consider in the pre-flight assessment to identify patients at risk for neurologic deterioration, particularly in patients with a potentially occult TBI (i.e., not identified by ICD). A case report by Helling[169] of a casualty with a frontal sinus injury with a pneumocephalus outlines potential clinical practice recommendations (e.g., CAR, position-supine versus upright, insertion of an angiocath to equilibrate pressure). *These recommendations require further evaluation and potential integration into a pre-flight clinical practice guideline*. An analysis[170] of 201 casualties with blast injuries found a significant

association (RR 2.76, 95% CI 1.91-3.97) between blast-induced tympanic membrane rupture and loss of consciousness. Of note, the association remained independent of the use of hearing protection. **No studies have been conducted to evaluate the prevalence of tympanic membrane rupture in AE patients, with a focus on concurrent neurologic injury or communication of potential risk. The** identification of occult neurologic injury is of concern given Johannigman's[171] findings related to en route hypoxemia in the walking wounded.

Three studies reported on the incidence of TBI and accompanying symptoms in samples of patients at Walter Reed[172], US – three months post injury[127] and during the immediate post-injury period in-theater.[173] One study reported outcomes for a subset of patients with TBI[174] and one study reported on characteristics of individuals with suspected brain injuries who were more likely to be evacuated. These studies provide insight into the population at risk. A limitation of these studies is a lack of en route care data. There is a need to integrate the results of these studies on pre-flight characteristics into a risk-assessment tool.

4.4.7 Mild TBI – Altitude Exposure. One gap identified in the DCoE review[114] was the need to document the effects of altitude exposure on mild TBI (mTBI) and blast-induced neurotrauma. In an observational study of patients with mild TBI (blast/non-blast) who were evacuated via AE and a control group (no AE) there was no significant difference associated with AE on short (30-90 days) and long-term (6-12 months) neurobehavioral symptoms or neuropsychological performance independent of the cause of the TBI.[145] This study provides important information on control groups (mild TBI – no evacuation and combat trauma without TBI) for comparison and addresses a gap regarding the relationship between the type of TBI and AE (hypobaria/hypoxia). A limitation of was the lack of information on time from injury to AE, or any en route management. **All patients had sequelae, which suggests the need for studies to evaluate strategies to mitigate deterioration (e.g., avoidance of hypobaria induced-hypoxia) and further analysis of time to transport.**

4.4.8 Stresses of Flight – TBI. In 2014, the 59th MDW published a review[175] of the effects of flight on patients with TBI, which was divided into a summary of literature on oxygen partial pressure or barometric pressure, thermal changes, fatigue, noise or vibration, humidity, G-Forces. The review cited eleven papers, with only two papers with a direct application to en route care.[176,177] No research gaps were noted in this review.

4.4.8.1 TBI - Hypobaria/Hypobaria + Hypoxemia. Preclinical (animal) studies have been used to explore the effects of the stresses of flight on neurological outcomes in animal models of TBI.[178] The primary research focus has been on hypobaric hypoxia. Skovira[179] studied the effects of a primary six hour simulated AE flight (hypobaria [568 mm Hg = 8000 feet] with variations in O_2) in a rat mTBI model. AE exposure was at 6, 24, 72 hours or 7 days after TBI. A second group of rats were exposed to six hours of hypobaria at 24 hours after injury and for 10 hours at 72 hours after injury (note: this exposure would simulate evacuation from the AOR to LRMC and from LRMC to CONUS). Results indicated that hypobaric exposure up to 7 days significantly worsened cognitive deficit, hippocampal neuronal loss, and microglial/astrocyte activation compared to controls. Hyperoxia (100% O2 compared to 28%) and repeated hypobaria exposures exacerbated memory deficit. In a swine model of TBI[180-182] exposure to a four-hour simulated AE (hypobaria 8000 feet with supplemental O2) or ground transport (normobaria) was initiated at 120 minutes post-injury. The animals exposed to hypobaria had a lower $PbtO_2$, cerebral perfusion pressure and mean arterial pressure during transport compared to the control group, although no information was provided on the adjustments of the FiO2 to maintain equivalence to normobaric conditions. A study[183] is ongoing to evaluate the effects of hypobaria and vibration associated with AE on neurotrauma and lung injury in a rat blast model. A recent study by Skovira[184] confirmed increased neuroinflammation (cell cycle activation) in a TBI model with hypobaria (8000 feet; 568 mm Hg for 5.5 hours) at 6 hours post-injury. The animals received 28% O2 to maintain a sea level SpO2. The

TBI increased neuroinflammation (cell cycle activation), which was further exacerbated with the hypobaria exposure. The administration of a cell cycle inhibitor (cyclin-dependent kinase inhibitor -CR8) at 3-hours post-injury significantly decreased the markers of cell cycle activation, improved spatial and retention memory and decreased lesion volume and neuronal cell loss. Further study of cell cycle inhibitors to mitigate the effects of hypobaria on neurological status is warranted.

A recent study[185] in a rat model of penetrating ballistic like brain injury (PBBI) evaluated the isolated and combined effects of hypotension (MAP 40 mm Hg) and hypoxemia (PaO2 < 40 -45 mm Hg) on histology and motor and cognitive performance. The acute response to combined hypotension and hypoxemia with PBBI was bradycardia that responded to volume resuscitation. The combined insult was also associated with worse cognitive impairments. **The implications for transporting a patient with pre-transport secondary insults has not been described**.

In Boyd's[138] retrospective review there were only four cases where there was documented hypoxia necessitating increased FiO_2 (80-100%); however, this study does not provide any additional information on en route supplemental oxygenation administration. One important aspect is to differentiate between isolated hypoxia and hypobaria and hypobaric hypoxia. Research by Ribon[186] found higher levels of oxidative stress and antioxidant enzyme activities in healthy subjects exposed to hypobaric hypoxia for 10 hours in contrast to normobaric hypoxia.

In a penetrating brain injury model,[187] animals were exposed to 4000 feet altitude for 72 hours before the injury. The injury in the high-altitude group was more severe compared to the normal altitude group. This study is novel in the use of a penetrating head injury. **A gap is whether transport of patients whose injury occurred at high altitude has different outcomes compared to those whose injury occurred at lower altitudes. Evaluation of the penetrating injury model in a manner similar to the blunt blast trauma models may be appropriate.**

4.4.8.2 TBI – Hyperoxia. A limitation of Skovira's [179] study is the assertion that TBI patients are managed with 70-100% O_2 during transport. No analysis of CCATT or AE data has been conducted to confirm this assertion. However, as demonstrated in Ahn's[188] study in a rat TBI model, hyperoxia may have negative effects. There was decreased oxidative damage to proteins compared to animals who received 100% during resuscitation, which is consistent with Brenner's[189] findings in civilian patients with TBI. A rat polytrauma model was used to study survival and neurological outcomes in a rat model of TBI plus hemorrhagic shock.[190,191] studied hyperoxic versus normoxic resuscitation in a rat polytrauma model of TBI plus hemorrhagic shock and found decreased mortality in the hyperoxic group, but worse neurological outcomes at 14 and 21 days.[192,193] As described by Davis,[194] further analysis of the incidence of hypoxia and hyperoxia during en route care is needed, as well as controlling for exposure in the pre-transport phase.

The most recent study in this series used a rat model with the animals exposed to an underbody blast followed simulated 6-hour transport. Simulated flights occurred at 6 hours, 24 hours, 72 hours or 6 days and in one group at 24 hours and 6 days. The rats were exposed to normobaria (80 feet) or hypobaria (8000 feet) with room air or 100% oxygen. All animals that were exposed to the blast had axonal injury at 7 days. In the groups exposed to hypobaria, there was increased cerebral axonal injury. Further in the group that had two flights there was further increase in axonal injury, that was greater than at either time point alone. Additionally, animals exposed to hypobaria and 100% oxygen had a further increase in axonal damage and impairment in motor function compared to the hypobaric hypoxia (~16%) group. Fine motor function was also impaired in the hypobaria/hypoxic group. This study demonstrates the negative effects associated with hypobaria (8000 ft) over a prolonged period, a second hit effect from repeat evacuations (24 hours/6 days), and the effects of exposure to 100% O2. Results in the civilian literature related to hyperoxia in TBI are equivocal, with a need to clearly define hyperoxia.[195] Further exploration

of the administration of titrated levels of supplemental oxygen compared to hyperoxia during the en route phase of care is required in models consistent with polytrauma, including hemorrhage and TBI.[195-197] Exploration of brain tissue oxygen levels during en route care and correlation with these systemic measurements (i.e., SpO2, PaO2, PaO2/FiO2) and outcomes is also warranted.[198,199] Identification of patients who had both hypoxia and hyperoxia (ideal range 110- 487 mm Hg) [194]is needed. Data from the CCATT pilot unit database could be queried to explore the en route oxygen management of these patients (controlling for FiO2 vs SpO2). Another area for research is the effect of cabin altitude restriction[59] and the combined effects of cabin altitude restrictions with titrated supplemental O_2.

Gaps

- ***Update analysis of TBI using definitions consistent with updated 2015 ICD definitions (concussion/mild TBI, moderate TBI and penetrating TBI or open head injury)***
- ***Effect of en route care on cerebral oxygenation (see Scultetus[180])***
- ***Effects of supplemental oxygen consistent with clinical use vs experimental protocol (100%) – analysis controlling for FiO2 and SpO2 (see Skovira[179])***
- ***Models demonstrate blast effect – need model of complex injury (e.g., type of TBI with/without polytrauma) - see Donovan[116] for description of patients***
- ***Standardization of models (type of injury), timing and duration of hypobaria/hypoxia exposure***
- ***Integrate results from ground based research – see Track-TBI study for long-term outcomes (http://www.brainandspinalinjury.org/research.php?id=189***
- ***Adherence to TBI guidelines during en route phase of care and association with acute and long-term outcomes (use civilian examples[153,161,162] for examples from civilian setting)***
- ***Integrate implementation dates of TBI CPGs and Directive Type Memorandum (mTBI – DTM 09-033, Jun 2010) on outcome evaluation (consider effect on in-theater en route care)***
- ***Development of a Living Systematic Review[154,200] process – see example (https://www.center-tbi.eu/)***
- ***Validation of a prognostic model (similar to IMPACT) that includes military relevant characteristics, including en route care[163,201]***
- ***Integrate data sets (TRAC2ES, DVBIC, etc.) to clearly define population for various operations and epochs of time (evaluate changes in practice on outcomes)***
- ***Integrate common data elements for TBI into database[202]***
- ***Specific criteria to identify complications proximally attributed to en route phase of care, including identification of en route care quality indicators***
- ***Pre-flight risk assessment tool (particularly for patients with mild TBI)***
- ***Standardize terminology/assessment methods for mTBI research[203]***
- ***Identify timing of first and second AE flights (See Proctor, Scultetus, Skovira)[179,180,190]***
- ***Based on Johannigman[171] study, evaluate effect of hypobaria/hypoxia on outcomes mTBI***
- ***Cabin altitude restriction (see Butler[59] CAR study – evaluate subset with TBI)***

Gaps previously identified in the DCoE review[114,204]

- ***Identify risks, benefits, intervention strategies and outcomes associated with military AE transport of TBI patients (identify ideal time to fly) and develop risk profiles and injury protocols to address the timing and use of interventions. (*****initial research has been conducted to address this gap)***
- ***Document the effects of altitude exposure on mild TBI (mTBI) and blast-induced neurotrauma.*** **(initial research has been conducted to address this gap)**

- ***Determine what, if any health risk or performance effects might occur among post-TBI/post-concussion military personnel who return to high altitudes (not in scope of this review).***
- ***Investigate the efficacy of pharmacotherapeutic interventions for the prevention of altitude-related and secondary brain injuries***

4.4.9 Pneumocephalus (see additional section - entrapped air). Boyd[137] conducted a retrospective study (unpublished) of 121 patients (192 patient moves) with severe TBI who underwent CCATT transport. Among these patients, there were 26 moves (13%) where pneumocephaly was documented.

Twenty-four papers were reviewed relative to pneumocephalus. Among these papers, only two were related to pneumocephalus and hypobaria,[116,205] and Donovan's study was the only published research specifically addressing pneumocephalus under military conditions. Three additional papers discussed TBI as it relates to en route care. The papers by Goodman, Fang and Reno were reviews, and none of these papers discuss pneumocephalus.[104,109,110,206]. The remaining papers present individual cases in civilian transport.[207,208] Two additional papers, which summarized recommendations from airlines and civilian physicians for air travel demonstrated a lack of agreement on recommendations for civilian air transport as it relates to the risk for pneumocephalus.[209,210] This latter research raises a similar question regarding standard recommendations for military air transport under non-acute conditions (e.g., transport to a medical facility closer to home following initial treatment).

Andersson's [205] mathematical model explored the relationship between ICP, entrapped air volume, and rate of ascent to altitude. This model demonstrated a 30% increase in air volume with ascent to 8000 feet, and an interaction between baseline (pre-flight) intracranial pressure, air volume of the pneumocephalus and rate of ascent to altitude (8000 feet) on changes in the ICP. For example, the expansion of a 30 ml pneumocephalus would be associated with a 12 mm Hg increase in ICP at an ascent of 500 feet/minute, and a 19 mm Hg increase in ICP with a 1000 feet/minute ascent. However, the clinical effects predicted by Andersson's model were not observed in 21 patients with injury, infection, or neoplasm of the brain (19 post-craniotomy; 19 trauma related injury) and a pneumocephalus (preflight volume 0.6 – 42.7 ml, mean 9.3 ml, median 4.2) evacuated (cabin altitude 5000-8000 feet).[116] This retrospective study found no documentation of temporary or permanent neurologic decline during transport. In the three patients with ICP monitoring, there was no documentation of sustained pressure elevations during flight. This study is limited by its retrospective nature, reliance on clinical records versus systematic data collection, and the lack of post-flight CT scans. Other data that were not available included time to transport (from injury or surgery), whether any flights had an altitude restriction and en route patient positioning. The incidence of pneumocephalus in Donovan's study was 33% (21/63 patients), which suggests a potential need to include pneumocephalus in models exploring the relationship between altitude and cerebral dynamics and oxygenation. Willson's case report[208] of a patient with a 0.51 cm^3 pneumocephalus provided a review of gas laws and mechanism of a pneumothorax, and applied the gas volume estimates from Andersson. This latter case, demonstrated the safety of air transport within 24 hours of an acute event for a patient who was stable with a small (repaired) pneumocephalus, and suggests the need to quantify a threshold pneumocephalus volume and clinical condition to inform recommendations for air transport in non-urgent patients.

Three studies evaluated the effect of normobaric hyperoxia on resorption of a pneumocephalus.[211-213] This research may have implications for pre-flight care of a patient with a pneumocephalus or the inclusion of an additional variable (FiO_2) when analyzing the effect of en route care on patients with TBI. Dexter's study applied a mathematical model that includes barometric pressure[214] to evaluate the effect of FiO2 0.21, 0.4 and 1.0 on resorption of a 50 ml air bubble. According to the model, treatment with FiO2 0.4 and 1.0 for 24 hours caused 16% or 44% of the air to be reabsorbed, respectively. After two days 30% or 72% of the air was reabsorbed. The air absorption is greatest early in the treatment. These effects were independent of the initial volume. Increasing the FiO2 from 0.21 to 0.4 caused the time to decrease the air

volume from 50 ml to 1 ml by 67%. In contrast, an increase in FiO2 from 0.8 to 1.0 was only associated with an additional 3%. In Gore's study patients were treated with normobaric hyperoxia (68%) via a non-rebreather mask over 24 hours versus room air (21%). In the hyperoxia group the mean air volume reduction was 65% (mean air volume change 35 ml, mean air absorption rate1.26 ml/h) compared to 31% in the control group. In a study by Hong, patients after posterior fossa surgery were treated in the immediate post-operative period with 3 hours of 100% oxygen via endotracheal tube versus room air. In the hyperoxia group the mean air volume change was 87 ± 3 ml, with air resorption rate of3.6 ± 0.13 ml/h compared to 71.3 ± 3.3, air resorption 2.9 ± 0.13 ml/h, p = .0015. The hyperoxia group were more alert as measured by the Stanford Sleepiness Scale, but there was no difference in Stroop test. Possible research questions include effect of hyperoxia on inflammatory response in TBI, reanalysis of pre-flight and inflight data to include oxygen therapy (potential effect on volume of pneumocephalus). The study by Hong also identified two instruments that may be useful in characterizing neurologic status during the acute post-operative period.

Gaps

- ***Effect of rate of ascent/descent on ICP and cerebral oxygenation***
- ***Validation of Andersson's calculations in animal model (effect of physiologic compensation response to maintain ICP) – establish guidelines/threshold/clinical condition associated with risk for tension pneumocephalus en route***
- ***Preflight/inflight therapy – administration of supplemental oxygen on pneumocephalus resorption (is there a beneficial effect with lower FiO2 versus 100%)***
- ***Incidence of altitude associated complications due to pneumocephalus during recovery phase and long term– association with injury type (e.g., presence of fistula, history of CSF leak post-repair). (see civilian articles)***
- ***Is cabin altitude restriction applied IAW recommendations Flight Surgeon's checklist?***
- ***Variations in response based on type of head injury (e.g., closed head injury, GSW, post-craniotomy)***

4.5 Spinal Cord Injury

There have been several epidemiologic studies conducted to characterize the incidence of spine injury and spinal cord trauma. A literature review summarizing these studies indicates a 5-10% incidence of spinal cord injuries in combat casualties.[215] Between 2005 and 2009, there were 7877 combat casualties, with 872 (11.1%) suffering a spine injury, with a rate of combat spinal injuries of 4.4/10,000.[216] In an analysis of the JTTR (2001-2009)[217] among the 10,979 patients evacuated, 598 individuals sustained 2101 had spine injuries (5.4%), and among these individuals, 104 had a spinal cord injury. The distribution of injuries was the lumbar region (41%), thoracic spine 28%), cervical spine (15%) and sacrum (11%). Among those patients with spinal cord injuries, 45% had a complete injury, but the level of the injury was not specified. Among these casualties 78% had associated injuries (average 3.4 associated injuries per patient), with the most common being non-spine musculoskeletal injuries, followed by chest, abdomen and TBI.[218] In a subset of 372 Canadian forces casualties admitted to Kandahar (2006-2009), 8% had spinal fractures identified.[219] Among these casualties, three individuals had spine injuries characterized as unstable. In a study of 275 combat casualties admitted in 2008, 6.9% sustained an orthopedic injury during an IED attack against their vehicle.[220] Among these 19 patients, 12 casualties suffered 16 thoracolumbar fractures; 3 patients with multiple fractures. Among 226 combat casualties who suffered a major lower extremity amputation, 13% had concurrent spine fractures.[221] There were 82 separate spine injuries, with a 75% of the injuries in the lumbar region. Injuries to the thoracic spine occurred in 18% of cases, and 6% of injuries involved the cervical spine. Nearly half of these individuals suffered bilateral

lower extremity amputations. Among individuals killed in action, there were more cervical spine injuries in contrast to survivors who suffered more injuries to caudal spine segments.[222] In an analysis of

The results of these studies identify a potential population of casualties who may require en route spinal immobilization thoracolumbar. Most of the spinal injuries involve the lumbar region, but there was insufficient information provided to determine how many casualties suffered an unstable (3 column instability) requiring transport using a vacuum spine board (VSB). Except for one study describing injuries during the pre-hospital period, none of the studies included information on time to transport or any en route specific variables that might be associated with outcomes for these patients.

Gaps:

- ***En route management/care of patients with spinal injury (with/without VSB requirement)***
- ***En route stresses of flight (hypoxemia, altered glycemic control) – factors potentially associated with long term outcomes***
- ***Number of patients evacuated with spinal precautions (adjudication of actual requirement)***
- ***Standardization of statistical methods to calculate rates[223]***
- ***Compliance rate for CPG during transport in patients with spinal injury (from AFMS gap analysis)***
- ***CCATT outcomes of movement of casualties with thoracic and/or lumbar spinal fractures utilizing the Vacuum Spine Board***
- ***CCATT outcomes of movement of casualties with thoracic and/or lumbar spinal fractures between (What AOR/what timeframe)***

4.5.1 Stresses of Flight – Spinal Cord Injuries. There are limited studies on the effects of the stresses of flight on spinal cord injuries.

4.5.2 Vibration. Studies have been conducted to evaluate the effect of vibration associated with ground based transport and MEDEVAC on animal model of SCI. These studies may be useful in controlling for effect of pre-AE transport and timing of transport on outcomes. A large animal model study[224,225] evaluated the effect of simulated vibration consistent with an MH60 helicopter on functional outcomes, timing of inflammatory marker release post-injury with/without vibration and spinal cord histology. There were no significant differences in any outcomes between the groups of animals. Important results were the patterns of the release of inflammatory mediators at 2.5, 3.5, and 5 hours' post-injury for IL-6, IL-8, MCP-1 and GFAP, which may inform decisions on time to transport during the immediate post-injury period. Similarly, a study using conditions similar to ground transport[226] (MRAP) and helicopter did not significantly impair functional outcomes in a swine model, but there was increased tissue damage around the injury site. These studies need to be replicated for ground transport to the aircraft (e.g., K-loader or AMBUS) and for fixed wing aircraft used for AE.

Gaps

- ***Effect of vibration studied in ground vehicles and MEDEVAC helicopters – no studies conducted on fixed wing aircraft or ground transport vehicles used to transport patients to aircraft (K-loader, ambus)***
- ***Effect of en route hypoxemia on neurologic outcomes***

4.5.3 Vacuum Spine Board. The JTS CPG: Cervical and Thoracolumbar Spine Injury Evaluation, Transport, and Surgery in the Deployed Setting specifies that patients with an unstable (3 column instability) thoracolumbar fracture "should be transported by CCATT using the vacuum spine board or a

standard litter with or without memory foam pad, depending on the type of fracture."[227] Two studies have been conducted evaluating use of the VSB for transporting combat casualties. An evaluation of the VSB, with regard to skin interface pressure on ground and during ascent/descent was conducted in 2009.[228] The skin interface pressure on the VSB was comparable to skin interface pressure on the NATO litter with the AE mattress and significantly lower than interface pressures on the standard spine board. Based on Kosiak's work[229,230] patients could be safely transported on the VSB for up to 6 hours as long as additional preventive measures are taken to protect the occiput and heels. There was no significant effect on skin interface pressure with ascent/descent. During ascent, the vacuum decreased (internal mat pressure increased) approximately 77% -81% (e.g. from -353 mm Hg to – 105 mm Hg). With ascent, the negative pressure vacuum was reestablished (285% increase in vacuum) as the internal pressure decreased (-98 mm Hg to -280 mm Hg). The VSB was noted to be more flexible at altitude due to the loss of vacuum, but the straps maintained the configuration of the VSB. An abstract presented in 2011 studied inflight and short-term outcomes of 73 severely injured combat casualties with spine injuries (103 moves), who were transported between Jun 2009 and 2010 by CCATT using a VSB.[231] Among these patients there were 10 cases of pressure ulcers (9.3%) reported as associated with the VSB, and two patients suffered neurological deterioration attributed to progression of the original injury. Ten patients received vasoactive medications (9.4%) and 13 received blood products (12.2%). Other adverse events included transient desaturation (2.8%) and transient hypotension (12.8%). A limitation of this study is that it does not provide the time sequence of events to create an associative model (e.g., when were vasoactive medications administered, timing of development of pressure ulcer). A study[232] compared outcomes in 30 patients transported on the VSB versus a historical control consisting of 30 patients with an unstable spinal injury. There were no cases of progressive neurological deficit or deformity in either cohort. In the VSB group, using a broad definition of pressure ulcer, incidence was 13 of 60 patients (22%). Using a strict definition, incidence was eight of 60 (13%): Stage 1 (n= 5), Stage 2 (n = 3). In the non-VSB group, incidence of pressure ulcers was 3/30 (10%), using either definition, all Stage II. Difference in incidence between the groups was not statistically significant. Intubated patients had a significantly higher incidence of pressure ulcers. Among all CCATT patients transported between 2008 and 2012, there were 164 patients with pressure ulcers (5% incidence).[233] The average physiologic values of CCATT patients who developed a pressure ulcer present as a normotensive patient with an HR in the upper range of normal and an MAP and ICP within normal limits. The duration of immobility ranged from 1.5 hours to 3.25 hours longer than the en route time. The number of days from injury to arrival at LRMC ranged from 1-2, while the number of days from injury to arrival within CONUS ranged from 3-9 days. Eight percent of the patients were transported in a VSB; however, there was no control group for comparison to determine if the VSB was an independent risk factor.

Gaps

- ***Case-control study to identify risk factors for pressure ulcer development (extension of Thomas study to include cases), with control for factors known to be associated with increased risk of pressure ulcers (e.g., vasoactive medication)***
- ***Mitigating strategies (pressure, shear) used in conjunction with VSB or other spinal immobilization devices***
- ***Adherence to standard pressure ulcer strategies (lateral rotation – offloading)***

4.6 Pulmonary

4.6.1 Hypoxemia and Altitude -Civilian. There are a number of studies describing the effect of flying (altitude) on oxygen saturation in both healthy civilians[234-236] and individuals with cardiopulmonary disease.[237,238] In national level athletes, the SaO_2 decreased 3-4 (98% to 94%), but there was no change in heart rate after 3 and 7 hours flight at an average of 5700 feet.[235] Based on a mathematical model[239] in healthy individuals (age 26-36) the following are estimates of PaO_2 at altitude: Sea level (96-100 mm

Hg), 5000 feet (77 ± 8.4 mm Hg), 6000 feet (70 ± 6 mm Hg), 8000 feet (62 ± 1.6 mm Hg), 10,000 feet (58 ± 8 mm Hg). The model further predicts that among healthy 25-35-year old individuals at 8000 feet less than 8% should have a PaO_2 < 50 mm Hg (SaO_2 ~85%).

In patients with pulmonary disease, there is greater desaturation with ascent to altitude. Using data from several small samples of patients with COPD (average age 65-70), the mathematical model derived by Muhm[239] predicts the following PaO_2 levels at altitude: Sea level (68-72 mm Hg); 5000 feet (51 ± 9 mm Hg), 6000 feet (57 ± 6 mm Hg), and 8000 feet (45 – 49 mm Hg). These results have been confirmed in numerous small civilian studies.[237-249] In the 65+ age range, at 8000 feet the model predicts at least 50% of healthy individuals will have a PaO2 < 50 mm Hg. No estimations were provided for individuals with cardiopulmonary disease.

4.6.2 Hypoxemia at Altitude – Military. There is limited research on the incidence of hypoxemia during the evacuation of combat casualties. Three papers summarize the injuries and the AE of casualties from the bombing of the USS Cole on 12 October 2000[250-252] The most common injuries were related to blast. Seven patients had a primary blast injury (perforated tympanic membranes; primary blast injury lungs -1), 12 patients with secondary blast injury (fragment wounds), 28 patients with tertiary (blunt force) blast injuries (orthopedics, closed head trauma, pneumothorax – 1, hemothorax – 1) and seven patients had quaternary injuries (toxic inhalation – 3; burns – 4). Twenty-six less seriously injured casualties were evacuated by AE, and 11 seriously/critically injured casualties (two ventilated) were evacuated from Djibouti (sea level – 760 mm Hg) to Germany by CCATT on a C-9A. For the CCATT mission, the mean cabin altitude was approximately 2400 m (7900 feet ~ 560 mm Hg). During the critical care evacuation, an unexpected finding was that all patients, except those already on mechanical ventilation were hypoxic upon ascent to altitude. All patients had an SpO_2 > 92% pre-flight at sea level, however at altitude with SpO2s in the low 80%s without reports of dyspnea and the patient with a pulmonary blast injury had an SpO2 of 50%. All patients were treated with supplemental oxygen (average 4 L/min) to achieve a SpO_2 > 92%. The need for increased supply of oxygen necessitated an additional non-refueling stop for LOX (aircraft – C9A):

Critically Injured Sailors (USS Cole)	
1	Gastric rupture, open fracture right tib/fib, pulmonary contusion, femur fracture, mechanical ventilation
2	Burns to the face/hands, pulmonary blast injury/edema, mechanical ventilation
3	Open compound fracture right femur
4	Compound fracture right femur, pulmonary blast injury/edema
5	Open fracture left femur, cranial trauma
6	Crush injury/fracture left ankle, sepsis
7	Left clavicular fracture, rib fractures
8	Left mandibular fracture
9	Internal right knee derangement
10	Concussion
11	Right ankle fracture

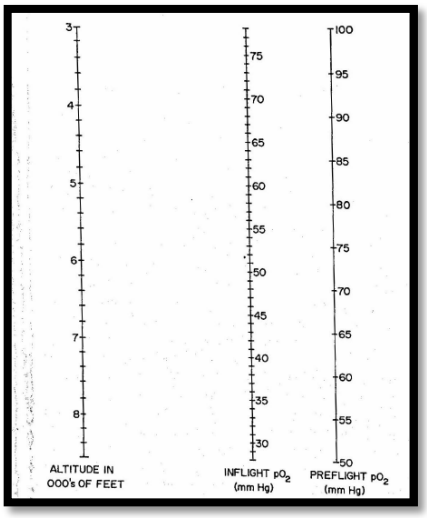
- Maximum 25 L of LOX; 1 L of LOX = 804 gaseous L oxygen; 25 L = 20,100L gaseous oxygen
- Requirements: 11 patients at 4 L/min x 13 hours = 34,320 L oxygen

Alkins posed several questions related to the lack of dyspnea in the patients evacuated from the USS Cole: narcotic effect (with consideration given to altitude-induced changes in pharmacokinetics) and fatigue. A limitation of the Alkins' paper was lack of information on the en route care provided to the patients. The results from the USS Cole are similar to recent results from Johannigman[171] In 61 non-critically injured patients there was an 85% incidence of occult hypoxemia, with 34% of the patients experiencing at least one desaturation to < 85%. The ten patients with a Hgb < 12 g/dl had a higher pulse rate (85 bpm) compared to patients (n = 48) with Hgb 12-15 g/dL (71 bpm), Of note, none of the patients had any documentation indicating dyspnea. **This study was limited by the inability to collect patient specific information or their en route condition or care.** These results are similar to a study[253] conducted in patients with BI/NBI and Disease who were evacuated from Viet Nam to Japan in 1969 on 12 AE missions (cabin altitude 3,000-7,500 feet). Preflight hemoglobin was > 12 g/dL for groups of 201 patients transported at low altitude (3,000-3,800 feet) and high altitude (6,700-7,500 feet). Arterial blood

gases were drawn pre-flight and inflight and none of the patients received supplemental O2. The time between injury and evacuation was approximately 6 days. In the high-altitude group, the PaO2 decreased from 79.9 mm Hg to 52.8 mm Hg (decrease 27.1 mm Hg). In the low-altitude group, the PaO2 decreased from 83.5 mm Hg to 66.6 mm Hg (decrease 15.9 mm Hg). Post-flight PaO2 was 78.5 mm Hg in the high-altitude group and 83.9 mm Hg in the low-altitude group. There was no significant effect from preflight medications (meperidine or phenothiazines). The estimated regression line was:

$$\mathbf{Y = (20.38) - (3.0)(X_1) + 0.67(X_2)}$$

Y = predicted inflight O_2 tension in mm Hg, X_1 - cabin altitude in thousands of feet, X_2 preflight oxygen tension in mm Hg. The Allcock and Jones nomogram[254] was used to predict inflight O2 tension (based on preflight O2 tension, and cabin altitude). Approximately 70% of the patients (both high and low altitude) were within 5 mm hg of predicted in-flight values (r = 0.83). Another finding was the change in PaCO2 (high altitude 34.1 mm Hg to 32.8 mm Hg/Ph 7.45-7.48; low altitude – no change in PaCO2 or pH (no data). These results are relevant to Johannigman's study. In this case the decrease in PaCO2 suggests an increased respiratory rate or tidal volume, and rules-out hypoventilation as the primary cause of the decrease in SpO2. Analysis of individual cases would be needed for a clearer exploration of factors associated with hypoxemia in these patients. Similar findings related to SpO2 at altitude were noted in a study of civilian airline pilots.[234] In these pilots, 53% developed an SpO2 < 90%, with altitudes above 7,500 feet associated with an SaO2 < 90%, although there was individual variability. Cottrells' study was important as it simultaneously captured the cabin altitude pressure and the SpO2.



These studies highlight the need for more sensitive risk profiles. **A case study involving patients with similar injury/transport characteristics who did/did not experience inflight complications may be warranted to inform the development of a preflight risk profile. For example, among the casualties on the USS Cole who suffered blast trauma, describe their location (above or below decks and distance from explosion), presence of secondary, tertiary and quaternary blast injuries, and preflight state (vital signs, SpO2, oxygen requirements), medications (including narcotics or sedatives). Johannigman's study similarly identifies the need for more sensitive indicators of sub-clinical pulmonary blast injury, and further analysis of potential effects of narcotic-induced respiratory depression** (no data provided in paper to support this assertion except for the lack of dyspnea) or fatigue/sleep deprivation. In the recent study by Blakeman,[255] healthy subjects were monitored during ascent to altitude with a respiratory monitor (Capnostream 20, Oridion Medical, Needham MA), which monitors pulse oximetry and heart rate via finger pulse oximetry and end-tidal CO2 ($P_{ET}CO2$) using a modified nasal cannula (Smart Capnoline, Oridion, Needham MA). **Future research should consider use of $P_{ET}CO_2$ or a similar indicator of ventilation to explore the relationship between narcotic/sleep-induced hypoventilation on hypoxemia during en route care (? effect of sitting in Evans seat).** An additional finding from Blakeman's study was the statistically but not clinically significant change in respiratory rate and heart rate from sea level (RR: 14.4 ± 3.1/HR 72.4 ± 9.2) to 14,000 feet (RR 13.8 ± 3.3/HR 78.7 ± 12.1), despite a decrease in SpO_2 (97 ± 1.5% to 84.3 ± 3.6%). In contrast, there were decreases in both the $P_{ET}CO2$ (39.9 ± 3.1 mm Hg to 36.0 ± 2.9 mm Hg – consistent with hyperventilation associated with a probable increase in tidal volume) and StO_2 (76.1 ± 6.1% to 72.5 ± 5.9%).

4.6.3 Hypobaric Hypoxia – Immune Response. Two civilian studies reported on altered immune response in the period post-flight.[256,257] Three studies with simulated altitude (8000 ft or 10000 feet) explored the effect of hypoxia on the circadian patterns of biochemical markers. [258-260] Hypoxia did not affect the circadian immune response (CD4, CD8 lymphocytes, plasma concentrations of IgA, IgG, or IgM).[259] Hypoxia was associated with a significant change in the circadian pattern of cortisol secretion with increased sympathetic tone and decreased parasympathetic tone as measured by heart rate variability[261] and commonly monitored electrolytes (e.g., sodium, glucose, creatinine, calcium).[258] **No studies were found on the effects of hypoxia on the circadian pattern of coagulation, although as discussed in the VTE section there is limited evidence that hypoxia directly affects coagulation activation. Changes in the circadian patterns in coagulation activation may have implications for ACS and VTE risk. Additionally, no studies have evaluated the interaction between transmeridian flights and hypobaric hypoxia (and other stresses of flight) in ill/injured patients on these biomarkers. Data from the Glue Grant: Inflammation and the Host Response to Injury (https://www.nigms.nih.gov/Research/specificareas/collaborative/gluegrants/outcome-assessment/Pages/gluegrant_history.aspx may provide useful baseline information to study the effects of flight inflammatory patterns.**

4.6.4 Oxygen Requirements. With regard to the oxygen requirements, a bench study found that pulsed-dose delivery of oxygen to the inlet of the ventilator can deliver an FiO2 of 0.76, with decreased O2 and electricity requirements compared to continuous flow.[262] This model was further evaluated in a swine model of acute lung injury.[263,264] The pulsed-dose method in volume control ventilation had a higher P/F ratio compared to continuous flow (169 ± 96 vs. 92 ± 65, p =.002); however, there was no difference in the pressure-control mode (89.0 ± 74.5 vs. 79.1 ± 65.4, p = 0.67). A recent study in 30 healthy subjects with ascent to 14,000 feet found that pulse-oxygen (48-192 ml) at the equivalent of 2 to 3 LPM continuous oxygen flow corrected hypoxemia, although an increased pulse dose was required due to probable increase in tidal volume at altitude. No studies have been conducted at altitude more consistent with AE (e.g., 8,000 feet). Research is ongoing to evaluate a closed-loop pulsed-oxygen delivery system for use in trauma patients in pre-hospital setting. Considering the relationship between the rate and depth of respirations and the actual oxygen delivered to the individual (FDO_2), further exploration is needed in combat casualties controlling for the effects of narcotics and fatigue/sleep on rate and depth of respirations. Additional calculations based on potential oxygen requirements can be derived using data from Alkins' study of the 11 casualties evacuated from the USS Cole, where the average supplemental oxygen delivered was 4 LPM to correct SaO2 to > 92%. Further research on the use of pulsed-dose oxygen needs to be conducted under en route care conditions and potential pathology.

Gaps – Oxygen Delivery

- **Effect of variations in respiratory rate/depth on pulse-dosed oxygen delivery (FDO_2) in spontaneously breathing individuals using pulmonary parameters consistent with casualties during AE (e.g., previous studies by Alkins[252] and Johannigman[171] report no dyspnea documented)**

Only one study has evaluated strategies to mitigate the effects of hypobaric hypoxia during suctioning.[265,266] In a swine model of acute respiratory distress syndrome, it was determined that ground-based pre-suctioning preparation (hyperoxygenation [100%]-plus hyperinflation [135%]) prevented clinically significant desaturation during suctioning with simulated altitude up to 10,000 feet compared to hyperoxygenation alone. An interesting outcome[267] of this study, which used the Impact 754 with an in-line suction, was that at sea level a suction pressure of 80 mm Hg would achieve the optimal suction flow rate (16 L/min), but above 6000 feet a suction pressure >120 mm Hg was required to maintain this desired suction flow rate. At 10,000 feet, suction pressure > 125 mm Hg caused *ventilator failure* (3 occurrences) and when PEEP > 10 cm H20 was used, suction pressure > 115 mm Hg caused the ventilator to fail.

These studies demonstrate the importance of evaluating ground based protocols, and evaluating the interface between these protocols, technology and the stresses of flight. Integration of these findings into en route CPGs is warranted.

4.6.5 Endotracheal Cuff Management. AFI 48-307 (vol 1) En Route Care and Aeromedical Evacuation Medical Operations provides guidance on ETT cuff management (Table 12).[268,269]

Table 12. Endotracheal Tube Cuff Management (AFI 48-307)[268]

- 8.4.8.3. The ERCC team may elect to fill endotracheal and tracheostomy tube cuffs with air and then attach to a cuff pressure monitor to minimize tissue trauma and the complications of re-intubation.
  - 8.4.8.3.1. Cuff pressure is usually maintained between 15-20 cm, and will be checked preflight, at cruise and hourly, on descent, and prior to deplaning. Document cuff pressures on patient's medical record. **(T-1)**
  - 8.4.8.3.2. If an ERCC team is unavailable and an ETT or tracheostomy tube cuff requires inflation for flight, ensure it is inflated with air. Use minimal occlusion volume/minimal leak technique in an effort to permit adequate ventilation and avoid tissue trauma. **WARNING**: Excessive pressure in the endotracheal or tracheostomy cuffs may decrease blood flow to tissue causing airway damage, while under inflation may permit air leak/ineffective ventilation and increased potential for aspiration of upper airway secretions.

There is a large body of literature describing endotracheal tube cuff pressure at altitude.[270-286] A recent study[273] by Britton compared four methods for managing ETT cuff pressure at altitude. This paper provides an excellent summary of research related to changes in cuff pressure at altitude. In these studies ascent to 3,000 feet was associated with cuff pressures > 40 mm Hg[272,277], at 8,000 feet cuff pressure was > 80 -100 cm H20,[283,287] and at 10,000 feet cuff diameter increased 4.5 cm (no pressure data).[280]

A series of studies have been conducted to evaluate various methods to maintain ETT cuff pressure (air – control, air-manual adjustment, automated pressure adjustment, saline). For the air-filled cuffs, the pressure is < 30 mm Hg at sea level and increases to > 80 mm Hg at 8000 feet. Manual correction decreases the pressure to < 30 mm Hg, and most of the automated systems maintain pressure < 30 mm Hg. In all studies, upon return to sea level (Figure 9), the pressure in the air-filled cuffs was lower than baseline, which may place patients at risk for aspiration. In all the studies, while there was less variability in the pressure in the cuff filled with saline, at sea level the cuff pressure exceeds 30 mm Hg, increasing the risk for tracheal damage. In Blakeman's study of four methods to maintain cuff pressure, there was no leakage of artificial saliva around the ETT. An important finding in Blakeman's 2017 study[286] was that tracheal wall pressure exceeded cuff pressure under all conditions.

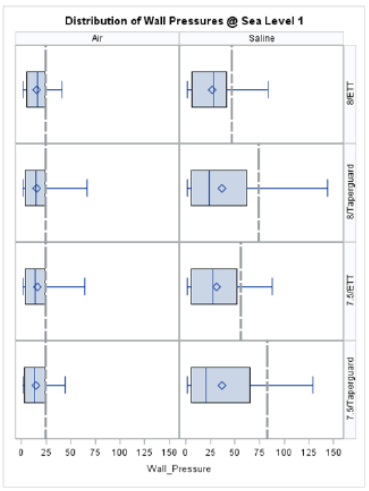


Figure 2. TW and ETT cuff pressures at baseline ambient pressure. *Diamond is the mean, vertical line inside the box is the median, box is interquartile range, whiskers are overall range, and vertical dashed line is mean ETT cuff pressure.*

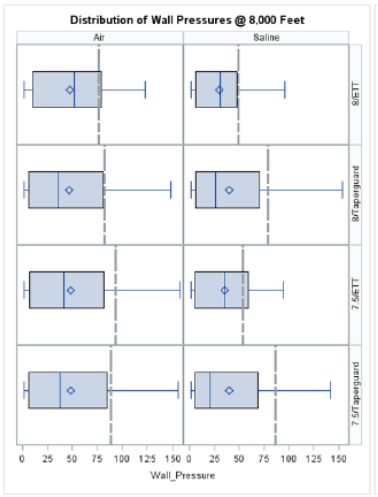


Figure 3. TW and ETT cuff pressures at simulated altitude of 8,000 ft. *Diamond is the mean, vertical line inside the box is the median, box is interquartile range, whiskers are overall range, and vertical dashed line is mean ETT cuff pressure.*

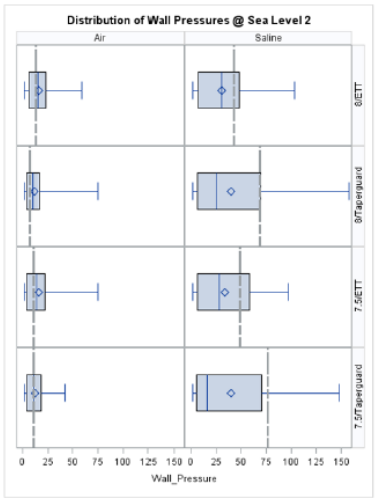


Figure 4. TW and ETT cuff pressures after return to sea level. *Diamond is the mean, vertical line inside the box is the median, box is interquartile range, whiskers are overall range, and vertical dashed line is mean ETT cuff pressure.*

Figure 9. ETT cuff pressure changes with altitude.

Three automatic cuff pressure controllers (pilot balloon pressure) were studied by Blakeman.[271] Compared to no adjustment, except at sea level, the three devices maintained a lower cuff pressure throughout the experiment at 0, 8,000, and 16,000 feet ascent and descent (Figure 10). A limitation of these studies is the use of the pilot balloon pressure as a surrogate for tracheal wall pressure as demonstrated in Blakeman's 2017 study, where the tracheal wall pressure is less compared to the cuff pressure.[286]

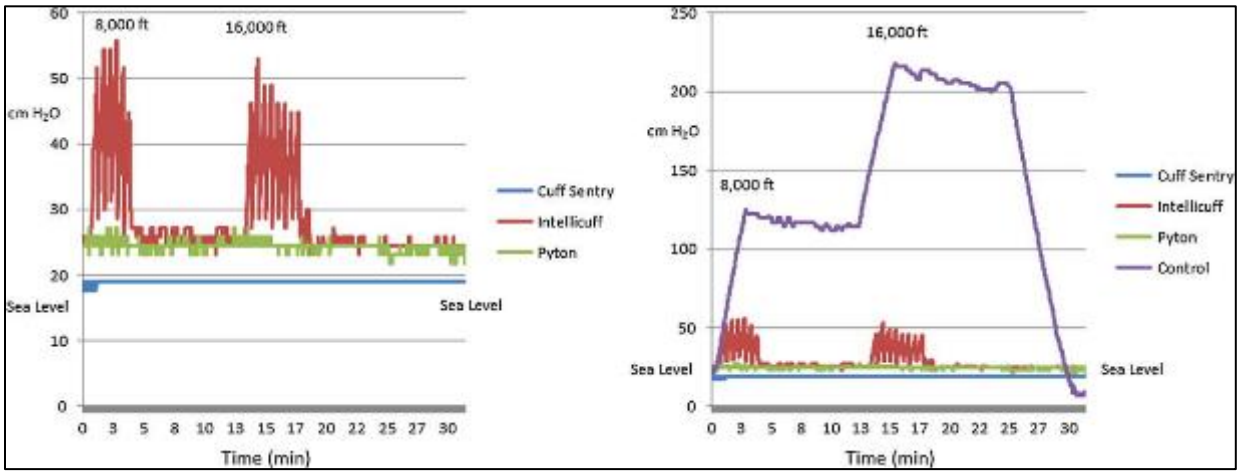


Figure 10. Continuous cuff pressure measurements with three devices (Cuff Sentry, Pyton, Intellicuff) without and with control during simulated flight (0, 8,000, 16000 feet) using an 8.0 ETT. From Blakeman.[271]

Note: Per Dr. Butler (1 Jun 2017) the TCCC is considering use of the i-gel supraglottic airway. The cuff is made of a thermoplastic elastomer, designed to create a non-inflatable anatomical seal of the pharyngeal, laryngeal and peri-laryngeal structures. A review of the 2014 bibliography on the company website presented cases related to pre-hospital care, primarily in Europe, but none specific to use during en route care.

4.6.6 Mechanical Ventilation. There is limited research on en route management of patients requiring mechanical ventilation. Barnes[288] conducted a retrospective review of continuously downloaded data (ventilator settings, tidal volume, respiratory rate, minute ventilation, HR, SpO2) obtained on 22 critically injured CCATT patients (ISS 25) transported from Balad to LRMC in 2006. These data were linked with medical records from TRAC2ES and the JTTR. Mean FiO2 was 49% ± 13%, PEEP of 6 ± 2.5 (range, 0-17 cm H_2O), RR of 15 ± 2.4 (range, 10-22 breaths/min), and VT of 611 ± 75 (range, 390-700 mL). Sixty four percent of patients had a tidal volume of 6-8 ml/kg. NB: the patients actual weight is not known as there was no in-theater capability to weight patients. Among these patients, there were three inflight desaturations (nadir 85% - 35 seconds; 86% nadir – 115 seconds, 89% nadir – 280 seconds). No interventions were noted in response to these desaturations. This study is important in demonstrating the potential use of continuously downloaded data. **These data need to be linked to the electronic health record to evaluate pre-event/post-event state. The study is also useful in describing the potential O2 requirement during a disaster evacuation, when a larger number of ventilator patients are simultaneously transported.**

A study[148] was conducted to identify preflight variables associated with post-flight outcomes (ventilator time > 72 hours and 30-day mortality) in CCATT trauma patients. Data were obtained from the CCATT pilot unit and the DoDTR. Injury severity score (OR = 1.04; 95% CI 1.03-1.06], preflight packed red blood cell units transfused (OR = 1.05 [1.04-1.07]), and preflight intubated status (OR = 11.9 [8.53-16.89]) were independently associated with increased ventilator days. Preflight ISS (OR = 1.06 [1.03-1.09]), prothrombin time (OR = 2.13 [1.18-4.47]), preflight intubated status (OR = 9.2 [1.88-166.11]), and whole blood (OR = 3.18 [1.38-7.04]) were associated with 30-day mortality. For every one-unit increase in ISS or PRBCs, there was a 4% or 5% increase in odds of prolonged mechanical ventilation (> 72 hours), and for every one-unit increase in ISS there was a 6% increased risk of 30-day mortality. Other risk factors for 30-day mortality were pre-flight intubation, 2-second increase in prothrombin time, and whole blood transfusion. **Areas not addressed by this study were the rationale for preflight intubation (physiological requirement, en route safety, need for additional surgeries), timing of blood administration (when preflight). There was no multivariate analysis (i.e., is mechanical ventilation a surrogate for injury severity). The study focused on post-flight outcomes, but did not address en route events. The timing of events (risk factors) was not delineated. The study does have Implications for post-flight resource requirements.**

Only one study[289,290] has evaluated the effects of en route ventilator management on patient outcomes. A retrospective review of patients requiring mechanical ventilation was conducted to evaluate adherence to the ARDSNet ventilator management recommendations and patient outcomes. Among the 650 patients requiring volume controlled ventilation, 400 (62%) were not compliant with the recommendations. The noncompliant group had a higher ISS, but there were no other significant demographic differences between the compliant and noncompliant groups. The subjects in the noncompliant group were more likely to have an occurrence of ARDS or acute respiratory failure and VAP (7% vs. 2%). The noncompliant group also had a higher incidence of inflight respiratory events (not defined), more ventilator and ICU days and higher mortality. A similar study[291] evaluated adherence with ARDSNet recommendations non-trauma CCATT patients. From 2007-2015 there were 672 non-trauma patients transported by CCATT; 125 requiring mechanical ventilation. Among these patients, the PaO2 was between 80-105 mm Hg in approximately 30% of the patients, < 80 mm Hg in 40% of patients and greater than105 mm Hg in 30% of patients. The SpO2 was between 92-96% in approximately 20% of

patients and greater than 96% in approximately 78% of patients. Adherence to ARDSNet VT recommendations was found in approximately 50% of patients and ARDSNet table (FiO2 and PEEP) in 40% of patients. This study is important in relative to recent research on potential iatrogenic effects of hyperoxia as well as implications for logistical support for O2. What was not addressed in these studies was the adjudication of patient requirement for lung protective ventilation (i.e., is this a requirement for all patients transported on a ventilator or only those with more severe respiratory dysfunction), implications for this mode of ventilation in patients with TBI, description of the timing of the adverse events (i.e., when did the ARDS or acute respiratory failure occur), and adherence to VAP prevention bundle. This study is important as it explores the adherence to recommended guidelines and care outcomes

Several ground based studies have been completed as a part of the development of closed loop control of oxygenation and ventilation.[292,293] These studies, which demonstrated an increase in time spent with the SpO2 in the desired range (92%-96%), no difference in the incidence of hypoxemia, and a 44% decrease in oxygen use compared to clinician control, are important in considering ventilator support under a resource constrained environment and with medical providers with less experience in ventilator management. No patient outcomes associated with variations in ventilator/oxygen control were reported. Jernigan[294] studied closed loop control of FiO2 in an animal model of hemorrhagic shock. Similar to the human studies, the closed loop system maintained at the target SpO2 of 94%. However, there were periods of prolonged hyperoxia (SpO2 > 97%), which may be related to the loss or attenuation of the pulse oximeter signal. Drawing on civilian literature, it will be important to clarify if the risk of hyperoxia is associated with an increased SpO2/PaO2 or increased FiO2.

Several studies have also been conducted evaluating ventilator performance (tidal volume, respiratory rate, PEEP) with ascent to altitude. Rodriguez[295,296] studied the Impact 754 and the LTV-1000 at sea level, 4,000, 8,000 and 15,000 feet, with tidal volume ranging from 0.25-1.0 L (test lung compliance 40 mL/cm H20 and resistance 5 cm H20/L. The Impact 754 delivered a VT < set amount at sea level, but with ascent the VT remained within 5% of the set tidal volume. The Impact 754 delivered a more accurate VT with FiO2 1.0 versus 0.21. With a lower tidal volume (300-500 ml) the VT was within 13% at 12,000 and 18,000 feet. The tidal volume for the LTV-1000 increased with ascent to altitude, with a 10% increase at 8,000 feet and 30% increase at 15,000 feet. Blakeman.[297] studied the Impact 731, Hamilton T1 and CareFusion Revel ventilators in pediatric (50 and100 mL) and adult (250-750 ml) tidal volumes, and PEEP (0 and 20 cm H20) at 21% and 100% FiO2. Tests were conducted at sea level, 8,000, 16,000, and 22,000 feet). The Impact 731 VT compensated for changes in altitude and remained within 10% of adult settings at all altitudes. The T1 triggered a critical alarm at 16,000 and 22,000 feet. Increasing altitudes resulted in larger VT than set for the Revel and the T1. A recent study[298] evaluated the VDR-4 ventilator (used by Lung Team and Burn Team) at altitude. At 8000 feet, there were significant changes in tidal volume, respiratory rate, peak pressure, and PEEP and experienced clinicians were not able to correct these parameters to ground level values. **Areas for further research include the accuracy of the VT at lower FiO2 (0.28-0.60). A description of the frequency of use of different ventilators for CCATT (versus ALeRT) or Burn team and the incidence of adverse events associated with specific ventilators is needed. Integrating this research on ventilator performance with the research on closed loop systems is needed to evaluate the ability of the closed loop controller to function given the altitude-induced changes in ventilator performance. Of note, Johannigman's study[293] used the Eagle Uni-Vent 754 Transport Ventilator as a part of the closed loop system. Analysis using the current CCATT ventilators is needed. These studies also highlight the importance of accurate and continuous monitoring of SpO2 under en route conditions. As discussed above in Maddry's study,[289,290] the ability of the closed system to provide lung protective ventilation during en route care is also needed. Models with different lung compliance and airway resistance developed by to test portable transport ventilators are warranted.[299-301]**

Another potential aspect of en route care related to ventilator function is the impact of storage temperature on ventilator function. Blakeman[302] studied the effect of extreme temperatures (60C/140F and -35C/-31F) on the Impact 731 Hamilton Medical T1, and CareFusion Revel portable ventilators. After 24 hours of exposure, the ventilators all demonstrated the need for a minimum of an hour acclimation at room temperature for accurate functioning. This study has implications for a policy on equipment storage and pre-flight preparation. No data were included on the effect of the extreme temperature on battery function.

The effect of ambient humidity conditions consistent with AE (15°C with 30% relative humidity) on the ability of heat and moisture exchangers (HMEs) to provide airway humidification in ventilated patients was studied using 10 commercially available devices.[303] All 10 HMEs studied maintained a patient-side relative humidity > 90%, but these values were still lower than the ANSI recommended levels of humidification**. No reports are available on en route issues related to HMEs, to include the loss of an airway or en route care requirements to mitigate the effects of low humidity on airway status.** NB: in a study[304] in the C-17, relative humidity was 5% within 30 minutes of ascent to altitude.

Similar to the findings related to ventilator function at altitude, a recent study[305] reiterated the importance of evaluating technology under en route care conditions. In a high-fidelity simulator, five video-assisted intubation devices were tested under normal airway lights-on, difficult airway lights on and difficult airway blackout (green ceiling lights) in mannequins positioned to simulate CCATT transport. Results indicated that both the GlideScope and Pentax AWS were appropriate for use en route by both novice and experienced providers. **A gap is the need to describe the requirement for en route intubation.** A review of data from the CCATT pilot unit should answer this question.

Gaps

- ***Describe characteristics of AE patients at increased risk for en route hypoxemia***
- ***Describe incidence of inflight desaturation controlling for pre-flight acclimatization; possible occult blast injury, in-flight care – narcotics, sleep state, and complete vital signs (HR, RR, SpO2)***
- ***Replicate effect of hypobaria c/w AE on SaO_2 and StO_2/SmO2 in healthy subjects/ill-injured controlling for ground SaO2***
- ***Validate Muhm's logistic predictive model using data from combat casualties (implications for Flight Surgeon pre-flight assessment)***
- ***Effect of vibration consistent with fixed wing transport on oxygen requirements (only studied in rotary wing)[306] and ability to monitor***
- ***Standardize animal model to simulate AE post-combat trauma –effect of varying time to fly***
- ***Characterize critical tissue oxygenation (StO_2/SmO_2) level for various outcomes (bacterial growth, cytokines, wound healing***
- ***Incidence of en route intubation***
- ***Control other factors potentially associated with wound infections (interaction with hypoxia, hypobaric environment; glucose, core/local temperature***
- ***Effect of negative wound pressure therapy (interaction effect)***
- ***Preflight predictors of risk for en route adverse events***
- ***Interaction between closed loop control of oxygenation and ventilation at altitude***
- ***Incidence of humidification related adverse events (i.e., loss of airway, mitigating care strategies)***

4.7 ECMO

The USAF has a long history of en route ECMO for pediatric patients,[307] In 2005, ad hoc medical teams successfully transported two patients using portable extracorporeal lung assistance (PECLA) – one from

AOR to LRMC and second from LRMC to University Hospital Regensburg, Germany.[308] In 2005 the USAF Acute Lung Rescue Team (ALeRT) was created.[100]

There have been several review papers on the ALeRT, and the transport of patients on extracorporeal membrane oxygenation (ECMO) or PECLA. [309-313] However, there are only three epidemiologic reports and two case studies providing specific information about these patients. Of note, the three epidemiologic studies include subsets of the same population (2005-2010). Dorlac[100] reported on the characteristics of the 11 ALeRT activations (5 transports) during the first two years (2005-2007) of the program. During this period, there were 924 CCATT transports, with 524 patients transported with mechanical ventilation. Among these patients, 15 additional patients had a diagnosis of acute lung injury/acute respiratory distress syndrome, pulmonary contusion, pneumonia or hypoxemia and an additional 167 patients had a PaO2/FiO2 < 300. Overall, the at-risk group compromised approximately 20% of all CCATT transports, and the ALeRT team accounted for 1% of all ventilator transports. A second report extended the study period (2005-2010) for ALeRT activations. During this period ALeRT was activated 40 times (28 trauma/12 non-trauma), with 27 transports from the AOR to LRMC.[101,314] In the remaining 13 cases there were four deaths and nine patients who stabilized and were transported by CCATT. Reporting on this same period, Bein[315] reported on 10 patients who received ECLS support in collaboration with the University Hospital Regensburg. This report is important as all patients were trauma patients, with 4/10 transported from the AOR. Two case studies[308,316] provide further insight into the pre-transport and post-transport status of two patients, however, neither report provides any information on en route management. Only one civilian study,[317] which summarized 16 cases requiring long-distance ECLS transport, reported on adverse events that occurred during transport (hypovolemia = 11, heart rhythm disorders = 3, cardiorespiratory arrest =2, bleeding from natural orifices = 2, thermal dysregulation = 7). This generalizability of this study to military en route care is limited by the patient characteristics (primarily cardiac), as nine patients ultimately received a heart transplant or ventricular assist device. However, the study does demonstrate potential adverse events (bleeding, thermal dysregulation, hypovolemia) that have not been described for the military patient population. **Gap: Need to describe the en route care requirements, patient's physiological status, adverse events, short and long-term outcomes.**

The ALeRT has been discontinued due to low requirement. A research gap is the effectiveness of strategies to maintain this capability. During the inception of the program, partnership with a civilian hospital (University Hospital Regensburg) supported the development of the capability. Cannon[318] reported on the development in 2011 of a sustainment program at SAMMC; however, no outcomes related to this program were reported. The status of this program is not known. Lessons learned from the pediatric ECMO program may also inform capability sustainment strategies.

Gaps

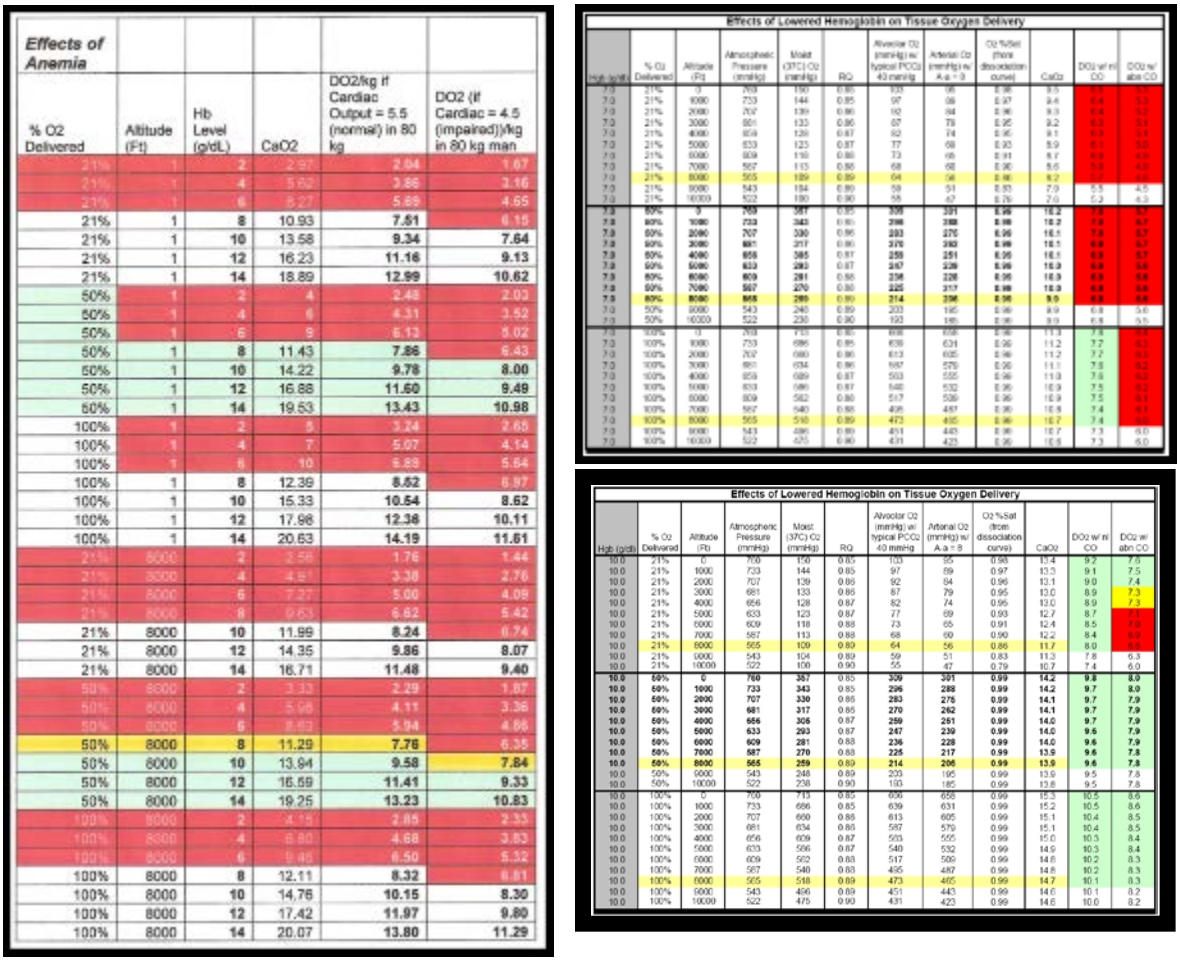
- **Description of patients at risk for pulmonary deterioration (see Edens[319])/patients who required advanced pulmonary support (timing of deterioration, time to implement advanced support, outcomes)**
- **Capability for prone position transport**
- **Outcomes based on mode of ECLS support (PECLA, ECMO) -for example with TBI patient. Separate outcomes for medical versus trauma patients (see Swol[320])**
- **Description of alternative advanced therapies implemented) (proning, epoprostenol) and feasibility and en route care capabilities/requirements**
- **Description of burn transport team support of patients requiring advanced lung support**
- **Timeline for activation and initiation of teams (ALeRT, SAMCC ECMO team)**

- **En route care of patients (care requirements, adverse events, acute outcomes), pre-post physiological status**
- **Comparison of outcomes related to current civilian ECMO transport programs**
- **Evaluation of sustainment training programs**
- **Theater implementation of ECMO in preparation for transport (requirements, implications of time delay to initiation of therapy)**

4.8 Cabin Altitude Restriction - Transport of Patients with Entrapped Air

The literature review for this section includes the general effects of hypobaria, the incidence of altitude restrictions ordered, outcomes associated with altitude restrictions, and specific conditions where altitude restrictions might be considered such as pneumothorax, pneumocephalus, ocular air, and post-abdominal surgery. The studies were limited to barometric pressure changes consistent with aeromedical evacuation (e.g., altitude maximum 13,000 feet**). Separate consideration should be given to the evacuation of casualties at high altitudes.**

A series of studies were conducted related to the use of cabin altitude restriction. Between 2001-2014 there were 83,745 patients transported on 92,530 transports.[321] Among these transports, 90,480 were non-CAR and 2,250 were CAR (note: unclear if number of patients exposed to CAR was determined – if one patient on aircraft flies with CAR designation, all patients fly with CAR). In an analysis[322] of 50 CAR and 50 non-CAR patients there was no significant difference in demographics, preflight oxygen delivery (DO_2), inflight status, ICU or hospital length of stay or discharge status. The CAR patients had fewer post flight procedures (4.98 vs 6.08, $p = 0.032$). An important aspect of this research was the demonstration of the internal validity of a DO2 calculator, with or without the use of ABGs (Figure 11/Figure 12).[323] **An area for further study is the relationship between en route DO2 (establish safe threshold) and post-flight outcomes. External validation of the DO2 calculator should be accomplished.**



Effects of Anemia					
% O2 Delivered	Altitude (Ft)	Hb Level (g/dL)	CaO2	DO2/kg if Cardiac Output = 5.5 (normal) in 80 kg	DO2 (if Cardiac = 4.5 (impaired))/kg in 80 kg man
21%	1	2	2.97	2.04	1.67
21%	1	4	5.62	3.86	3.16
21%	1	6	8.27	5.69	4.65
21%	1	8	10.93	7.51	6.15
21%	1	10	13.58	9.34	7.64
21%	1	12	16.23	11.16	9.13
21%	1	14	18.89	12.99	10.62
50%	1	2	4	2.48	2.03
50%	1	4	6	4.31	3.52
50%	1	6	9	6.13	5.02
50%	1	8	11.43	7.86	6.43
50%	1	10	14.22	9.78	8.00
50%	1	12	16.88	11.60	9.49
50%	1	14	19.53	13.43	10.98
100%	1	2	5	3.24	2.65
100%	1	4	7	5.07	4.14
100%	1	6	10	6.89	5.64
100%	1	8	12.39	8.62	6.97
100%	1	10	15.33	10.54	8.62
100%	1	12	17.98	12.38	10.11
100%	1	14	20.63	14.19	11.61
21%	8000	2	2.58	1.76	1.44
21%	8000	4	4.81	3.38	2.76
21%	8000	6	7.27	5.00	4.09
21%	8000	8	9.63	6.62	5.42
21%	8000	10	11.99	8.24	6.74
21%	8000	12	14.35	9.86	8.07
21%	8000	14	16.71	11.48	9.40
50%	8000	2	3.33	2.29	1.87
50%	8000	4	5.96	4.11	3.36
50%	8000	6	8.62	5.94	4.86
50%	8000	8	11.29	7.76	6.35
50%	8000	10	13.94	9.58	7.84
50%	8000	12	16.59	11.41	9.33
50%	8000	14	19.25	13.23	10.83
100%	8000	2	4.19	2.85	2.33
100%	8000	4	6.80	4.68	3.83
100%	8000	6	9.46	6.50	5.32
100%	8000	8	12.11	8.32	6.81
100%	8000	10	14.76	10.15	8.30
100%	8000	12	17.42	11.97	9.80
100%	8000	14	20.07	13.80	11.29

Effects of Lowered Hemoglobin on Tissue Oxygen Delivery

Hgb (g/dl)	% O2 Delivered	Altitude (Ft)	Atmospheric Pressure (mmHg)	Moist (37C) O2 (mmHg)	RQ	Alveolar O2 (mmHg) w/ typical PCO2 40 mmHg	Arterial O2 (mmHg) w/ A-a = 8	O2 %Sat (from dissociation curve)	CaO2	DO2 w/ nl CO	DO2 w/ abn CO
10.0	21%	0	760	150	0.85	103	95	0.98	13.4	9.2	7.5
10.0	21%	1000	733	144	0.85	97	89	0.97	13.3	9.1	7.5
10.0	21%	2000	707	139	0.86	92	84	0.96	13.1	9.0	7.4
10.0	21%	3000	681	133	0.86	87	79	0.95	13.0	8.9	7.3
10.0	21%	4000	656	128	0.87	82	74	0.95	13.0	8.9	7.3
10.0	21%	5000	633	123	0.87	77	69	0.93	12.7	8.7	7.1
10.0	21%	6000	609	118	0.88	73	65	0.91	12.4	8.5	7.0
10.0	21%	7000	587	113	0.88	68	60	0.90	12.2	8.4	6.9
10.0	21%	8000	565	109	0.89	64	56	0.86	11.7	8.0	6.6
10.0	21%	9000	543	104	0.89	59	51	0.83	11.3	7.8	6.3
10.0	21%	10000	522	100	0.90	55	47	0.79	10.7	7.4	6.0
10.0	**50%**	**0**	**760**	**357**	**0.85**	**309**	**301**	**0.99**	**14.2**	**9.8**	**8.0**
10.0	**50%**	**1000**	**733**	**343**	**0.85**	**296**	**288**	**0.99**	**14.2**	**9.7**	**8.0**
10.0	**50%**	**2000**	**707**	**330**	**0.86**	**283**	**275**	**0.99**	**14.1**	**9.7**	**7.9**
10.0	**50%**	**3000**	**681**	**317**	**0.86**	**270**	**262**	**0.99**	**14.1**	**9.7**	**7.9**
10.0	**50%**	**4000**	**656**	**306**	**0.87**	**259**	**251**	**0.99**	**14.0**	**9.7**	**7.9**
10.0	**50%**	**5000**	**633**	**293**	**0.87**	**247**	**239**	**0.99**	**14.0**	**9.6**	**7.9**
10.0	**50%**	**6000**	**609**	**281**	**0.88**	**236**	**228**	**0.99**	**14.0**	**9.6**	**7.9**
10.0	**50%**	**7000**	**587**	**270**	**0.88**	**225**	**217**	**0.99**	**13.9**	**9.6**	**7.8**
10.0	**50%**	**8000**	**565**	**259**	**0.89**	**214**	**206**	**0.99**	**13.9**	**9.6**	**7.8**
10.0	50%	9000	543	248	0.89	203	195	0.99	13.9	9.5	7.8
10.0	50%	10000	522	238	0.90	193	185	0.99	13.8	9.5	7.8
10.0	100%	0	760	713	0.85	666	658	0.99	15.3	10.5	8.6
10.0	100%	1000	733	686	0.85	639	631	0.99	15.2	10.5	8.6
10.0	100%	2000	707	660	0.86	613	605	0.99	15.1	10.4	8.5
10.0	100%	3000	681	634	0.86	587	579	0.99	15.1	10.4	8.5
10.0	100%	4000	656	609	0.87	563	555	0.99	15.0	10.3	8.4
10.0	100%	5000	633	586	0.87	540	532	0.99	14.9	10.3	8.4
10.0	100%	6000	609	562	0.88	517	509	0.99	14.8	10.2	8.3
10.0	100%	7000	587	540	0.88	495	487	0.99	14.8	10.2	8.3
10.0	100%	8000	565	518	0.89	473	465	0.99	14.7	10.1	8.3
10.0	100%	9000	543	496	0.89	451	443	0.99	14.6	10.1	8.2
10.0	100%	10000	522	475	0.90	431	423	0.99	14.6	10.0	8.2

Figure 11. Estimated effects of anemia on DO2 controlling for altitude and supplemental oxygen. From Mitchell.[323]

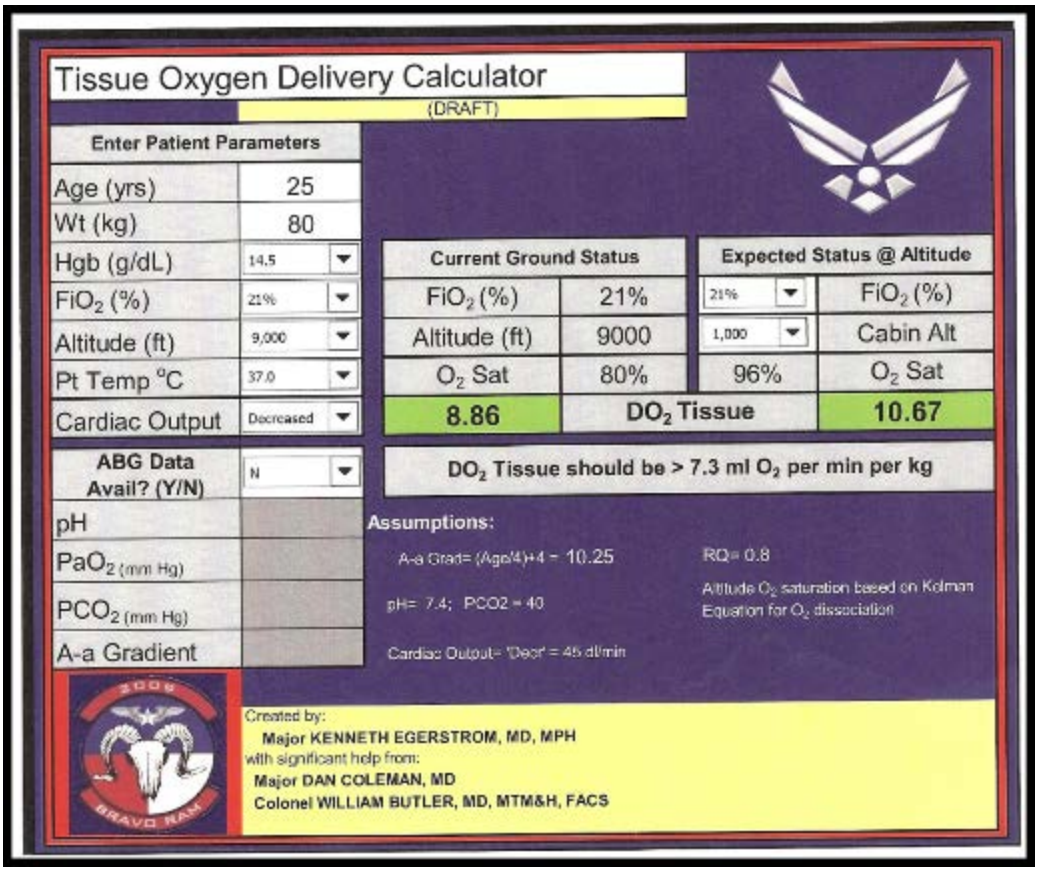


Figure 12. Tissue O2 delivery calculator (under development).

Butler[59,324] studied complication rates in patients undergoing priority or urgent evacuation with/without cabin altitude restriction. Data were obtained from the JTTR to identify post-flight complications recorded at LRMC and TRAC2ES for period 2006-2008. An important point in the study was the delineation of post-flight complications for 11 categories (pulmonary, infectious, resuscitative, coagulation, gastrointestinal, orthopedic, renal, metabolic, dermatologic, neurologic, and cardiac). There was a significantly inverse association between post-flight complications and CAR (r = -0.57) but there was no significant difference in length of stay (average LOS 3.5 ± 4.5 days); although the LOS may be affected by the timeline for CONUS evacuation. A limitation of the study was lack of information on the rates of complications by categories (i.e., change in rate for pulmonary or infectious) and the timing of the complication relative to the flight. The study is important for the hypothesis-generating discussion of possible causal factors associated with complications that can be mitigated by the use of CAR.

4.8.1 Pneumothorax. Many papers were found related to pneumothorax within the context of en route care, including pre-transport diagnostics. However, only three papers were directly relevant to the acute evacuation of patients with a pneumothorax.[325-327] The remaining research papers summarized civilian literature describing commercial air transport 14 days post-pneumothorax resolution or individual case studies.

According to Boyle's Law, with ascent to 8400 feet, gas may expand 30-35%, potentially resulting in a tension pneumothorax. However, in a bench study, with altitude changes from 0-5000 feet (consistent with helicopter transport), there was a 1.27% to 1.52% increase in gas volume for each 500 feet of altitude (~13-16% increase in gas volume with ascent from 726 to 5700 feet MSL)[328] or an estimated 21 to 26% increase in gas volume at 8400 feet. No large studies of the military population have been

conducted related to the safety of transporting a patient with a known pneumothorax not relieved by a tube thoracostomy. A systematic review by Bunch[329] related to commercial air travel in patients with a pneumothorax found only two prospective studies and two retrospective studies. This limited evidence supports the existing recommendation of waiting 14 days post-resolution of the pneumothorax before a commercial flight, although there was no recommendation differentiating time restrictions for spontaneous versus traumatic pneumothorax. Literature on transport of patients during the more acute phase was limited. A civilian study[330] of 66 patients (55 blunt trauma, 11 penetrating trauma) with a confirmed pneumothorax who were transported via rotary wing (mean ground elevation 5,700 feet, altitude gain 1890 feet, average barometric pressure 586-600 mm Hg, average flight duration 28 minutes, range 3-70 minutes). During transport, all patients received supplemental oxygen and 14/66 were ventilated. Eleven patients (17%) had a chest tube placed before flight, and 4/66 (6%) had a chest tube placed during flight. Seven patients deteriorated during transport with three unrelated to pneumothorax. The remaining four patients deteriorated most likely due to pneumothorax, which was successfully managed with placed of a tube thoracostomy. No data were provided on post-flight condition. Baude's study was limited by the small change in barometric pressure (5700 to 7590 feet], in contrast to a larger potential change in barometric pressure (and subsequent gas expansion) associated with ascent from sea level to a cabin altitude of 6000-8000 feet. A study[326] was conducted in Salt Lake City in 20 patients with a small or resolved traumatic pneumothorax. Fourteen of the subjects had been treated with a chest tube (6 with supplemental oxygen), with the tube removed on average 19 hours (range 4-43 hours) before the simulated two-hour flight (12,650 feet (471 mm Hg) or 8400 feet (554 mm Hg). This simulated flight profile to 12,650 feet created a barometric pressure change comparable to ascent from sea level to a cabin altitude of 8400 feet. For the flights with ascent to 8400 feet, compared to preflight, the pneumothorax increased from 4.5 ± 4.9 mm to 10 ± 0.7 mm (average increase 5.6 ± 0.6 mm, p = .02) at altitude without any symptoms. At four hours post flight (654 mm Hg) all pneumothoraces were not significantly different from preflight size (3.8 ± 0.5 mm). With ascent to 12,650 feet, the pneumothoraxes increased 8.7 ± 7.5 mm Hg, with three subjects developing a visible pneumothorax at altitude. There was no difference in size four hours' post-flight. These results suggest that transport is safe for patients with a small pneumothorax; and are consistent with the findings in patients who had a post-biopsy pneumothorax,[331] and a mathematical model which found that positive pleural pressure occurred during ascent to 8000 feet cabin altitude only when the sea-level based pneumothorax was greater than 45%.[332]

Schmelz[333] conducted a study to determine the effects of the position of chest tube draining on volume drained and pressure. This research, which involved an animal model, was conducted under conditions to mimic AE (narrow litter), where it may be difficult to avoid the tubing hanging off the side of the litter. To simulate required drainage, 500 ml was instilled into the pleural space with drainage measured for one hour. When the tubing had a dependent loop, there was significantly less fluid drained (65 ml) compared to coiled on litter (301 ml), straight on litter (337 mL) or lift and drain every 15 minutes (250 mL). Internal tube pressure was significantly higher in the dependent loop with/without lifting and draining. **These results demonstrate the importance of evaluating standard care under en route care conditions. These findings should be integrated into the en route CPG.**

Gaps - Pneumothorax:

- ***Describe incidence/outcomes for patients transported with small pneumothorax unrelieved by a chest tube.***
- ***Effect of time since resolution of the pneumothorax or discontinuation of the tube thoracostomy before transport.***
- ***Effect of needle decompression versus tube thoracostomy on relief of pneumothorax under hypobaric conditions. Describe need for placement of tube thoracostomy during extended flight.***

Methods for the relief of a pneumothorax in the en route environment, excluding pre-transport, have been studied only in a swine model. A study,[325] conducted by Canadian forces, was unique in that it evaluated the effect of arm adduction (caused by the litter and the litter strap) and movement on the TALON folding combat military stretcher (NATO Stock Number 6530-01-452-1651) on kinking of the angiocatheter. The study involved placement of segments of porcine chest walls on volunteer soldier's chest, with a simulated needle decompression performed using a 14 gauge, 1.5-inch angiocatheter placed either in the midaxillary or midclavicular location. Twenty-eight procedures were performed (14 each site). The midaxillary catheters were noted to have more kinks and were more occluded compared to midclavicular catheters, which may result in insufficient ongoing relief of the pneumothorax.

There is ground-based research that demonstrates the effectiveness of vented and non-vented chest seals in resolving a pneumothorax, but under conditions of continued air accumulation only the vented chest seal was effective in continued relief of the tension pneumothorax.[334]

Gap:

- ***No studies related to the use of a vented chest seal under hypobaric conditions (including prolonged flight). Compare with needle thoracostomy, and under conditions with assisted ventilation where the development of a tension pneumothorax may be more severe compared to spontaneous ventilation.[335]***
- ***Confirm that model used to analyze chest seal function consistent with injury patterns (hemopneumothorax) and recommended positioning (to include litter straps) on function of chest seal***

Only one case report was found describing placement of a tube thoracostomy during MEDEVAC helicopter evacuation[336] and no cases were reported during military fixed wing transport. In the MEDEVAC case, the patient was diagnosed with a pneumothorax using ultrasound. A tube thoracostomy was placed with resolution of symptoms. The remaining case reports, which were not included in the gap analysis, discuss chest tube or needle thoracostomy before civilian transport.

Gaps:

- ***Efficacy of needle decompression versus tube thoracostomy in relieving hemo-pneumothorax[337] under hypobaric en route conditions,***
- ***Safety of placing a tube thoracostomy in the en route setting.***
- ***A potential research gap consideration is that procedures now performed by TCCC and MEDEVAC may need to be provided during urgent evacuation on fixed wing aircraft under A2AD conditions.***

4.8.2 En Route Diagnosis of Pneumothorax. Only one paper, a case study, reported on the effectiveness of ultrasound to detect pneumothorax during flight.[336] Another case study demonstrated the use of ultrasonography in the pre-hospital combat environment to rule out pneumothorax/pneumomediastium,[338] which may have implications for describing the incidence of pneumothorax or pneumomediastinum pre-transport and the incidence of indicated/non-indicated needle or chest tube decompression in the en route setting.
[339,340]

4.8.3 Ocular Air. The presence of ocular air is a potential indication for a cabin altitude restriction. In a study of 2009 TRAC2ES records, 18% of PMRs listed ocular as an injury.[76] An analysis[341] was conducted of the Walter Reed Ocular Trauma Database (WROTD), which includes all ocular patients seen at

WRAMC 2001-2011. There were 895 eyes in 654 patients evacuated from Afghanistan to WRAMC. Among these patients, 265 (29.7%) in 239 had final vision worse than 20/200, with 206 open-globe injuries and 56 closed-globe injuries.

Several laboratory studies in civilian patients (post-surgery) have studied the effects of altitude on gas expansion on intraocular pressure. In 17 eyes (nine with10-20% gas – post op surgery 10 to 42 days) and controls intraocular pressure was measured at an average peak altitude of 6533 feet (2500-8900 feet).[342] In seven patients with 10-15% gas volume, the intraocular pressure increased 109% during the initial ascent to altitude (7429 feet) and then decreased to 30% above baseline at cruising altitude. In one patient with 20% gas, the study was stopped due a high intraocular pressure. There were no altitude related changes in the control eye or in control subjects. Similar results were found in a more recent study of post-surgical patients with 10% gas exposed to a peak altitude of 8000 feet. Intraocular pressure was measured 4-6 weeks post-surgery. During ascent to altitude, intraocular pressure increased from 13±3 mm Hg to a peak of 26± 9 mm Hg at 8000 feet. There were no significant altitude related changes in the contralateral eye or in the control. A limitation of these studies is that they address the kinetics of long-acting gases used in ophthalmologic surgery, such as fluorocarbons and sulfur hexafluoride, that may take up to six weeks to resorb,[343] in contrast to air trapped as the result of an ocular injury. Another limitation of these studies is that they are post-surgery (not injury) with time to travel up to six weeks post-surgery. **Further research is needed to describe the acute effects of en route care in combat casualties, controlling for rate of ascent consistent with military transport. No reports or studies were found for military population on pre-transport care, the incidence of adverse events related to en trapped air or the incidence of cabin altitude restriction due to ocular injury. Additionally, no data are available on the time to transport post-injury or surgery. Description of current medical management to mitigate intraocular air is also needed. Integration of the data from the Walter Reed Ocular Trauma Database (WROTD) with the DoDTR and the AER is needed to provide a more comprehensive analysis of care across the continuum**

4.9 Abdominal Disease, Injury/Surgery

An epidemiologic study published by MSMR, identified 1243 individuals evacuated a disease of the digestive system (rate of 1.8/1000)[48] from 2001-2012. Similar results were found in the analysis of 36,160 military and nonmilitary personnel evacuated from Iraq and Afghanistan between 2004 and 2007.[344] Among the patients with non-war related injury of diseases, 7% of all military transports and 9.4% of non-military transports were for gastrointestinal issues, and 3.7% of military transports and 11.2% of non-military transports were for noncardiac chest or abdominal pain. A review of papers specific to the transport of critically injured casualties found limited documentation regarding transport of patients with abdominal conditions. After the attack on the USS Cole in 2000 there were 11 seriously/critically injured patients evacuated.[252] Among these patients, one had a polytrauma, which included gastric rupture. Among the 28 less seriously injured casualties, only one of the 28 less seriously injured casualties had abdominal trauma (closed fracture sacrum/coccyx). There was no comment on any gastrointestinal complications in any of these patients. In CCATT patients transported from 2001-2006, 31% had injuries to the abdomen.[90] An analysis of 290 CCATT patients transported in 2011 identified ICD-9 code 878.0-8 (Open wound to groin/testes/penis) as the fourth most common (5.9%) primary or secondary diagnosis.[95] The difference in the incidence reported may have been that Bridges' study included all diagnosis. Of note, the DoDTR does not include abdominal complications on the standard list of complications. A systematic review by Sapsford, [345] was the only paper specific to the en route care for patients with an abdominal injury. However, they found no papers from 1967-2001 that specifically addressed aeromedical evacuation after abdominal surgery. One civilian study[346] reported four cases of small bowel obstruction that appeared to be associated with a flight. All patients had a history of abdominal surgery, with one patient with surgery 20-years before the event. All patients had an

uneventful recovery and could continue on a follow-on flight. No reports have been published of in-flight abdominal complications in AE patients, independent of the time since the abdominal event.

Studies in patients with irritable bowel disease suggest a relationship between air travel and inflammation (no clear delineation of hypoxia or hypobaria).[347,348] **Further research is needed on the association between en route hypoxia (or hypobaria) and IBD and inflammatory biomarkers (analyze biomarkers specific to gut function). Is there an alteration in the gut microbiome with hypoxia/hypobaria exposure?**

A report and subsequent paper by Greenwald,[349,350] characterized the volume of gas in the gastrointestinal tract (111 ml) in healthy subjects. Ascent from 745 mm Hg (~ 500 feet) to 350 mm Hg (20,000 feet) did not result in a significant increase in air volume or intraabdominal pressure and did not cause any reports of fullness or pain. In an earlier study by Peterson,[351] healthy volunteers had 400 ml of air introduced into their stomach followed by ascent to 30,000 feet. The subjects reported fullness in the stomach, but the gas expansion did not affect pulmonary status. A subsequent analysis by Peterson using an animal model, also found that up to 10,000 feet gas expanded approximately 1.5 times, but if the initial air volume is small with a limited altitude is minimal (e.g., with 100 ml air pressure in the abdomen did not increase markedly between sea level and 10,000 feet) independent of the rate of ascent. Thus, in the altitude range for AE, there appears to be limited clinical effect from decreased barometric pressure, even under conditions where release of abdominal gas is not possible. No studies have been done on the effect of barometric pressure induced gas expansion and tension on surgical anastomoses, although the textbook Aeromedical Evacuation [352] provides recommendations for the use of gastric decompression for patients with abdominal injuries or disease. There are no reports on transporting patients with intraabdominal hypertension or the use of bladder pressure monitoring en route.

Fang's[353] study of en route use of negative pressure wound therapy included patients with 41 separate wounds (29 lower extremity, 7 upper extremity, 3 perineal/buttocks and 2 torso – location not described). Thus, there is limited information on the use of NPWT in patients with open abdomens. However, the JTS CPG: Critical Care Air Transport (CCAT) Negative Pressure Wound Therapy[354] lists includes open abdomen along with soft tissue, fasciotomy, etc., as possible indications for the use of NPWT. However, there are no guidelines in the CPG specific to the abdominal wounds.

Gaps

- ***Description of complications in post-abdominal surgery/damage control surgery***
- ***Bladder pressure monitoring during AE***
- ***Negative pressure wound therapy on open abdomen***

4.10 Cardiology

The incidence of patients evacuated for circulatory disorders (non-injury) varies depending on the phase of the conflict and the mode of transport (AE versus CCATT). On average, circulatory disorders accounted for approximately 3% of all US evacuations from OIF/OEF/New Dawn.[47,48,51] Similar results were found for Royal Air Force evacuations, accounting for 3.1% of evacuations of military personnel and 8.2% of non-military evacuations.[50] Over a 2.5 year period an in-theater cardiologist evaluated 1,495 patients for cardiac complaints, with 15% requiring evacuation, primarily for acute coronary syndrome, pulmonary embolus or ventricular tachycardia.[355] For CCATT, there were 1995 patients transported from the AOR to LRMC from 2001 to 2006, with 275 patients (14%) with a primary cardiac diagnosis (rule-out acute coronary syndrome – 81%; isolated arrhythmias -11%).[90] In a prospective observational study[92] of 134 CCATT transports from Iraq to Germany over a 12-month period (2005-2006) a majority (65%) of

the transports were for trauma. There were 46 patients (35%) transported with a medical diagnosis. Among these 46 patients, 68% had a cardiac diagnosis (heart failure 6%, arrhythmias/syncope 16%, myocardial infarction 22% or chest pain 56%). Additionally, 9% of patients had signs and symptoms of a stroke. Among the seven patients with a documented myocardial infarction, four received a thrombolytic before flight, and two had suffered a pre-transport cardiac arrest. No specifics were provided on the timing of transport or the en route care for this subset of patients, but no patients died or suffered a cardiac arrest during transport. In 2011, there were 290 CCATT transports, with 7% of the transports for patients with acute coronary syndrome.[95] Although patients with a circulatory disorder (particularly ACS) represent one of the most common medical reasons for evacuation from the AOR, there have not been any studies published on their characteristics, en route care requirements or outcomes. In general, civilian studies are not generalizable given the time post-MI,[356,357] and the distance and/or time of the transport and the general recommendations are to avoid air travel for 2-4 weeks after a major cardiovascular event.[358-363]

The 59th MDW presented a report[175] on the stresses of flight for patients with acute coronary syndrome. The review cited two papers, one related to the transport of a patient with a biventricular assist device[364] and the second related to the use a flashlight to enhance adherence to chest compressions under noisy conditions.[365] No research gaps were identified.

There have been only three studies specific to military AE transport of patients with an acute cardiovascular diagnosis. Castillo[366] presented a case series of 59 patients with unstable angina evacuated in the Pacific theater from 1992 to 1996. There was no information on preflight status (e.g., time to flight, physiologic status) and only 31/59 patients had inflight records. Among these patients, all had supplemental oxygen, with one episode of hypoxia (SpO_2 88%). A strength of this study was the analysis of outcomes. Post-flight evaluation found that 61%of these individuals had occlusion of at least one vessel >90%, and 36% had three vessel disease. Fourteen patients had a complication during the admission, but none of these events was thought to be secondary to AE**.** Interpretation of these findings is limited due to the lack of a control group (e.g., similar patients not undergoing AE). A second case series[367] reported on seven patients transported to LRMC (1995) who had a diagnosis of acute MI and were complication free for at least 24 hours pre-flight (airlift 48 hours – 7 days after symptom onset). All patients had received thrombolytic therapy. There were no reports of bleeding during or post-flight and no complications were reported. Neither Castillo's or Connor's studies reflect current practice, nor can be generalized to patients requiring acute transport either before definitive therapy or with ongoing complications. A third study[368] described adverse events in 93 patients transported in AE (1994). This study was unique in describing adverse events both during transport and in the aeromedical staging facility (ASF). During this period, cardiac patient represented 7.2% of all patients evacuated, 37.5% of all AE patients with an adverse outcome during flight, and 11.4% of those who had an adverse event in the ASF. The unanticipated need for oxygen during flight and the development of chest pain were the two most common en route adverse events. The adverse events were related to failures in addressing two key processes – stresses of flight (hypoxia – unexpected need for oxygen in flight) and preparation for flight. **This study is important as it provides one of the largest studies of this target population, but also introduces a systematic structure to evaluate adverse events (e.g., stresses of flight, preparation for flight). The study is limited by a lack of description of the timing of events (e.g., time since pain free, time since infarction).** A relevant civilian study[369] was conducted an RCT to evaluate routine versus *prn* supplemental oxygen on inflight complications in patients two-weeks post-MI. Five patients had transient hypoxia (SpO2 < 90%), five had complex ventricular arrhythmias and one patient had a self-limiting episode of ischemia. There were no differences in hypoxia or other complications (e.g., chest pain, arrhythmias) between the routine versus supplemental O_2 groups. The results cannot be generalized to patients during the more acute phase of illness. In all of these studies, hypoxia is defined as < 90%, and a study be Essebag[357] defined hypotension as an SBP decrease by > 15 mm Hg requiring introduction or

increase in vasopressor**. There is a need for a standardized set of definitions for en route and post-flight[366] complications to allow for comparison across studies.**

A study of civilian patients by Essebag[357] is the only study that describes the relationship between time to transport and inflight complications. In patients transported within 3 days of admission for an MI, minor complications occurred in 50% of patients with a complicated MI versus 13% of uncomplicated MI patients. In patients transported 48-72 hours there were no complications in uncomplicated group and only in one patient with a complicated MI (no data available on patients transported <48 since last chest pain). **Need for analysis of en route complications based on time to transport, pre-flight physiologic state (complicated/uncomplicated) and preflight care (e.g., thrombolytics).**

An important aspect of gap analysis is to consider the requirements for en route care at sea. A case study[370] reports on the 2013 evacuation of a patient who suffered a myocardial infarction complicated by hemodynamic instability while onboard an aircraft carrier without capabilities to perform any reperfusion therapies. The patient was transported via helicopter (300 miles) with the Flight Surgeon and a rescue corpsman in attendance. During the flight, the patient was treated with sublingual nitroglycerin, morphine and IV metoprolol despite hypotension. The flight was complicated by the loss of the peripheral IV, necessitating placement of an external jugular line (no intraosseous equipment available). No description of en route monitoring or sequelae was provided, other than a comment on the inability to auscultate. The patient ultimately underwent interventional cardiology with an ejection fraction of 45%. No specific information was provided regarding time from initial presentation to transport, time of transport or time to definitive therapy. A report from the French Navy[371] provided results that are generalizable to the acute transport of patients. From 2001-2009 there were 286 helicopter medical evacuations at sea (average distance 72 miles, transport time 32 minutes at 1500 feet), with 132 evacuations for trauma and 154 for medical emergencies. The patients were professional sailors or ferry passengers. Among the medical issues, acute chest pain was the most common cause (n = 36 missions). All patients were treated with a peripheral IV, monitoring and oxygen. There were two cardiac arrests, three patients required defibrillation, one patient received a thrombolytic and nine patients received anti-platelet medications. One patient desaturated during transport and one patient became hypotensive during winching. Of note, 42% of the initial diagnoses were revised, suggesting that the focus of this short transport should be considered therapeutic, but not diagnostic. Finally, a unique case[372] reported on the potential conversion of new onset atrial fibrillation during a catapult launch. During the launch, the patient was exposed to approximately 2.0G for 2.7 seconds. **This unique event highlights the physiological stress of the catapult launch, and identifies a gap related to consideration for the evacuation of other critically ill/injured patients from a ship.**

4.10.1 Cardiac Arrest. According to PMQ-R data there have been 100 events of cardiac/respiratory arrest over the past eight years, with a majority of the patients with polytrauma. However, no systematic analysis has been completed of these events to differentiate the cause of the arrest (respiratory versus cardiac versus PEA), the timing of event (e.g., in-theater, intra-theater), outcomes or the patient status (DNR).

4.10.2 Cardiac arrest – Cardiopulmonary Resuscitation. In the event of a cardiac arrest the current AHA Advanced Cardiac Life Support (ACLS) guidelines[373] recommend immediate cardiopulmonary resuscitation (CPR) followed by defibrillation for a shockable rhythm followed by two more minutes of CPR. For a pulseless electrical activity (PEA) arrest, CPR is continued. AFI 48-307: Aeromedical Evacuation Patient Considerations and Standards of Care (2017) specifies adherence to the current ACLS guidelines. Air Force Instruction 11-2AE, Volume 3: Aeromedical Evacuation (AE) Operations Procedures[374] specifies that a patient may be defibrillated on a litter with aluminum handles or moved to the aircraft deck, with a blanket placed under the patient. There are no instructions on strategies to optimize cardiac compressions.

An animal model of CPR under field conditions[375] was used to determine if there was a difference in the efficacy of CPR on the standard NATO (canvas) litter, the decontamination (mesh) litter with and without a backboard, and a hard surface (control). Outcomes included end-tidal carbon dioxide level ($ETCO_2$), coronary perfusion pressure (CPP) and return of spontaneous circulation (ROSC). After four minutes of ventricular fibrillation, CPR was initiated for eight minutes followed by defibrillation (periods based on average times reported in research on pre-hospital resuscitation and recommendation that to be effective CPR must be initiated within four minutes and defibrillation within 12 minutes). There was no difference in the efficacy of CPR on the NATO litter with/without the backboard with the chest positioned over the cross-member strap on the litter, mesh litter with a backboard and hard surface. However, $ETCO_2$ and CPP were significantly lower on the mesh litter without a backboard compared to all other surfaces and ROSC was lower on the mesh litter compared to the NATO canvas litter. These results indicate the need for a backboard when performing chest compressions on the mesh litter. A follow-on study was conducted to determine if there was a difference in the rate of ROSC if CPR/ACLS was initiated immediately on the NATO litter without a backboard versus a two-minute delay with CPR/ACLS on a hard surface (simulation of movement of the patient from the litter to the floor). In this study two minutes of ventricular fibrillation was followed by immediate CPR/ACLS on the NATO litter without a backboard (simulate conditions in field) compared to a hard surface with delayed onset (2 minutes ventricular fibrillation followed by 2-minute delay to simulate movement of the patient off the litter to the floor) before initiation of CPR. In the NATO litter group (2 minutes ventricular fibrillation without delay), ROSC occurred in 13/15 (87%) animals compared to ROSC in 7/15 (47%) animals in the hard surface with 2-minute delay. These results indicate that if moving a patient is necessary (safety or access concerns), defibrillation should be attempted before moving the patient and are consistent with previous research that demonstrated a 5-10% decrease in survival for every one-minute delay in the onset of CPR. This research and current practice represents a gap in the research and education and practice for en route care as well as pre-evacuation ground care. A study by Barazanji[376] explored the ability to perform tasks on a MEDEVAC helicopter based on the spacing between the litter pans. With a 37-inch separation between liters, 4/15 test participants correctly performed CPR. **A similar study, describing required care related tasks and the ability to perform these tasks based on litter separation may be warranted for en route care, with consideration to conditions requiring the transport of a larger number of patients (i.e., what is the minimum space between litters/maximum number of litter patients).**

4.10.3 Targeted Temperature Management Post-Cardiac Arrest. A case study of a casualty suffering a blunt trauma cardiac arrest (*commotio cordis*) with post-arrest induction of targeted temperature management. The patient was transported approximately nine-hours after arrival at Balad. En route the CCATT team maintained hypothermia (32.4-32.6°C) by turning off the heat in the cargo compartment, uncovering the patient and administering refrigerated IV fluids. The patient had hypotension, which was treated with norepinephrine. The patient was maintained on Propofol and vecuronium to prevent shivering. There was no hypoxia (ventilated with 50-60% oxygen at a cabin between 6000 to 7000 feet). Considering the equivocal evidence on the optimal temperature for post-cardiac arrest targeted temperature management, **further review of civilian literature is warranted to identify possible strategies to support long-distance en route care in the post-cardiac arrest period. Consideration should also be given to research related to the induction of hypothermia in trauma patients at increased risk for coagulopathies.**[377]

4.10.3.1 Cardiac Pacemaker. There was one case report of the use en route of improvised transvenous cardiac pacing in response to unstable bradycardia/asystole arrest after failure of transcutaneous pacing.[378] This case report recommends that resources be available in theater to support transcutaneous pacing. However, there are insufficient data to determine the need for this therapy.

4.10.3.2 Cardiovascular Considerations in Disaster. Consideration should also be given to evacuation from disasters. For example, after the Great Hanshin-Awaji earthquake in Japan in 1997 there a 3.5-fold increase in MIs.[379-381] Similarly there was an increase in the incidence of myocardial infarctions and sudden cardiac arrest after the 1989 Loma Prieta earthquake in California,[382,383] and the 2001 Nisqually earthquake in Washington state.[384] and Hurricane Sandy.[385] The results of studies on the incidence of cardiovascular events (myocardial infarctions, unstable angina, sudden death) after September 11, 2001 were equivocal, with some studies reporting an increase and other studies reporting no difference when controlling for seasonal variations.[386-389] These studies suggest a potential gap related to characterizing the types of non-trauma patients who may require immediate care and evacuation associated with a disaster.

4.10.3.3 Cardiovascular Effects of Stresses of Flight. Smith[361] published an excellent review of research related to the stresses of flight and flight for individuals with cardiovascular disease. Although this paper was developed to inform civilian transport recommendations, it should be referenced for all studies related to this patient population. There was an inverse relationship between CO and simulated altitude.

There is limited research on the relationship between hypoxemia and cardiovascular function. In 24 ambulatory patients with existing ischemic heart disease who were evacuated in PACOM, the SpO2 decreased from 97% (ground) to 91% at altitude.[390] The decrease in SpO2 was not predicted by age, smoking history, preflight spirometry, or cabin altitude achieved. No patients reported cardiac symptoms and only 5/24 had an SpO2 < 90% (three treated with supplemental O2).

An older study evaluated the effect of isocapnic hypoxia on cardiac output (CO) in healthy subjects.[391] There was a negative dose-response curve between CO and SaO2, with the change in CO directly related to increases in HR (Table 13). Of interest was the lack of a respiratory response, which was consistent with the observation in Johannigman's study[171] related to hypoxemia.

Table 13. Hemodynamic and Ventilatory Response to Hypoxemia[391]

SaO2	99% (100% O2)	97% (RA)	90%	85%	80%
CO (L/min)	6.8 ± 0.5	7.0 ± 0.5	7.1 ± 0.5	7.9 ± 0.5	8.4 ± 0.5
Stroke Index (ml/min^2)	60.6 ± 4.3	60.4 ± 4.3	55.7 ± 4.3	60.1 ± 4.3	60.7 ± 4.3
HR (beats/min)	61 ± 2.8	63 ± 2.9	70 ± 2.8*	72 ± 2.8*	75 ± 2.8ǂ
RR (breaths/min)	16.3 ± 1.1	17.1 ± 1.1	17.3 ± 1.1	16.6 ± 1.1	16.8 ± 1.1
ETCO2 (%)	5.0 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.2 ± 0.1	5.1 ± 0.1

*p < .005 compared to 100%, 90%; ǂp < .005 compared to 100%, RA, 90%

Under simulated conditions and during commercial air travel the pulmonary artery pressure is significantly higher at altitude. In healthy subjects,[392] there was a progressive increase in the PA pressure (5 ± 1 mm Hg), with an 18% increase (peak 35 ± 1 mm Hg) at 8,000 feet. In these subjects, there was no change in HR or CO. During commercial air travel in healthy subjects, the PA Systolic pressure increased 6 ± 1 mm Hg to 33 ± 1 mm Hg (20% increased) at a cabin altitude of 5840-7170 feet.[393] In a single case of an individual with hypoxic pulmonary vasoreactivity, the PAS pressure increased 50% to a peak of 45 mm Hg during a 6-hour commercial flight.[394]

In healthy subjects and individuals with coronary artery disease, the heart rate and rate-pressure product increased significantly with exposure to normobaric hypoxia (4500 meters for healthy subjects/2500 meters for individuals with CAD), indicating increased cardiac workload.[395] In the CAD group there was also a significant decrease in cardiac reserve during exercise, and increased ST segment elevation indicating potential activity intolerance at 8,000 feet. In a study by Veglio,[396] healthy subjects (children, adults, older adults) were studied at sea level and at 2950 meters. Measurements included routine vital

signs at baseline and 1 and 24 hours after altitude exposure (transported by 30-minute gondola ride), 24-hour blood pressure, corrected QT interval, pulse oximetry, and HR and BP changes indicative of sympathetic-parasympathetic tone. There were small increases in SBP, DBP and HR at altitude, and after 1 hour at altitude a decrease in SpO2 from 95%-96% to 88.5 ± 1.7% in the children, 93.5 ± 2.2% in the adults and 91.4 ± 3.6% in the older adults. An interesting finding was the circadian pattern of the 24-hour blood pressure. A cursory evaluation of the data graphs indicates retention of the circadian pattern, despite the increase in BP. **Although there is research on the effects of airline travel and critical illness on circadian rhythms (cardiovascular, endocrine, immune), there are no studies on the effects of long-distance transport on ill/injured casualties.** This study did not demonstrate a change in sympathetic tone with altitude exposure (using indirect measures), although other studies using higher altitude exposure demonstrated changes in HRV.[397] The interactive effect between hypobaria/hypoxia and sympathetic/parasympathetic tone has implications for en route monitoring using HRV as an indicator of physiologic stress (e.g., hemorrhage).[398,399]

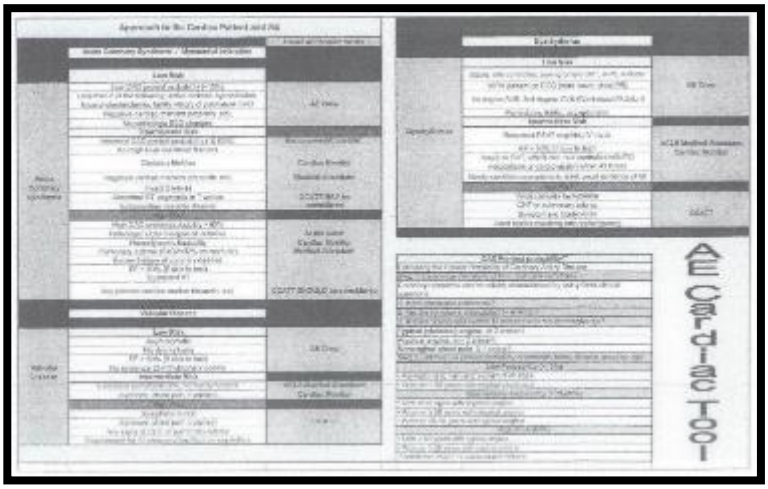
Supplemental oxygen is routinely used to treat patients with cardiopulmonary compromise during en route care. A study[400] in healthy subjects explored the effects of normoxia, hypoxia and hyperoxia under conditions of normocapnia on cardiovascular parameters.[400] During hypoxia (average SpO2 86.6 ±1.0%, the HR (mean 11.7 ± 0/8 beats/minute; 18.2 ± 1.2%), which resolved with correction of the hypoxia. During hypoxia, the cardiac index increased (mean 0.80 ± 0.08 L/min/m2; 20.2 ± 1.8%) and SVRI decreased (mean - 3.24 ± 0.27 arbitrary units; 15.2 ± 1.2%). In contrast, hyperoxia (end-tidal O2 79.6 ± 2.0%) was associated with bradycardia, stroke index (-7.3 ± 1.3%) and cardiac index decreased (-10.3 ± 1.7%) and SVRI increased (mean 3.82 ± 0.46 arbitrary units; 18.9 ± 1.9%). These hemodynamic changes were sustained for an hour after return to normoxia. Neither hyperoxia or hypoxia significantly affected markers of antioxidant activity. Analysis of CCATT data for the clinical response to hypoxic events during AE with the administration of supplemental O2 (risk of hyperoxia) is warranted to guide clinical practice recommendations.

4.10.3.4 Gravitational Forces. Although there is a large body of literature related to high G force exposure consistent with fighter aircraft, there is only one observational study[401] of the effects of G force exposure as an orthostatic stress and one case study relevant to the G-force (acceleration/deceleration) exposure during AE. An observational study to quantify orthostatic stress (as measured by changes in heart rate) was undertaken using G force parameters from AE and civilian aircraft flown in Denmark. These data are important as no research studies were found to provide this information for US aircraft used for AE. These data were replicated in an ambulance. With the feet forward with 0.45-0.8G exposure for 2.5-4.5 seconds, the average heart rate increased from 73.9 to -83.4 beats/minute. With the head forward with 0.45-0.75G exposure for 2.6-4.5 seconds the heart rate decreased from 75.6 to 64.4 beats/minute. When the subjects were positioned transverse with 0.35-0.75 G exposure for 2.6 to -5.7 seconds, there was no change in heart rate (65 to 67.2). These changes were consistent with expected gravitational forces and resulted in a modification of positioning of patients on Royal Dutch Air Force transports. A limitation of this study was the use of ground based simulated exposure. No studies have been found in US AE to replicate this work. In a series of six patients undergoing civilian AE transport on a Lear Jet (positioned head to the front of the aircraft), there was a decrease in SBP and MAP and systemic vascular resistance with ascent at 500 feet/min; HR was unchanged and stroke distance (a linear index of stroke volume) varied from -7% to + 68% in patients and -55 to 28% in healthy crew members.[402] The hemodynamic changes were not deemed clinically significant. A case report[364] summarizes the hemodynamic status of a patient with a biventricular assist device (BiVAD) who underwent a 12-hour transport on a civilian fixed wing aircraft (Gulfstream III) from Great Britain to the US (cabin altitude 6000 feet). The patient was positioned head aft, with the BiVAD pumps at knee level. During takeoff (30 seconds of climb) the flow in both devices decreased 33% (from 4.35 L/min to 2.8 L/min) with a return to baseline associated with the patient auto-flexing their calf muscles. The decrease in flow did not generate a tachycardic response. During landing, the abrupt deceleration was associated

with an increased in flow (4.3 to 5.2 L/min – RVAD; 4.5 L/min to 5.1 L/min – LVAD). The increase in flow resolved within 30 seconds after completion of braking. The hemodynamic changes were thought to reflect gravitational effects in a patient with probable hypovolemia. Pre-post flight vital signs were not significantly different. Two more cases represent more extreme exposure to gravitational forces. One case describes the spontaneous cardioversion of atrial fibrillation during the acceleration phase of a catapult launch off an aircraft carrier.[372] The second paper[403] reports on a centrifuge experiment in two older men (75 and 79 years old) with histories of atrial fibrillation and implanted dual-lead, rate-responsive pacemakers. The subjects completed +Gz runs (peak +3.5Gz and +6Gz) without any physiologic sequelae, including acceleration-related arrhythmias. Note, this latter experiment exceeds the acceleration forces associated with take-off/landing in AE; although there are no published documents describing acceleration/deceleration forces during AE. In a study by Johannigman,[167] G forces during takeoff (backrest 30-degrees/feet aft) were approximately 0.4 to 1.0g (based on graph) during takeoff and minimal during deceleration and landing. Similarly, in helicopter transport the mean peak was from 0.32g to 0.83g.[404] A case study by Ehlers[405] of a patient with ARDS described the hemodynamic changes during ambulance and fixed wing transport as measured by the PiCCO monitor (CI, SV, MAP, HR, systemic vascular resistance index [SVRI], global end diastolic index [GEDI], intrathoracic blood volume index [IBVI], extravascular lung water index [EVLWI], and stroke volume variation [SVV]). The IBVI decreased during takeoff and increased during landing, but there was no flight variation in EVLWI. The SVV varied between 9% - 12% during the flight (no information on ventilator parameters limits interpretation of the SVV). A ground-based study,[406] which explored the relationship between acceleration/deceleration in an ambulance and observed changes in blood pressure, found that the position of the transducer relative to the catheter site affected the reported blood pressure. In the lab setting, the position of the transducer relative to the insertion site (head of bed or next to insertion site) and tubing length (100 to 150 cm) were associated with significant pressure variations during acceleration and deceleration (-0.2g to 0.2g). Similarly, in six patients, when the transducer was positioned on top of the arterial cannula there was no relationship between acceleration and pressure variation (r = .09) in contrast to when the transducer was positioned at the head of the stretcher (r = 0.5). **This finding of artifactual variation in blood pressure versus physiologic response needs to be confirmed during transport, particularly in patient with potentially altered cardiovascular response or who may be affected by blood pressure variability.**

Gap- Circulatory Disorders

- ***Characteristics (low/moderate/high risk for ACS/MI – see AE Cardiac Tool developed by Steinkraus)[407] and outcomes (initial diagnosis/confirmed diagnosis) for patients evacuated for circulatory disorders (e.g. ACS/MI and cardiac arrhythmias)***
- ***En route care (care provided, complications/adverse events – See Saenger[368])***
  - ***Preflight order for supplemental oxygen adjusted for altitude – incidence of en route hypoxemia requiring supplemental oxygen greater than anticipated/ordered***



- *Factors (stresses of flight, preflight preparation) associated with adverse events (e.g., failure to order supplemental oxygen in an at-risk patient)*
- ***Describe acceleration forces during standard ascent/descent and combat maneuvers and cardiovascular response***

4.11 En Route Care – Infection

Research gaps related to en route care and infections address two major areas: 1) infection transmission and prevention in en route care and 2) the relationship between en route care and the exacerbation of infections

4.11.1 Infection Transmission and Prevention. There is no standard definition of en route related infections, thus, the incidence of en route related infections is not known. Murray postulated that the delayed evacuation of non-US personnel creates a reservoir for infections, with colonization of US casualties who are rapidly evacuated.[408] Studies from earlier in the war have demonstrated the importation of multidrug resistant organisms to medical facilities in the US and UK.[409-416] A 2010 study of US troops evacuated from Iraq and Afghanistan, found that Acinetobacter *baumannii* was the prevalent isolate. At one-week post injury there was bacterial isolation in 28% of the wound biopsies, 31% at second week and 37% at $\geq$ third week. [415] Overall the study found that most of the wounds did not have a significant bacterial burden upon arrival to CONUS. No data were presented on en route care or time from injury, to explore relationship between en route stresses of flight (hypoxia) and contamination or infection. A limitation is that none of these studies address any aspects of en route care, including time to transport. However, given the high incidence of casualties who are colonized at the time of transport these studies have implications for the potential effects of the en route care environment on the exacerbation of colonization/infection and the provision of en route care (including infection prevention strategies) to mitigate infections/infection transmission. Linking studies of en route care with data from TIDOS and the Armed Forces Health Surveillance Branch (https://health.mil/afhsb) is warranted. In addition, disease transmission associated with the evacuation of patients from other regions of the world has not been reported.[417]

Analysis of infection rates in casualties from Iraq (2003-2006) infectious complications in approximately one-third of patients (wound, pneumonia).[418] The Trauma Infectious Disease Outcome Study (TIDOS),[419-421] which is a prospective observational study, provides the most complete data on outcomes associated with infections. An initial TIDOS report included 356 wounded/injured patients at LRMC and 192 patients at CONUS MTFs. Among these patients there were 133 unique infectious disease events. Trauma-related infections were documents in 5.9% (n = 21) at LRMC and in 24.5% (n = 47) at Level V MTFs. At LRMC the most common infection among patients admitted to the ICU was pneumonia (10.6%). At the CONUS MTFs the most common infections were wound infections (17.7%), blood stream infections (8.9%) and osteomyelitis (8.9%). An important finding reported in preliminary data was the time to the first infection from the initial trauma (Table 14).

Table 14. Time in Days to 1st Infection from Initial Trauma, Median (IQR)[421]

Pneumonia	3.0 (2.0-4.0)
Bloodstream infection	7.5 (4.0-11.0)
Osteomyelitis	12.0 (8.0-27.0)
Skin and soft tissue infections	13.0 (7.0-22.0)
Any infection	6.5 (3.0-12.0)

A limitation of this study is that it does not describe the time to admission from injury, if colonization or the infection were present before transport, or the number of days post-transport. Thus, it is not clear if the infection was the cause of the evacuation (i.e., pneumonia) versus an adverse event (e.g., BSI, SSTI). No information on en route care was noted. These data have been used to population a registry attached to the JTTR, and should be integrated into studies related to en route related infections. These findings are important as they demonstrate the number of patients being evacuated who are colonized or infected.

A study[422] of adherence to the antibiotic prophylaxis clinical practice guidelines[423] found adherence rates as low as 75% in patients with soft tissue trauma. However, the study did not include any data from the en route phase of care. The JTS CPG: Infection Prevention in Combat Related Injuries (CPG ID: 24)[424] provides guidance on the administration of antibiotics for post-injury/delayed evacuation as suggested by the CoTCCC, but it does not address any aspects of infection prevention during en route care. There are also a series of papers related to infection prevention for combat-related injuries.[425,426] [416,427] However, all of these reports and guidelines are specific to ground based care. Only AFI 48-307[268] outlines standard infection control guidelines during AE. A gap is that **no studies have been conducted to evaluate adherence to the JTTS CPGs or AFI 48-307.**

4.11.2 Pulmonary Infections. The incidence of pulmonary infections is dependent upon the definition used, with between 3.7% to 8.5% of combat casualties with documented pneumonia.[418,419] In the TIDOS study, pulmonary infections were the most common infections among patients admitted to the ICU at LRMC in 2009-2010.[428] In this cohort there were 36 patients (8.5%) who met criteria for pneumonia. Among these patients 30/36 (82%) were on mechanical ventilation within 48 hours of diagnosis (ventilator associated pneumonia). **A limitation of this study is that no information on en route care (including adherence to VAP prevention guidelines), the timing of the diagnosis of pneumonia/VAP relative to transport, and the continuation of intubation for transport were not reported. Thus, exploration of the relationship between time to transport, en route care and the occurrence of pneumonia is not possible.**

The JTS CCATT CPG: Mechanical Ventilation[429] includes for VAP prevention, including backrest elevation (30 degrees), chlorhexidine (not specific frequency) and oral care every 4 hours if workload allows. These recommendations are consistent with the JTS CPG: Ventilator Associated Pneumonia,[430] which recommends every four hour oral care with chlorhexidine and backrest elevation, along with other general infection prevention strategies (e.g., hand hygiene, chlorhexidine bathing). No studies have been conducted to evaluate adherence to these guidelines during the en route phase of care. Of note, a recent study[431] related to pressure injury prevention noted that maximum backrest elevation achieved on the NATO litter was 24 ± 4.5° (range 18-28°), thus it is not possible to achieve the recommended backrest elevation given the current litter/backrest. The potential effect of continuing intubation for transport versus extubation should be considered as a risk factor for en route exacerbation of VAP. The aggressive adherence to guidelines to prevent VAP under deployed conditions (Balad) was associated with a significant decrease in VAP per 1,000 ventilator days from 60.6/1000 in May 2006 to 11.1/1000 ventilator days in August 2006. [432] These data are important as they provide baseline data to control for the effect of en route care on VAP and demonstrate the feasibility of strict adherence to prevention guidelines under austere conditions. No research has been conducted to evaluate adherence to VAP prevention guidelines during en route care.

4.11.3 En Route Care Specific Guidelines. The Guidelines for the Prevention of Infections Associated with Combat-Related Injuries: 2011 Update[426] contain only three recommendations specific to en route care: bandaging of the wound during initial care/transport from the field, administration of supplemental oxygen during transport, and use of negative pressure wound management (Table 15). The summary table provides recommendations only by ground-based level of care, with recommendations only related to care

if evacuation is delayed. The recommendation related to the administration of supplemental oxygen during transport were based on extrapolation of civilian research related to surgical site infections.

Table 15. Summary of En Route Care Related Recommendations for Infection Prevention from 2011 Guidelines for Prevention of Infections Associated with Combat-Related Injuries[426]

Initial Care in the Field	• Wounds should be bandaged with sterile dressing and fractures stabilized before transportation to higher level of care (IB) o Given the unpredictable nature of casualty evacuation in a combat zone, point-of-injury antimicrobial agents should be provided if evacuation is delayed or expected to be delayed (**IC**). • Provide single-dose point-of-injury antimicrobials if evacuation is delayed or expected to be delayed – based on TCCC recommendations (**IC**)
Should Supplemental Oxygen be Provided During Transportation of the Wounded to Medical Facilities Outside the Combat Zone?	• During aeromedical evacuation, supplemental oxygen (to maintain oxygen saturation _92%) may be beneficial in patients with combat-related injuries (IIC).
Can NPWT be Used in the Management of Combat-Related Wounds?	• NPWT should be used in the management of open wounds (excluding CNS injuries) to include during aeromedical evacuation of patients (IB). o NPWT is effective in the management of open wounds (excluding CNS injuries) to include during aeromedical evacuation of patients out of the combat zone. Battery power may be a limitation to its use on longer transports (_8–10 hours)

The JTS CPG: Infection Prevention in Combat Related Injuries[424] uses a similar structure, but does not include the recommendation related to the use of supplemental oxygen, nor does it contain any reference to en route care. A recent analysis[433] was conducted of evaluate adherence to the recommendations for post-injury antibiotic prophylaxis for the period 1 Jun 2009 to 31 May 2014 was conducted as part of TIDOS. Among the 5,916 military personnel admitted to LRMC during this period, the most common injuries requiring prophylaxis were open fractures (27%), skin and soft tissue trauma (25%) and closed injuries (i.e., no evidence of open injury) (24%), maxillofacial (9.1%), penetrating abdomen (4.7%).

An area for research is to explore the use of en route supplemental oxygen (adherence with the guideline recommendation), the relationship between en route SpO2 and wound infections for both CCATT and AE patients, controlling for time from injury. Extension of Lloyd's study[422] on adherence to antibiotic guidelines during the en route phase of care is required (continuation, timing of medications). Further updates to these guidelines should address en route care considerations. There is limited research on the relationship between en route care and short and long-term outcomes. Integration of data from the Trauma Infectious Disease Outcomes Study (TIDOS)[419-421] and collaboration with the Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study Group (https://intranet.idcrp.org/public/research/trauma-infections) may address this gap.

Disaster Evacuation. Evacuations in response to a humanitarian crisis/disaster presents a challenge to the prevention of infection transmission. Maegele[434] discussed the injuries, including bacterial contamination in 17 patients evacuated by the German Air Force after the 2005 tsunami. Injuries included large soft-tissue trauma of lower extremities (88%), upper extremities (29%), and head (18%). The victims also had thoracic trauma with hemopneumothorax, rib fractures (41%), extremity fractures (47%). Wounds were

contaminated with Pseudomonas 54%, Enterobacteria 36%, Aeromonas spp. 27%, and 18% with MDROs (Acinetobacter, ß-lactamase-positive E. coli). Additionally, the patients all demonstrated acute stress response. In a study[435] of 233 civilian patients who were hospitalized for 4-10 days in an international hospital and then evacuated to France, approximately 7% had a MDRO. These studies have implications for en route infection control, similar to military studies related to infection transmission across the continuum of care.

4.11.4 En Route Care – Exacerbation of Infections. As described in the section on soft tissue trauma and wound infections, there is increased bacterial growth in a complex wound in animals exposed to hypobaric hypoxia (simulated altitude 8000 feet for 7 hours). In contrast, bacterial growth was attenuated with the administration of supplemental O2 to maintain an SpO2 > 93%.[436,437] An interesting study by Makely,[143] which used a murine model of injury, did not find differences in cytokine concentrations, neutrophil recruitment or vascular permeability in mice in a simulated AE environment compared to ground controls. In a follow-on study,[113] an interesting finding was that there was a lower pneumonia rate in a murine TBI model exposed to simulated AE, which was consistent with civilian TBI research. The proposed mechanism is thought to be an alteration in Substance P.[438]

Gaps:

- ***Correlate en route SpO_2 and wound infections***
- ***Integrate en route care data with outcomes data from TIDOS (*****The Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study[439])**
- ***Mechanism – TBI-Pneumonia***
- ***Integration of en route care variables (time to transport, en route adverse events, adherence to standards and guidelines), timing of diagnosis of infection relative to transport (i.e., within 48-72 hours)***
- ***Infection transmission in en route care***

4.12 Highly Contagious Infections

Several regulations provide general guidance on the transport of patients with a communicable infectious disease. AFI 48-307 v1[269] has general recommendations, including patient positioning relative to aircraft airflow, restrictions on the use of the C-17, C-21, and C-130 for the transport of patients with airborne agents, and the use of personal protective equipment. The US TRANSCOM Handbook 41-1,[440] provides an overview of transport capabilities using the Patient Isolation Unit and Transport Isolation System and outlines patient movement of contaminated or contagious patients, specifically:

> Patients with a known or suspected Center for Disease Control "Category A" highly contagious disease (Ebola, Plague, Smallpox), and patients with an unknown potentially contagious disease (weaponized/novel), where adequate infection control measures are not well defined or feasible, will not be moved within AE system.

NATO Standard AAMedP-1.1. Aeromedical Evacuation[441] also provides general guidance on the transport of patients with a highly communicable infectious disease and high-level containment care. The Air Mobility Command CONOPS for AE of EVD Exposed Asymptomatic, Non-infectious Patients and Symptomatic Infectious Patients[442] presents a detailed plan for transport, and specifies a timeline to train AE personnel, with transport capability established in 2018-2020. The TIS has passed airworthiness testing and is now available for use.[443]

Until recently there was little published on the transport of patients who are contaminated or are contagious. Several papers summarize the epidemiology of AE for infectious diseases (e.g., malaria, HIV/AIDS, Q fever. etc.). Based on reports from US, France, and Poland, approximately 0.5-2% of medical evacuations were due to infectious disease.[47,51,69,70,444,445] Lamb[446] summarized the general principles of en route care in a mission in 200X to repatriate a patient with Lassa Fever to Great Britain.

A study of individuals who flew on seven US-bound flights carrying SARS patients was conducted. Among the 1766 passengers and 339 crew, 312 individuals completed a questionnaire and 127 provided a blood sample. Serology was negative for all 127 participants, including three of four who met the clinical case criteria for SARS, and the fourth had a mild illness that lasted only 5 days. Although this study suggests that the risk of transmission is not increased by the aircraft environment, the generalizability of the results is limited by the small sample size. A second study[447] identified an increased risk for infection in passengers seated within three rows in front of an index case (fever x 4 days, with exposure to family member with SARS) (RR 3.1, 95% CI 1.4-6.9). In contrast on a second flight carrying four symptomatic individuals (all had been on the previously described flight), only one possible transmission occurred and no transmission occurred on a flight with a single asymptomatic individual. The results suggest the risk is associated with the stage of the infection in the index case and proximity. The results of this study emphasize the need for pre-flight screening and isolation of individuals at risk and en route infection prevention strategies (i.e., availability of alcohol hand gel for all passengers and crew, which is consistent with the 2004 ASMA guidelines.[448]

More recently, papers have described the planning, pre-hospital care and the transport of patients with highly contagious diseases, such as Ebola Virus Disease (EVD). A summary of operational research conducted in facilities supported by Médecins Sans Frontières (MSF) exemplifies challenges associated with the conduct of research during a humanitarian crisis.[449] A limitation of this report is the absence of any discussion regarding the transport of these patients. In 2014-2015 Operation United Assistance was completed in support of the Ebola epidemic in Liberia. Specific guidance on the care of patients exposed to or with Ebola was provided on the Centers for Disease Control website (https://www.health.mil/Military-Health-Topics/Health-Readiness/Pandemic-Diseases/Ebola/Military-Medical-Information-on-Ebola/Information-for-Healthcare-Workers) and in personnel policies/information from the Joint Chiefs of Staff (CJCSI 4220.01) and the DoD.https://www.health.mil/Military-Health-Topics/Health-Readiness/Pandemic-Diseases/Ebola/Military-Medical-Information-on-Ebola.In a Joint Forces document[450] summarizing the army role in support of Operation United Assistance, a lack of designated evacuation aircraft (referred to as MEDEVAC) was identified as a limitation. No details on the 15 missions to evacuate patients to LRMC was provided. None of these documents addresses en route care of these patients. An older article[451] refers to the USAMRIID aeromedical isolation team, but it does not appear that this capability still exists, with the 2012 decommissioning of the containment unit at USAMRIID.[452]

The British Royal Air Force plan for the transport of patients with EVD [453] includes a discussion of the types of procedures feasible during transport given the risk of contamination, plans for ground transport (including security), decisions related to the need to stop and perform procedures during ground transport, handoff at the aircraft, and en route care onboard C-17 (available drugs and equipment), potential impact of the stresses of flight and plans if the patient deteriorates (no capability for intubation or mechanical ventilation), and ground transport in the ATI. In contrast, the AMC CONOPS[442] for the transport of EVD patients outlines roles for cardiac arrest response, but similar to the British the equipment list includes only nasal cannula – nonrebreather mask, but no intubation or mechanical ventilation supplies.

A unique aspect of the transport of patients in the ATI is the risk for motion sickness. A study by Lucertini[454] described the triaxial acceleration parameters experienced inside an ATI during a test flight. These parameters were applied to the method described by Lawther-Griffin[455] to predict motion sickness and vomiting. Based on these parameters it was estimated that there was a low risk (~2%) for motion

sickness inside the ATI. Rather than administer prophylactic antiemetics to all patients, a preflight assessment of the patient's risk (i.e., previous history of high sensitivity to motion, infection-induced gastric disorders, or residual signs/symptoms of motion sickness associated with the ground transport). This method was applied to a patient evacuated in the ATI, with the determination that the patient was a low risk. No antiemetics were administered and the patient did not suffer motion sickness during the transport. No other literature was found addressing en route motion sickness**. A model[455,456] could be used to evaluate the risk for en route motion sickness. Inclusion of pre-screening for motion sickness should be documented in TRAC^{2}ES (no description exists on the incidence of motion sickness during en route care), with an analysis of administration of antiemetics in low versus high-risk patients.**

Two papers summarize the transport of patients with high contagious diseases (Ebola Virus Disease, Lassa Fever)[457].[458] The Italian Isolation Team has transported three patients (2- EVD/1 disseminated Herpes Virus). The two patients with EVD were stable (no details were provided of en route care) and the patient with disseminated herpes virus deteriorated during transport and required intubation and ventilation. A limitation of the report is that no specific details of en route care of the logistics associated with intubation in a closed system were described. The second report was a civilian transport from Sierra Leone to Sweden for a patient with Lassa Fever. No details of the en route care was provided, but a discussion of the limited capability to care for an unstable patient was presented.

A consistent theme in all the papers is the limited ability to care for a patient who is deteriorating, with a comment specific to the level of monitoring provided and airway management (no capability to support mechanical ventilation). A paper by Clay[459] provides case vignettes and discusses ethical issues noted during the British response to the Ebola epidemic (Operation GRITROCK), and provides recommendations for ethical considerations. Two other studies[460,461] address ethical issues and the use of a model for ethical decision making under operational conditions. **Exploration of the use of an ethical model and vignettes related to ethical dilemmas experienced during the transport of these high-risk patients, to include limitations on care provided, is warranted.**

Withers'[462] paper is important as it summarizes research on the airframe as a microbial environment (airflow, humidity, air recirculation, air exchange rate, presence of stagnant airflow areas). A recent review by Mangili[463] presents an updated review of the literature related to the aircraft cabin, and outlines risk and risk mitigation associated with various infectious diseases (i.e., tuberculosis, SARS, MERS, influenza, measles, rubella, *Neisseria meningitidis*, Ebola Virus Disease, mosquito-borne illnesses, diphtheria, pertussis, multidrug-resistant organisms, and bioterrorism – small pox, plague, anthrax). An older study by Clayton[464] evaluated the environment on Canadian Forces aircraft (C-130, Boeing 707), using smoke patterns, contamination of a non-pathogenic organism, and the recovery of respiratory tract viruses on an international flight. The findings indicated that in the Boeing 707, contamination was restricted to the rear of the aircraft, whereas contamination occurred throughout the entire C-130. Two recent studies[465,466] on civil aircraft describe the methods to evaluate biological contamination. **Consideration of the use of these methods for current military aircraft potentially used to transport patients with infectious diseases is warranted.**

Gaps

- **Description of care provided en route for patients with highly contagious disease**
- **Ethical dilemmas experienced and use of standardized ethical approach to establish policy and inform pre-deployment preparation; translation of ethical lessons learned in ground-based facilities to en route care**
- **Code TRAC^{2}ES for infectious disease transports (see Lang[467])**

- **Incidence of en route motion sickness; delineation of high-low risk patients, use of anti-emetics (see Lucertini[454])**
- **Analysis of current policies/regulations specific to infection control – adherence for infection prevention (e.g., MDRO transmission)**
- **Description of aircraft risk environment (airflow, humidity)**
- **Preflight screening (adherence)**

4.13 Venous Thromboembolism (VTE)

The initial JTTS CPG: Prevention of Venous Thromboembolism was published in 2004, with updates in 2008 and 2012.[468] The CPG notes a civilian incidence of 8-10% of asymptomatic DVTs after an extended flight and a 20% incidence of pulmonary embolism in patients with a proximal DVT. The CPG recommends initiation of DVT prophylaxis (e.g., early mobilization, sequential compression devices, enoxaparin or unfractionated heparin) as soon as a coagulopathy is corrected, and a removable IVC filter is recommended if systemic prophylaxis is not possible. The CPG also notes that massive transfusion and hypothermia on arrival to a Role III hospital may be risk factors for developing a PE (no data provided).

4.13.1 Epidemiology. The Armed Forces Health Surveillance Center [469-471] reports on the incidence of DVT/PE during deployment and the first 90 days after returning from deployment with a peak incidence of 19.8/month in 2007 and 19.9 cases/month in 2011. However, these data do not provide a rate (#/at risk) or control for the presence of a risk factor or whether the individual required aeromedical evacuation. Hatzfeld[472] analyzed data from 2007-2009 from TRAC2ES and M2 to describe the incidence of VTE in patients transported in AE. The main finding was that U.S. military personnel (including active duty, guard and reserve members) age 25-31 who underwent aeromedical transport during 2007-2009 were at higher risk for developing a VTE than service members age 18-21, keeping rank and sex constant. However, the study was not able to control for any other variables (e.g., severity of injury, time to transport, prophylaxis). A limitation noted in this study was the incomplete or duplicate data in TRAC2ES and M2, which precluded a more complete analysis**. This latter issue highlights the importance of creating robust medical records to facilitate both medical care and research.**

In 1107 patients with burns admitted to the BAMC ISR (2003-2005), only 11/1107 (0.99%) developed a VTE.[473] There was no difference in incidence between burn casualties evacuated from Iraq/Afghanistan 5/381, 1.31%) compared to patients admitted from the south Texas region (6/726, 0.83%). The only risk factors in a multivariate regression that predicted the development of a VTE were ISS and ICU admission. Of note, the standard of practice at the BAMC ISR is to initiate chemoprophylaxis (enoxaparin or unfractionated heparin) on all patients at admission, although information on pre-admission prophylaxis during en route care was not reported.

In a study of combat casualties (OEF/OIF) admitted to WRAMC (2009-2011) there were 1288 admissions, with 29 patients with a VTE (2.2%) before admission (during triage or AE). Although there were differences in chemoprophylaxis and mechanical prophylaxis among the patients who did (n = 328) versus did not (n = 960) receive regional anesthesia, there was no increased risk for VTE at 30-days post-admission. No information was provided on patient position, en route activity or use of supplemental O2 during transport. In 231 patients admitted to the ICU at a CONUS MTF (2003-2004), 40 patients (17%) developed a VTE during hospitalization and five patients died (one due to a PE).[474] There was no difference in the development of a VTE in patients who did (16.9%) versus did not (17.8%) receive pharmacologic prophylaxis. Similarly, in 119 patients transported by AE to WRAMC (2003), there was a 1.7% incidence (two patients – neither received thromboprophylaxis during flight).[135] (Note, these studies were conducted before the 2004 institution of the JTTS CPG on DVT prevention). In a study[475] of 506 combat casualties admitted to WRAMC (2009-2011), 18 (3.6%) of patients had a VTE before admission

(coded as during AE). However, it was not clear when the VTE event occurred (before AE or during AE). The only risk factor for pre-admission VTE was unit of PRBCs (OR 1.84, 95% CI 1.2-3.0). The study was limited by an absence of data specific to en route care (e.g., flight information, time from injury to transport, en route thromboprophylaxis, supplemental O2, activity/position), thus direct attribution of events during the en route period is not possible. A subsequent letter[476] notes that rapidity of evacuation has resulted in transport (and exposure to hypobaric hypoxia and prolonged immobility) during the acute injury phase (first 48 hours), which is a period of increased risk for DVT development. However, both the primary study and the subsequent letter note the lack of information on en route prophylaxis limits this analysis. No studies have described compliance with the JTTS CPG for VTE prophylaxis (particularly are related to en route care), and as noted in the Hatzfeld study,[472] the lack of complete datasets restricts this analysis.

In contrast to the limited research in military patients, there is a large body of research related to civilian transport. A study[477] of 7,592 civilians undergoing long-distance commercial transport provides a baseline for comparison of incidence of en route related VTE. The odds of VTE in three individuals who had surgery within the past three months and VT was (19.8; 95% CI 5.6-70.1) compared to controls. Similarly, there was a 24.4-fold increase in risk for patients who traveled with a plaster cast. Other risk factors were oral contraceptives (OR 8.2; 95% CI 2.3, 28.7) and hormone replacement therapy (OR 6.8, 95% CI 1.4, 32.8). A meta-analysis[478] identified a 2-fold increased risk for VTE associated with air travel; however none of the studies included trauma or military patients.

4.13.2 Stresses of Flight and VTE. There is a large body of literature related to the stresses of flight and risk for VTE, all from the civilian literature. The three major potential factors identified in the literature associated with AE and risk for VTE are dehydration, hypobaric hypoxia and prolonged immobilization.[479-484] Chee[485] reviewed the research related to these factors and noted that there is a weak association between long distance transport and VTE; however there are few data to support a causal association between the combined stresses of flight (e.g., dehydration, hypobaric hypoxia) and thrombosis. Since Chee's review, several studies have been conducted to determine the relationship between stresses of flight (e.g., hypobaric hypoxia) and prolonged sitting and activation of the coagulation cascade. In healthy civilians, there was increased activation of the coagulation cascade after exposure to an 8 hour flight compared to 8 hours of sitting.[486] In contrast, in another study of healthy individuals exposed to hypobaric hypoxia in an altitude chamber compared to a 8 hours of normobaric hypoxia, there was no difference in coagulation or fibrinolysis.[487] **All of these studies related to prolonged immobilization in civilian literature refer to a seated position. Thus, generalizability of these results to AE can be applied only to those less seriously injured individuals able to sit during AE.** A recent study by Venemans-Jellema[488] evaluated the effects of prolonged supine position (60 days at -6°) or prolonged exposure to high altitude (6 months at 4000 m/12,800) without activity restriction in healthy subjects. In both cases there was no increase in coagulation activation. These studies indicate that in healthy individuals' exposure to hypoxia and immobilization (supine) are not associated with increased coagulation activation. A limitation of these studies, is that they involve healthy subjects or civilians during long-distance commercial travel or simulated travel. Thus, there is limited generalizability to the en route care of ill/injured patients. Schobersberger[489-492] concurred that hypoxia does not appear to be an independent risk factor, but suggested that psychophysiological stressors and chair design should also be considered as risk factors for the activation of coagulation.

<u>Gap VTE</u>

- ***Compliance with the JTTS CPG for VTE prophylaxis during en route care***
- ***Is there a high-risk period for coagulation activation during en route care (see Bendz[479,493]) – implications for timing of administration of LMWH***

- ***Temporal relation of events (time from injury to evacuation, en route care/risk factors – time of detection of VTE). Compare with civilian data for outcomes in high risk group (spinal injury, delayed or interrupted prophylaxis, age, surgery, blood product administration).***
- ***Effect of aircraft seats on risk for VTE (web-seats, C-17 fixed seats, leg room etc.)***
- ***Effect of standardized activity requirement for all seated patients on VTE (preventive activity – see Coppens[494])***

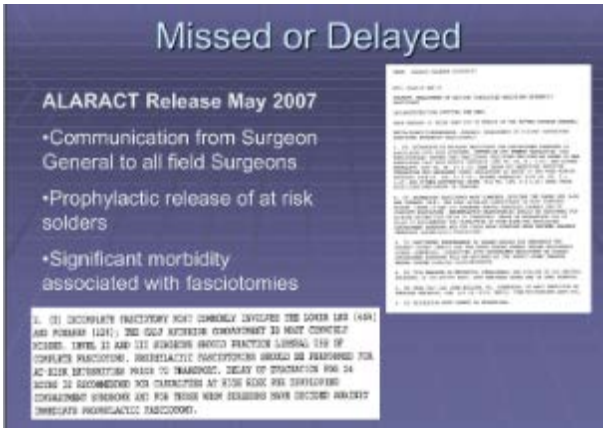
4.14 Soft Tissue Trauma/Orthopedics

This section addresses three major areas related to soft tissue trauma: 1) extremity compartment syndrome, negative pressure wound therapy, and immune response as related to soft tissue trauma

4.14.1 Extremity Trauma. As described in the epidemiology section, the most common injury type is musculoskeletal. From January 2003 to December 2011 there were 17,278 patients with extremity injuries in the JTTR. There are several reports related to the Military Orthopedic Trauma Registry (MOTR), which links to the DoDTR.[495,496] This registry provides in-depth orthopedic data, to include complications such as delayed amputations and heterotopic ossification. Currently, this registry does not include any information specific to en route care. In the future, it should be linked to the AER to evaluate factors related to en route care and long-term outcomes. As described in the section on pain, patients with orthopedic trauma, particularly those with external fixators have higher pain scores during en route care.[497] The 59th Medical Wing developed a report on the effect of flight on patients with extremity compartment syndrome.[175] The report cited 13 papers, however, none of the papers was related to flight. Gaps identified in the review were the need to explore the effects of vibration on the prevention of lower limb compartment syndrome and exploration of the thermal conditions and the effects of flight humidity levels on compartment syndrome. Two studies[498,499] explored the effect of the Army telemedicine program for orthopedic consults. Relevant to this gap analysis was the demonstrated provision of early consultation and a decrease in the number of patients requiring evacuation.

4.14.2 Extremity Compartment Syndrome. Among the 17,278 patients in the JTTR (2003-2011) with an extremity injury, 416 had documentation of compartment syndrome (current rate 9.4/1000) and there was documentation of 1414 fasciotomies (current rate 93.5/1000). There were 24 papers reviewed specific to the relationship between extremity compartment syndrome (ECS) and the hypobaric and hypoxic effects of en route care. Only five were directly related to en route care and the remainder provide baseline (normobaric) data. Additional papers discussed in the VTE section related to the effects of hypobaric, hypoxic and low humidity conditions also inform this section.

A commentary by a physician at LRMC[500] summarizing the rapid evacuation of casualties from the theater suggested that altitude (more specifically aeromedical evacuation) was associated with exacerbation of ECS. Ritenour's 2006 study[501] retrospective medical record evaluated differences in outcomes for patients with early (in-theater) versus delayed (performed at LRMC) or revised fasciotomies. Delayed or revised fasciotomies occurred in patients with more severe injuries (ISS), burns, vasopressors and fluid resuscitation (no data provided regarding en route care). The results of this study led to a policy change,[502] and the development of an education



program, with the latter associated with an increase in the rate of early but not late fasciotomies.[503] Of note, these studies were not designed to address the issue of whether altitude (or aeromedical evacuation) caused or exacerbated ECS. ***An identified gap was the need for case-control (patients who did/did not require delayed fasciotomy) or patients who did/did not develop ECS (early or delayed).***

Animal models have been developed to explore the relationship between hypobaric conditions and ECS. In a swine model using uninjured extremities,[504] there was a small (average 2.7 mm Hg) increase in intracompartmental pressures with ascent to 10,000 feet for 5 hours. An accompanying letter[505] posited several explanations for altitude associated ECS that may merit exploration: *(1) Is there an association between hypobaric injury to cells and the release of vasoactive substances that increase endothelial permeability and potentially increase tissue pressure? (2) What is the association between excessive fluid resuscitation and increased edema in injured muscle? (3) Does hypobaric environment consistent with AE induce the presence of reactive oxygen and alter oxidative stress[186] and can this effect be mitigated by antioxidants (i.e., Vit E)[506] or supplemental O2.*

Three studies have used animal models (rats, swine) to evaluate the effect of hypobaria on edema and ECS formation. In Ritenour's[507] study a rat model was used with a 2-hour ischemic injury (tourniquet) followed by 5.5 hours at 10,000 feet without supplemental oxygen compared to 6-hours at sea level. Results found no difference in severity of edema, inflammatory or anti-oxidant indicators. There was a loss of body weight under hypobaric conditions that was attributed to total body water loss (fluid status not monitored). These results suggested that hypobaric hypoxia did not contribute to increased edema. *Limitations of this study were the short ischemic period (versus 3-4 hours when edema formation is maximum), isolated extremity injury, no administration of supplemental oxygen, and no simulation of fluid resuscitation.*

Kalns[508-510] developed an animal model, to evaluate the effect of hypoxic hypobaria on ECS. All animals were exposed to increased intracompartmental pressures (balloon inflation) of approximately 145 mm Hg (30 mm Hg > MAP) for 5-6 hours, followed by an observation period of 8 hours at either ground level (770 feet) or simulated altitude (7000 feet). Post hoc the animals were characterized as ± ECS (MAP-ICP < 45 mm Hg), and muscle histology and proinflammatory cytokines were characterized. This model reflects exposure to a diffuse focal ischemic injury followed by the ± development of ECS, and subsequent exposure to hypobaric conditions in the immediate 8-hour period (e.g., AE 8-14 hours post-injury). Results indicate that the development of ECS has a threshold (diffuse ischemia ~6 hours), but exposure to hypobaric conditions immediately following this period (simulating AE) was not associated with increased incidence of ECS. However, some inflammatory mediators were consistently affected by hypobaric exposure: TNF, IL-1 b, IL-6, IGFBP5, and TGFB2 were increased ($P < 0.05$); FGF, IGF1, IGFBP4, BMP4, nitrotyrosine, and nitrate were unchanged. In limbs manifesting ECS, similar patterns were observed, except TNF-alpha and BMP-4 were not significantly different between hypobaric and normobaric conditions.

An animal model of hemorrhagic shock (direct exsanguination to 25 mm Hg with 60 minutes of shock) and resuscitation with LR or shed blood followed by simulated altitude exposure with hypobaric hypoxia (8,800 feet x 5 hours) at 1 or 24- hours post-resuscitation.[511,512] Although the hemorrhage and sham animals in the simulated altitude group had a significantly lower SaO2 at the end of the 5 hour exposure, compared to normobaric controls (600 feet), there was no significant difference in serum cytokines (granulocyte macrophage colony-stimulating factor IL-6, IL-10, MCP-1, MDC, MIP-1α, MIP-2), neutrophil recruitment or vascular permeability (organ injury) in the lung, ileum and colon. These results are important as they suggest that hypobaric hypoxia does to contribute to an increased infection risk due to altered immune response. Of, note – these results are different from another study by this team of investigators that found in a model of mild traumatic brain injury exposure to simulated AE 1 hour after injury resulted in secondary brain injury.[142] ***Further exploration may include a trauma model (versus***

exsanguination) with ongoing volume resuscitation under hypobaric hypoxia or hypobaria with supplemental oxygen and measurement of cytokines including ROS, and vascular permeability in the extremity.

4.14.2.1 Monitoring for ECS.
Near Infrared Spectroscopy – Skeletal Tissue Oxygen Saturation (StO_2). Ground-based research has demonstrated a potential use of near-infrared spectroscopy (NIRS) to detect ECS.[513,514] In a swine trauma model, NIRS was correlated with intracompartmental pressure under normal and injured extremity conditions.[514-517].

Intracompartmental Pressure Monitoring. As suggested by Kalns[508] intracompartmental fluid specimens may allow for metabalomic/proteomic analysis, which may be useful in exploring pathways in subjects with/without ECS.

4.14.2.2 ECS – Clinical Assessment/En Route Documentation. A study by George[*518*] titled "Documentation of Acute Compartment Syndrome During Medical Evacuation" found that there was poor documentation of signs and symptoms indicative of compartment syndrome in patients who subsequently required a fasciotomy. However, it was unclear if the study included inflight medical records to allow for delineation of onset, in contrast to use of pre-flight information included in the Patient Movement Request (PMR). ***This study suggests a need to standardize documentation/assessment requirements for patients at risk for compartment syndrome and further medical record review***

Research Gaps

- ***Included all patients with extremity trauma (not based on severity) – need to differentiate monitoring requirements and outcomes for CCATT vs. AE***
- ***Inadequate documentation related to patients at increased risk for compartment syndrome to facilitate continuity of care (evaluate critical information to communicate/standardize)***
- ***Effects of hypobaric environment on compartment syndrome (continue focus area – integrating multiple stresses of flight)***
- ***Correlation design (regression) to identify risk factors***
- ***Describe time frame for complications (when occurred, en route care)***
- ***En route compliance with established CPGs/standards***
- ***Enroute care (research reflective of transport environment, variable timing from injury, phase of care)***
- ***Mitigating interventions (en route focus – preflight/inflight interventions)***

Gaps – ECS:

- ***Effect of hypoxic hypobaria versus normoxic hypobaria on ECS[508,509] versus outcomes associated with supplemental oxygen administration (inflammatory markers)[507]***
- ***Control for threshold effect (case-control – casualties with prolonged unrelieved ischemic injury compared to < 6-hour resolution) followed by aeromedical evacuation (control for preflight care – e.g., MEDEVAC and volume resuscitation).***
- ***Effect of hypobaria at a later point post-injury (e.g., > 14 hours) on ECS – using variable time to transport***
- ***Is there a serial biomarker or physiologic indicator (e.g., StO_2) associated with progressive development of ECS, or a threshold indicator of increased risk for ECS?***
- ***ECS model[509,510] with crush injury (current animal model does not create a crush injury), primary blast injury or penetrating trauma controlling for en route volume resuscitation***

- ***Do altitude related stressors (hypobaria, hypoxia, vibration, humidity) and immobility have a differential effect on coagulation under conditions of extremity trauma?[487,519] and is there a variable effect in cases with/without ECS***
- ***Need to control for humidity during experiments related to coagulation response to be consistent with en route conditions[304,519]***
- ***Different study design (case-control) similar injury distribution and severity of casualties who did and did not undergo fasciotomies at LRMC – identify risk factors, acuity (isolated extremity injury versus polytrauma), pre-flight status, en route care/events. Determine if there are any pre-flight or inflight indicators.***
- ***Pre-flight assessment – should there be a targeted preflight assessment (needs description – does this include noninvasive StO2 assessment or intracompartmental pressure assessment for patients at risk for compartment syndrome (RN vs MD documentation/assessment).[503,518] – need to delineate normal hyperoxic response to injury versus indicators of ECS***

For soft tissue trauma research, consider partnering with CDMRP sponsored program – Major Trauma Extremity Research Consortium (METRC.org). METRC currently has one study by Schmidt: "Predicting Acute Compartment Syndrome using Optimized Clinical Assessment, Continuous Pressure Monitoring, and Continuous Tissue Oximetry (PACS Study)", which may apply to en route care.[520,521]

4.14.3 Negative Pressure Wound Therapy. Although negative pressure wound therapy has been used successfully in theater to treat combat wounds, there were numerous logistical (portability, electricity) and safety (loss of suction – wound infection) issues to overcome to use this therapy in en route care.[522] Although it was initially introduced in theater in 2006 for short-distance transport, there was a delay in approval for use in long-distance aeromedical evacuation. There are only two research papers that specifically address the use of negative pressure wound therapy during en route care.[353,523] Pollack's retrospective medical record review of 218 patients (298 wounds) transported from 1 Oct 2006 to 30 Sept 2007 with NPWT. Patients with NPWT used for open abdominal/thoracic wounds were excluded. In four cases, the pump/system failed and in nine cases there were problems with the system identified upon arrival to LRMC (suction, dressing). This preliminary study suggested that NPWT was safe and feasible. This finding was confirmed in Fang's prospective observational study of patients transported in 2008[353]. No specific gaps were identified by the authors in either of these papers. Research funded by USAF is ongoing to evaluate a multi-channel NPWT pump.[524] A recent study[525] evaluated the use of clinical biomarkers, including those obtained from NPWT to predict wound failure (dehiscence) compared to healing. One model demonstrated in univariate analysis that serum IL-7, RANTES, VEGF, IFN-γ, IL-10, EOTAXIN, MCP-1, IL-6, IL-2R, HGF, IL-2, IL-17 and EGF and the effluent IL-7, IL-6, IFN-γ, IL-2R, IL-4, and IP-10 differed significantly (adjusted $p<0.05$) in wounds that ultimately failed, compared to those that healed uneventfully. A limitation of this study is that all data were collected at CONUS facilities, and no data were available on en route care. Linkage of en route data to these outcomes would enhance the exploration of factors that may cause or mitigate the inflammatory response during the acute phase of injury.

Several animal studies that have demonstrated increased bacterial growth under hypobaric hypoxic conditions. As demonstrated in a caprine model of a complex wound[436,437] there is a significant decrease in arterial oxygenation with ascent to altitude (Figure 13). In this model, animals had a complex wound seeded with Pseudomonas aeruginosa, and 20-hours post-surgery they were exposed to a simulated flight (7 hours at 8,800 feet) with/without supplemental oxygen compared to ground control. There was increased bacterial growth in the hypobaric hypoxia group (PaO_2 ~ 50 mm Hg). Supplemental O_2 titrated to maintain an SpO2 > 93% attenuated bacterial growth (Figure 14). This experiment is important as it reflects the approximate timing of the transport of a casualty from the AOR to LRMC.

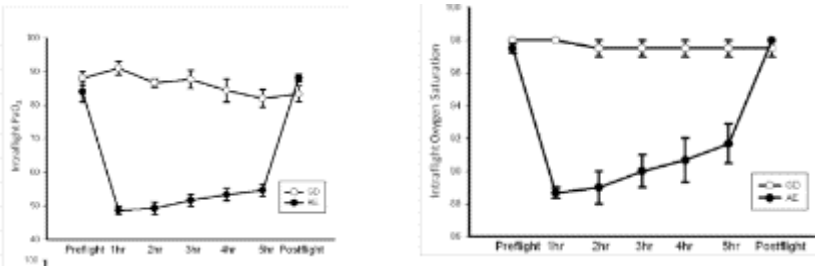


Figure 13. Arterial oxygen (PaO2) and oxygen saturation (SpO2) in caprine model at ground and simulated altitude.[436,437]

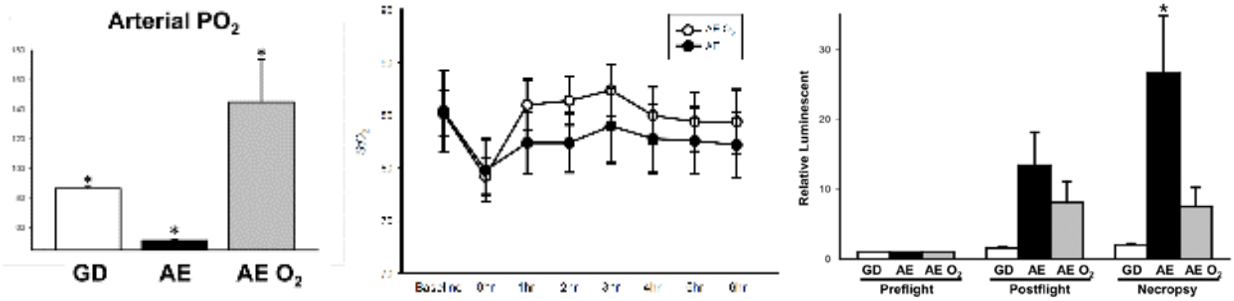


Figure 14. Effect of hypobaric hypoxia and supplemental oxygen at altitude on bacterial growth.[436,437] A. Arterial PO2 on ground (GD) and at simulated altitude without/with supplemental O2. B. Skeletal tissue oxygen saturation (StO2) at altitude, with/without supplemental O2. C. Bacterial wound growth in complex wound preflight (20 hours post-surgery), postflight (7 hours from preflight), and at necropsy (24 hours from preflight/44 hours from surgery).

An interesting finding in this study was that there was a higher skeletal tissue oxygen saturation (StO_2) in the supplemental O_2 group, however, the StO_2 did not decrease below what is generally considered a critical value (70%), thus, further exploration of the mechanism of the O_2 effect is warranted, particularly considering research that suggests that hypoxia may inhibit the uptake of Pseudomonas aeruginosa into host cells.[526]

An animal model[527] of a crush injury and exposure to hypobaria found suppression of macrophage-related genes (e.g., CD68 and ccl2) and macrophages within crush-injured muscle. This suppression may lead to impaired or delayed muscle regeneration. A second study[528] using this same model, with the rats exposed to 8-9 hours of hypobaria, did not affect bone marrow and blood monocytes/macrophages; however, there were macrophage changes in injured muscle that might be related to mechanisms of migration into the injured muscle, with varied at 32 versus 96 hours post-injury. ***The study documents did not include details on time post-injury for the hypobaric exposure. In addition to exploring mechanisms of variation in the macrophage response, further study of timing post-injury and the effects of supplemental oxygen to offset hypobaria are needed.*** **A recent** murine model of crush injury described the time course for inflammation under normobaric conditions.[529] This latter study will provide baseline data to determine the effect of the en route stresses of flight on the inflammatory response.

Gaps

- ***Timing post-injury on effects of hypobaric exposure on altered inflammatory response***
- ***Effect of supplemental oxygen to offset hypobaria effect***
- ***Effect of hyperoxia -SpO2 > 95% on bacterial growth***

- ***Association between hypoxia and clinical presence of infection versus wound contamination***

<u>Gaps – Negative Pressure Wound Therapy</u>

- ***Use of negative pressure wound therapy for temporary closure of abdominal wounds – safety in the en route care environment and effect on inflammatory markers/infection (i.e., reduction in sepsis or wound infection)***
- ***Use over closed wounds – safety, effect on tissue edema, post-transport care modification (e.g., wound debridement, amputation management)***

4.14.4 Medical Maggots. The Walter Reed Army Institute of Research (WRAIR) has the capacity to generate medical maggots. The effects of the en route care environment on the function (weight gain) and mortality of medical maggots were studied.[530,531] Under lab conditions low humidity resulted in desiccation and growth rates were lower at altitude (10,000 feet) and lower temperature. At higher temperature (39°C vs 26°C) growth rate was increased. During rotary wing transport no maggots escaped the specialized dressing. For the fixed wing evaluation (C17 Andrews-Germany, with a 2.3-hour layover at McGuire AFB) the maggots were transported in petri dishes in a box placed on a seat in the front of the aircraft. Cabin altitude was approximately 8000 feet. Maggot growth rate during flight was lower that baseline, although the exact mechanism cannot be identified (temperature, hypoxia, vibration). No reported cases of the transport of patients with medical maggots were identified.

Gaps

- ***Requirement for use of medical maggots during transport***
- ***Use of model simulating human body (temperature, humidity) during transport***
- ***Effect of combined effect of stresses of flight during prolonged transport***
- ***Case-control outcomes for patients treated with/without medical maggots***
- ***Delineation of policies and procedures for approval and the evaluation of biologic therapies onboard aeromedical evacuation aircraft is needed.***

4.15 Renal

There are several recent studies that describe the prevalence of rhabdomyolysis and/or acute kidney injury (AKI) in combat casualties. The largest epidemiologic study is a medical record review of data in the DoDTR for the 6,0111 admissions to the ICU at LRMC from 2002 to 2011.[532] In a subset of 3,807 combat casualties with complete medical records, 474 (12.5%) developed acute kidney injury (AKI) within the first seven days of injury. Among these patients, 14 required RRT at a median of 15.5 (IQR 8.8-20.3) days after injury and 3 of 14 required dialysis within the first seven days. In a second analysis of these same patients, rhabdomyolysis, as defined by a CK > 5000 U/L within the first four days of injury, was present in 656/2,109 patients with available lab data. A limitation of both these studies is the lack of information on the timing of the onset of the rhabdomyolysis or AKI. However, the latter study used a CK value within the first four days of injury, which is within the transport window for a majority of critically injured patients. In another cohort of 318 trauma patients (excluding burns) admitted to the ICU at LRMC, the prevalence of rhabdomyolysis was 24.8%.[533]

A secondary analysis[534] of data from two cohort studies (Damage Control Resuscitation and Urine Biomarkers[535]) of critically injured casualties found an overall AKI rate of 34.3%, with a 80.5% of these patients developing AKI within the first two days of injury. In the cohort from the Urinary Biomarker study,[535] six patients required RRT, with the start of RRT at a median of 3 days (range 1-8 days) after injury. Among these patients, 3/6 died (median day of hospital death 4 (3,13). At the time of urine sampling (within 48 hours of admission), 18% of patients had AKI and 17 additional patients

subsequently developed AKI (time of onset not reported). Only one study described outcomes. In a cohort of 51 casualties who had post-traumatic AKI requiring RRT who were transported to the US (Walter Reed), the 60-day mortality was 22%. Among these patients, four received RRT in the AOR and 30 (59%) had RRT before reaching the US. The median days from injury to onset of RRT was 4 (1-66) – of note, until 2010 there was no standard capability to provide RRT in theater. These data are important in describing a subset of patients with/or at risk for AKI undergoing LRMC-CONUS transport. Only one study addresses RRT in the pre-transport period. Zonies[536] describes the feasibility of a sustained RRT program in the AOR. Nine combat casualties with AKI (peak K^+ 6.4 ± 0.4; 8/9 with rhabdomyolysis) received RRT at Bagram. All patients completed RRT approximately 6 hours before transport. There were no details on the transport phase (AOR-LRMC), except that all patients survived transport. There are several papers[537,538] describing the use of RRT in burn patients, but no papers discussing the requirements relative to en route care. **A gap in these studies is a description of the specific timing of the onset of rhabdomyolysis or AKI, time to transport, en route care requirements and adverse events and outcomes and discussion of any need for en route advanced treatment.**

Gaps

- ***No description of timeline for onset of AKI and rhabdomyolysis (is there a safe time to transport before onset)***
- ***En route care requirements/treatment strategies for patients with AKI and/or rhabdomyolysis***
- ***Requirements for disaster nephrology[539] (e.g., earthquake crush injuries)***

4.16 Thermal Stress

A gap identified by the AFMS was the lack of a solution to effectively regulate patients' body temperatures to minimize the risk of hyper/hypothermia as patients are moved through the continuum of care. Research relevant to this gap includes a description of the thermal environment, descriptions of when in flight these interventions would be needed (e.g., when does fever occur in patients with TBI), and extant operational research related to mitigation of thermal stress (hypothermia prevention).

4.16.1 Thermal Environment on AE Aircraft. Two studies[304,540] have been conducted to describe the thermal environment and human response to the thermal environment onboard cargo aircraft configured for AE (C-130, C-141, C-17). No description of the thermal environment on the KC-135 or any other aircraft used for AE has been reported.

4.16.1.1 C-130. Data were collected on 10 C-130 flights during winter months in the southwest US. Additional data were collected on core (tympanic) and skin temperature, thermal perception and comfort, which provides insight into the patient experience.

Ambient Air Temperature (°C) on C-130 (10 flights)										
Litter Location	Preflight	Inflight (q 15 min)								Post-Flight
		1	2	3	4	5	6	7	8	
Front/Top	15.5 ± 2.8	23.2 ± 1.7	24.7 ± 2.1	24.7 ± 1.8	25.3 ± 2	24.8 ± 1.7	25.1 ± 1.7	25.8 ± 2.2	26.7 ± 1.1*	25.6 ± 1.5
Front/Bottom	15.9 ± 2.2	21.6 ± 1.9	22.6 ± 3	23.3 ± 2.2	23.8 ± 2.3	23.1 ± 2.1	23.7 ± 1.8	25.3 ± 1.4	25.3 ± 1.6	22.9 ± 3.4
Back/Top	16.7 ± 3.7	22.8 ± 1.9	23.9 ± 1.9	23.9 ± 2.1	23.6 ± 2.5	24.1 ± 2.5	24.3 ± 2.7	24.1 ± 2.5	23.9 ± 2.4	23.4 ± 2.5
Back/Bottom	16.7 ± 4.3	23.2 ± 2.5	22.5 ± 2.6	22.1 ± 3	22 ± 3.6	22 ± 3.2	22.4 ± 2.6	22.5 ± 2.9	22.6 ± 2.8*	24.2 ± 1.8

*p < .05

Air Flow (m/sec) on C-130 (10 flights)										
Litter Location	Preflight	Inflight (q 15 min)								Post-Flight
		1	2	3	4	5	6	7	8	
Front/Top	0.09 ± 0.09	0.11 ± 0.17	0.09 ± 0.09	0.14 ± 0.2	0.13 ± 0.11	0.04 ± 0.08*	0.03 ± 0.08	0.08 ± 0.13	0.04 ± 0.09	0.02 ± 0.04
Front/Bottom	0.1 ± 0.09	0.11 ± 0.16	0.1 ± 0.12	0.13 ± 0.18	0.14 ± 0.16	0.09 ± 0.09	0.13 ± 0.13	0.12 ± 0.16	0.12 ± 0.16	0.33 ± 0.31
Back/Top	0.17 ± 0.12	0.15 ± 0.17	0.08 ± 0.14	0.13 ± 0.14	0.09 ± 0.12	0.18 ± 0.18	0.17 ± 0.16	0.21 ± 0.15	0.19 ± 0.22	0.16 ± 0.2
Back/Bottom	0.22 ± 0.31	0.14 ± 0.12	0.2 ± 0.18	0.22 ± 0.17	0.2 ± 0.18	0.29 ± 0.12*	0.21 ± 0.12	0.13 ± 0.1	0.23 ± 0.21	0.11 ± 0.24

*p < .05

On the C-130 there was a significantly lower perception of comfort and skin temperature in the back/bottom litter compared to the front/top litter tier. Additionally, there was a significant correlation between ambient air temperature and thermal perception, tympanic temperature and skin temperature. Air flow was also significantly correlated with thermal perception.

4.16.1.2 C-141. A study of thermal stress was conducted on the C-141. Although this aircraft is no longer in the inventory, the study provides an examples of the inclusion of composite ambient thermal stress measure and subcomponents (wet bulb-globe thermometer temperature reflects overall thermal stress and is a composite measure: The WBGT Index = 0.7 wet bulb temperature + 0.2 black globe temperature + 0.1 shaded dry bulb temperature), air flow velocity, and measures of the physiological response to the thermal environment (auricular temperature, protected skin temperature, exposed skin temperature and forearm-finger temperature gradient). Overall there was no significant difference in WBGT on the C-141 based on litter position (front-back, top-bottom, side-center) due to a large amount of variability in the ground temperature at takeoff and individual aircraft variability. However, there was a significant decreased in WBGT throughout the aircraft from preflight through the first hour of flight (approximately 30 minutes to cruising altitude plus an additional 30 minutes of flight) (Figure 15). For example, on average the WBGT decreased from a preflight measurement of 19.8 ± 6.0 (68°F) to 16.5 ± 5.6°C (62°F) at cruising altitude and continued to decrease to a nadir of 15.4 ± 4.2°C (59.7°F) at 60 minutes.

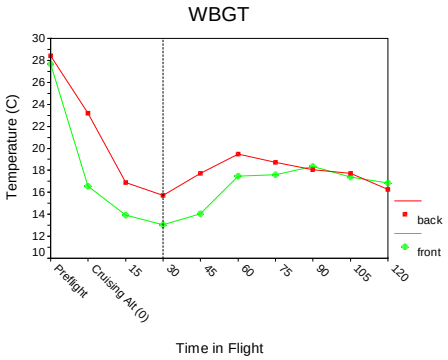


Figure 15. Thermal stress on C-141 in front and back of aircraft.

A subset analysis was conducted based on the ground temperature at takeoff. The median temperature was 19.6°C (25th percentile = 15.1°C; 75th percentile = 24.6°C). If the ground temperature was greater than 25°C there was a significant decrease in temperature over the first hour of the flight, with the nadir occurring at 60 minutes of flight (~30 minutes reflects the ascent to altitude). The WBGT decreased from an average of 27.5°C (82°F) to 15°C (59°F) throughout the aircraft. If the ground temperature was less than 15°C, the temperature did not markedly change throughout the flight, remaining at an average of 15 ± 1°C at all time points (Figure 16). For each subset, the subject's skin temperature and their overall thermal sensation/aversiveness were closely related to the WBGT.

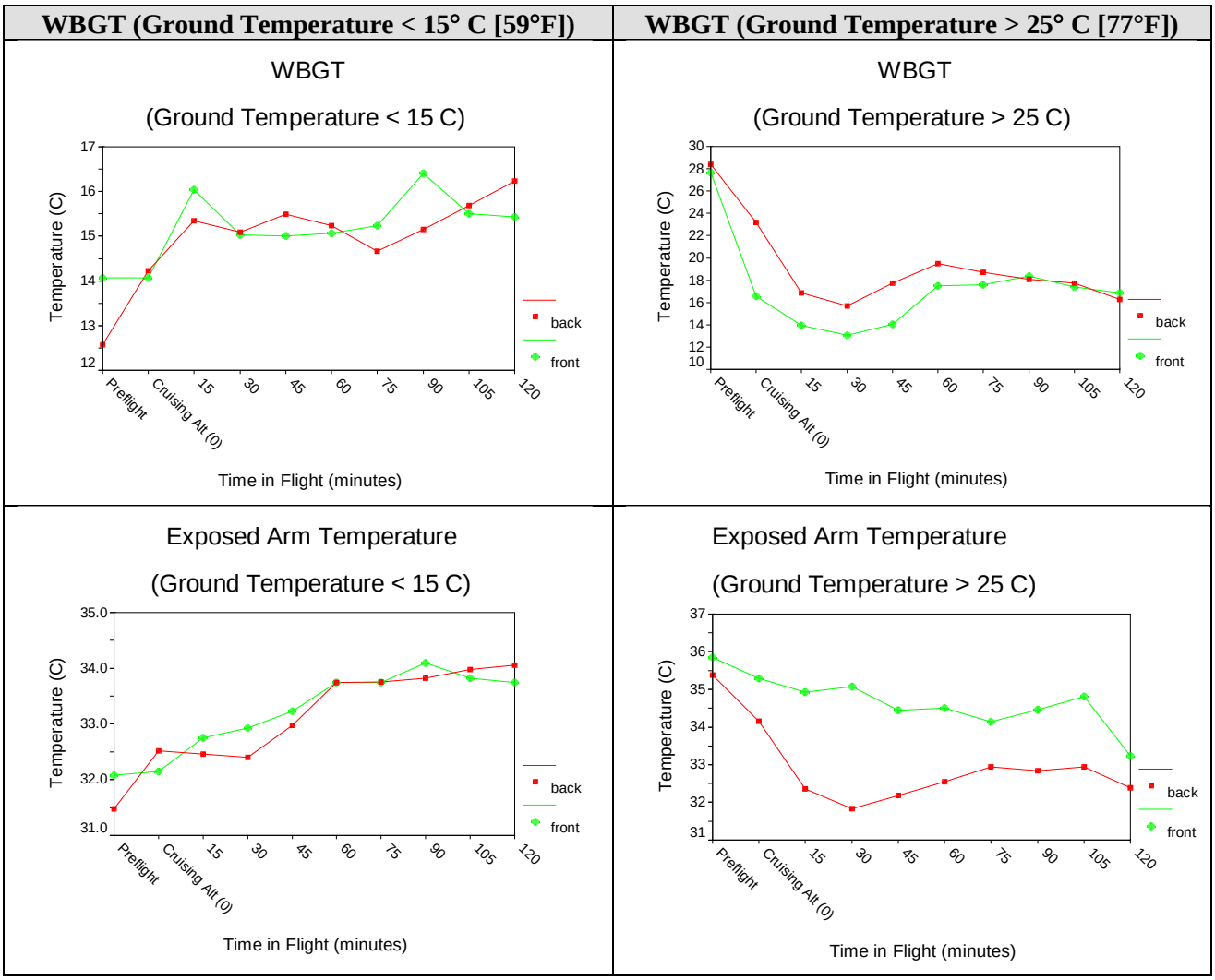


Figure 16. Thermal stress and human response on C-141.

4.16.1.3 C-17. Data were collected on two C-17 missions (no human data). Although the small sample size precludes conclusions, there was the trend toward a significant temperature difference between the front/middle and the back of the aircraft ($p = .054$). The wet bulb globe temperature (WBGT) in the back of the aircraft decreased from an average of 20°C ± 0.6°C (68°F) to a nadir of 12.6°C ± 0.6°C (54.7°F) at 45 minutes into the flight compared to the front of the aircraft where WBGT decreased from preflight 20.6°C ± 0.6°C to a 14.7°C ± 0.5 (58.5°F) at 30 minutes of flight and 15.2°C ± 0.4 °C (59.4°F) at 45 minutes of flight (Figure 17). The air ducts in the back of the aircraft are the most likely cause of the marked decrease in temperature in the back of the aircraft. Patients in the back-bottom litter tier are exposed to high airflow, which increases convective heat loss and may be particularly problematic if the patient is intolerant to the increased

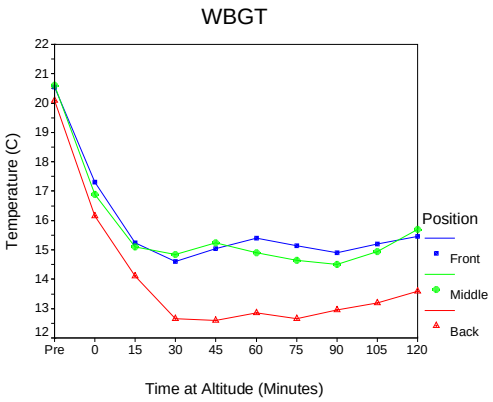


Figure 17. Thermal conditions on C-17.

airflow over their body (i.e., burns). This finding suggests the need for strategies to shield patients in back litter tier positions (particularly the bottom tier) from the airflow. Overall, the thermal gradient on the C-17 was maintained throughout the flight. The temperature characteristics on the C-17 appear to be similar to the C-141. In addition, the ascent to altitude (the period with the largest decrease in cabin temperature) is a period of physiological stress for the patient, due to the combined effect of the stresses of flight (hypobaric pressure, hypoxia, gravity, vibration).

These studies are important as they demonstrate the variability in the thermal environment (ambient temperature and airflow) throughout the aircraft, and may serve as baseline data for future research. Limited research has been done to describe the thermal environment on the C-17 (only two studies, to include airflow and circulation of air throughout the cabin). No studies have been conducted with high risk patients. For example, a report on the en route care of severely injured patients with burns did not report on any en route adverse events, including hypothermia.[93] Additional description of the thermal environment on other aircraft used for AE (KC-135) are also needed. No studies have been conducted to evaluate strategies to mitigate the effects of the thermal environment onboard aircraft used for AE.

4.16.1.4 Humidity. There is limited research on humidity during long-distance AE. Thermal stress, including humidity were described onboard five missions originating in CONUS on the C-17.[304] Humidity and thermal data were collected using a Metrosonics HS-32 WBGT Heat Stress Monitor, with measurements obtained in the top and bottom - back, middle and front litter tier positions. On all flights, the relative humidity decreased to < 5% within 30 minutes of takeoff (generally noted upon reaching cruising altitude). In civilian studies, testing related to en route humidity uses a range from 10%-40% at an air temperature of 21-25°C.[541] No research has been conducted relative to the effects of low humidity on physiological parameters sensitive to this dry environment.

Gaps

- **Evaluate strategies to mitigate the effects of the thermal environment onboard aircraft used for AE.**
- **Study effects of low humidity on physiological parameters sensitive to this dry environment (fluid loss – particularly in patients with altered skin integrity) and airway maintenance/humidification**

4.16.2 Hypothermia Prevention. In 2003, a series of randomized controlled studies using an animal model of hemorrhagic shock with thermal protection were initiated to identify a field expedient bundle for hypothermia prevention under combat conditions.[542-544] These studies explored wools blankets, the single layer space blanket, Blizzard Blanket (baffled space blanket), the Thermal Angel (battery powered fluid warmer), and the Chillbuster thermal blanket under conditions consistent with AE (50°F; airflow 0.2-0.4 m/s), which was based on the above studies related to the thermal environment. In this series of studies, a combination of active heat transfer and prevention of heat loss with a space blanket maintained core temperature. A limitation was that the Chillbuster required electricity. Of note, Dubick,[545] in a bench-study found that the Thermal Angel did not adequately warm fluids (LR, Hextend, PRBCs) and confirmed a limitation noted in Bridges' study, that while the Thermal Angel was battery power, it required frequent recharging, with a recharge time of 14 hours. De Jong[544] evaluated the Ready-Heat Blanket plus the Blizzard Blanket under thermal conditions with MEDEVAC or a cold/wind environment (2°C with 3.6 m/sec airflow) (Figure 18). These studies informed the recommendations in the 2006 JTTS Clinical Practice Guideline: Hypothermia Prevention[546] and the creation of the current Hypothermia Prevention Management Kit (HPMK), which is currently in use in the AOR. An anecdotal limitation of the Ready-Heat is the approximate 30-minute lag to begin to warm the patient, which was confirmed in the model analysis described below; thus, it may have limited utility during a rapid transport. However, a recent study using a human torso model under field conditions confirmed the effectiveness of the Blizzard

Blanket and the Ready-Heat II in preventing heat loss.[547] Similar results were also observed in a second bench study, in which the HPMK was most effective in maintaining heat.[548] An important finding in Allen's study was the variability in results when a component of the HPMK was altered, which emphasizes the need to evaluate each new iteration for effectiveness. These evidence-based recommendations were integrated in the 2006 CPG related to hypothermia prevention. A pre-post implementation study[549] demonstrated a decrease in the incidence of hypothermia post-CPG, however, the study also found a general lack of adherence to the CPG, with a wool blanket used as the most common method. Similarly, a study by Lairet[550] of pre-hospital life-saving interventions performed in 2010, identified the use of hypothermia prevention in 429/692 casualties (62%), with the most common methods being a wool blanket (84%), space blanket (8.5%), and HPMK (5.6%). There was one reported case of a burn associated with the HPMK. No data were reported on admission temperature. Nesbitt and Lairet's studies indicate a gap in the implementation and continuous follow-up a clinical practice improvement.

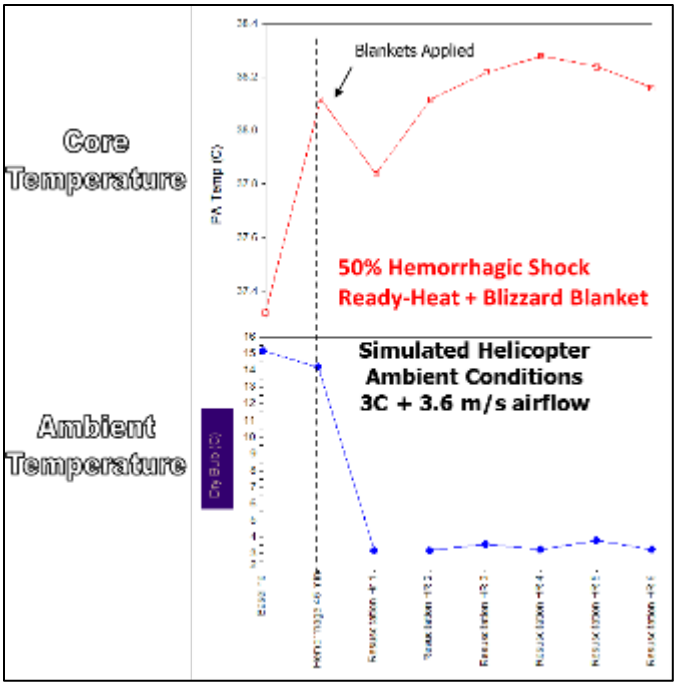
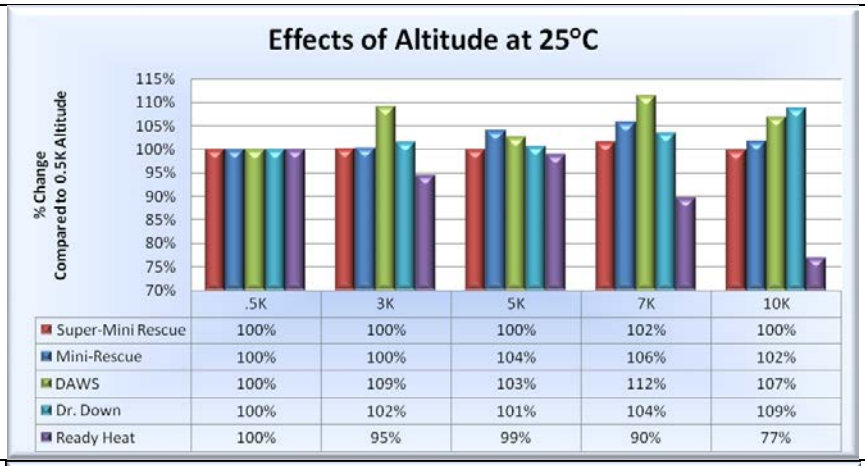
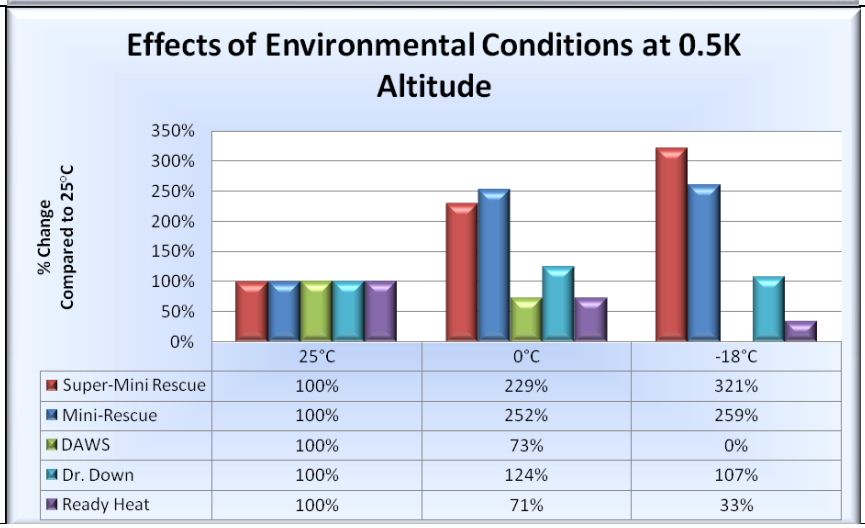


Figure 18. Core temperature stabilization for 6 hours under cold conditions using the Ready-Heat and the Blizzard Blanket in a swine model of hemorrhagic shock.

The Navy has also evaluated several devices using a Phantom to simulate a hypothermic casualty and measure the energy gained or lost under various environmental conditions (temperature, altitude).[551] In addition, infrared red temperature measurements were obtained to identify potential hot spots. The HPMK and the Deployable Active Warming System (DAWS) were evaluated in conjunction with the Absorbent Patient Litter System (APLS), which is a passive insulation device. The results of this study were that the Ready-Heat system was affected by extremes of altitude (0.5K versus 10K) and ambient temperature (-18°C/0°C/25°C) compared to the electrical devices (Super Mini-Rescue) and the Mini-Rescue (Figure 19). At all altitudes, the Ready-Heat took approximately 22 minutes to reach 37C, in contrast to the Super-Mini Rescue and Mini Rescue (~ 10 minutes). No data were provided on the electrical requirements of the Super-Mini Rescue or Mini-Rescue. The website indicates 5-7 hours of battery life and any power supply compatible with an AC~DC power adapter (http://www.rgmd.com/geratherm_medical_warming_system.html). The availability of electricity and utility of these technologies for short versus long-distance AE should be explored.



Notes: The Ready-Heat operated at 77% at 10K compared to 0.5K.



Notes: Ready-Heat operated at 33% at -18C compared to 100% at 25C.

Altitude (10K) affected the Ready-Heat at all temperatures

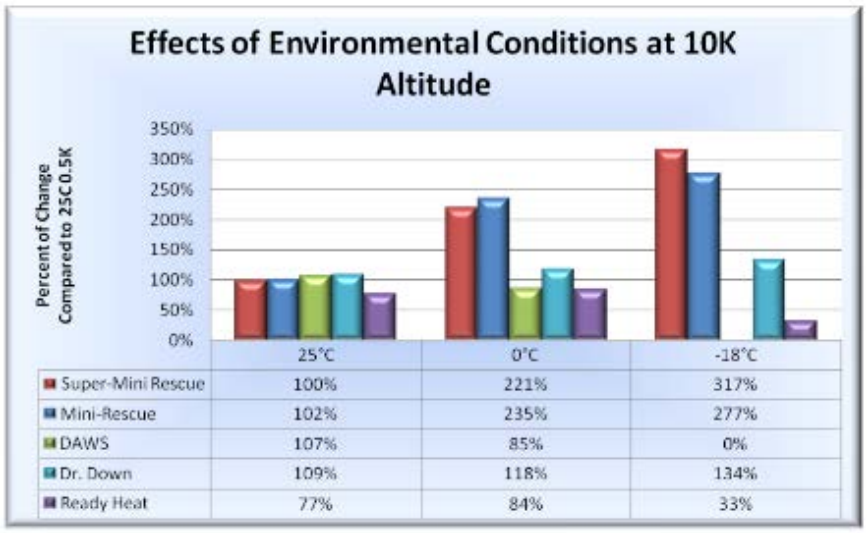


Figure 19. Evaluation of Patient Active Warming Systems (PAWS).

Note: The 2017 TCCC guidelines[552] recommend the following regarding hypothermia prevention (Table 16).

Table 16. TCCC Guidelines: Hypothermia Prevention

• Minimize casualty's exposure to the elements. Keep protective gear on or with the casualty if feasible. • Replace wet clothing with dry if possible. Get the casualty onto an insulated surface as soon as possible. • Apply the Ready-Heat Blanket from the Hypothermia Prevention and Management Kit (HPMK) to the casualty's torso (not directly on the skin) and cover the casualty with the Heat-Reflective Shell (HRS). • If an HRS is not available, the previously recommended combination of the Blizzard Survival Blanket and the Ready Heat blanket may also be used. • If the items mentioned above are not available, use dry blankets, poncho liners, sleeping bags, or anything that will retain heat and keep the casualty dry. • Warm fluids are preferred if IV fluids are required.

Gaps

- **Evaluation of currently used HPMK over extended period (6 hours) in trauma model (simulate rapid evacuation of unstable/stabilizing casualty**
- **Evaluate uptake of clinical practice changes (use translational science evaluation)**
- **Evaluate HPMK in physiological model of hemorrhage at altitude (c/w long distance transport – See results of McKeague[551] – effect of hypoxic environment on function of Ready Heat)**
- **Evaluate adherence in en route environment to JTS CPG and TCCC guidelines related to hypothermia prevention**

4.17 Fever

Two studies have described the incidence of fever during en route phases of care. In a retrospective medical record review[177,553] of 248 CCATT trauma patients evacuated in 2009-2010, 101 patients (41%) had hyperthermia (> 100.4°F/38°C) at some point in their en route phase of care. Among these 101 patients, 37% received treatment (antipyretics, intravenous fluids, cooling blanket/icepack) for hyperthermia. Among these patients, 24 had a TBI and among patients with a fever, 59% had received a blood transfusion in contrast to 39% in the afebrile group (NS). Fever occurred in 66/80 ventilated patients, with a 3.9-odds of having fever compared to the non-intubated patients; however, there were no data on the severity of injury of the casualties. There were no results related to the timing of the fever onset relative to the injury or blood transfusion, whether the fever spike occurred during transport or was a continuation of a preflight condition. Dukes[105,120,121] studied the incidence of fever in 67 CCATT patients with an isolated head injury who were transported from 2003-2006. Among these patients there was a 42% incidence of fever; either as an isolated secondary injury or in conjunction with hypoxia (25%), hypotension (25%) or hyperglycemia (15%). There was an increased incidence of fever with increased severity of injury (OR 1.16) and among patients with a blast injury versus non-blast injury. Fever occurred in all phases of care: POI - AOR MTF 13/56 (23%); at AOR MTF 6/31 (19%), AOR-LRMC 5/24 (21%), at LRMC 17/44 (39%), LRMC-CONUS 7/17 (41%). To determine the timing of fever occurrence relative to the injury the results were compared to 10-year analysis of 975 patients transported by CCATT,[107] where the median time from injury to LRMC was 38 hours (IQR 25.3-50.3). Thus, assuming a 6 to 8-hour flight, the evacuation from the AOR to LRMC occurred at approximately 30-32 hours post-injury. A limitation of this study is the lack of documentation of when the fever spike occurred, but it does provide evidence of a potential en route care requirement, particularly during the later transports. Timing of fever could also be compared with the inflammatory response to TBI as outlined in Goodman's summary on when the brain is fit to fly.[104] However this latter paper focuses primarily on the effects of hypoxia on the inflammatory response and does not address fever as a result of the inflammatory response or secondary injury. A limitation of these studies is that they did not evaluate

longer term outcomes as there is also an association between hyperthermia and impaired cognitive outcomes in civilian patients with mild TBI.[554]

In the civilian literature, there is limited research on the timing of hyperthermia in patients with TBI. Relative to the issue of time to transport several civilian studies report the incidence of fever and outcomes. Jiang studied 846 patients with severe TBI. Among these patients in the first 48 hours, 33% had a temperature < 37°C, 42% had a temperature between 37°C and 39°C, and 25% had a temperature > 39°C. There was an association between temperature and one-year outcomes. Among these three temperature groups there were good neurological outcomes at 1 year in 35%, 33% and 24%, respectively. In contrast, there was increased mortality with increased temperature (21%, 26%, 47%), respectively. A second study described the association between temperature during ICU stay and outcomes.[555] In a subset of 618 patients with TBI, 29% had no fever (< 37.5°C), 33% had a low fever (37.5-38.4°C), 18% had a moderate fever (38.5 – 39°C) and 20% had a high fever (> 39°C). Among all patients in the study there was an association between fever and length of ICU stay; and among the TBI subset there was an increase in mortality with increased temperature (8.6%, 19.6%, 22.8%, 48.8%), respectively. However, this study is limited by a lack of information on the exact timing of fever onset and lack of a specific analysis of the TBI subset controlling for severity of injury. In a study of 76 civilian trauma patients with severe TBI, 68% were hyperthermic within the first six hours of admission. Among the patients with a fever, 11.8% were neurogenic (non-infectious), with GCS, diffuse axonal injury, frontal injury and skull fracture as risk factors.[556] The results of Thompson's study may not be generalizable due to the increased incidence of penetrating trauma in military casualties, which may affect the cause of fever. These studies provide important baseline data for the comparison of outcomes.

4.17.1 Prophylactic Hypothermia. The 2016 TBI guidelines from the Brain Trauma Foundation[557] do not recommend early (within 2.5 hours) short term (48 hours post-injury) prophylactic hypothermia for patients with diffuse injury. In support of this guideline recommendation, the background documents [558] discussed research related to prophylactic hypothermia. In a study by Clifton,[559] patients were enrolled within 2.5 hours of injury. Although the study was stopped due to overall futility, there were differences in the incidence of poor outcomes based on the type of injury and hypothermia versus normothermia (Diffuse injury: 70% vs. 50%, p = .9; surgically evacuated hematoma 33% vs 69%, p = .02), which suggests a potential benefit in post-surgical patients. A subset of patients who underwent hypothermia before surgical evacuation of the evacuation had a lower incidence of poor outcomes (41%) compared to patients who were normothermic (60%; RR 0.74; 95% CI 0.49-1.13).[560] Similarly, in a recent meta-analysis, hypothermia was associated with improved outcomes in patients who had undergone a decompressive craniectomy (RR 1.43, 95% CI 1.13–1.82), but there was no discussion on outcomes related to the use of hypothermia to treat fever.[561] These results support a potential benefit for the induction and maintenance of hypothermia, which would have implications for en route care.[562]

4.17.2 Prophylactic Hypothermia – Fever Mitigation in AE. No research studies were found regarding fever mitigation in the en route care environment. The summary report on optimal time to transport[103] does not specifically address issues related to en route fever management or consideration of temperature state and the decision to fly. The JTS CPG Neurosurgery and Severe Brain Injury[563] recommends aggressively avoiding fever (> 99F), but similar to the Brain Trauma Foundation TBI guidelines[557] provides no recommendations for fever management. Research indicates improved outcomes with fever avoidance.[564,565] However, a recent review[566] of fever management in neurologic patients had no discussion regarding fever management strategies in patients with TBI. A systematic review and grading of literature is warranted on strategies for fever avoidance and management, including acetaminophen and controlled normothermia, during the en route phases of care.

Gaps

- ***Incidence of fever in patients with isolated TBI (mild[554] to severe) and TBI with polytrauma***
- ***Timing of fever (compare to civilian control group without transport) – larger sample size (studies currently report median)***
- ***Association between fever and longer-term outcomes (re-analyze Bell's[150] data with integration of early secondary insults and en route care)***
- ***Description of patient population who may benefit from prophylactic hypothermia (hematoma evacuation) with consideration of generalizability to TBI with polytrauma***
- ***Monitoring brain temperature versus systemic temperature – implications for management***
- ***Recommendations for fever management during en route care***

4.18 Pressure Injury Prevention

The prevention of pressure injuries in critically ill and injured patients is complex. A recent study by Dukes, found that between 2009-2012, 4.9% of critically injured patients transported from the combat zone by US Air Force Critical Air Transport Teams developed a pressure injury.[567] Since July 2010, 39 severely injured combat casualties were admitted to the Burn ICU (BICU) at the US Army Burn Center, San Antonio TX. Among these patients, 36% had at least one pressure ulcer on admission in contrast to 9% in civilians admitted to the BICU.(Shingleton 2014, personal communication), Additionally, during 2004 to 2006, 165 active duty members admitted to a Veterans Affair Polytrauma Rehabilitation Center.[568] Of the 88 casualties who suffered injuries in Iraq, 62 had Stage I pressure ulcers and 26 had lesions of another stage, although when the pressure injury occurred was not specified. Among these patients, occipital lesions accounted for more than 50% of the pressure injuries.

Two studies have evaluated the pressure reducing characteristics of the AE mattress. In a 2003 study,[569] skin interface pressure (a risk factor for pressure injuries) was measured on the NATO litter alone, litter plus blanket, litter plus AE mattress and a Maxifloat mattress (control). The orange mattress, which was the standard of care the standard of care in AE until 2007, significantly decreased interface pressure for all body areas compared to the NATO litter without a mattress (Table 17). This study is relevant as it describes the interface pressure on the NATO litter without a mattress.

Table 17. Peak Interface Pressure (mm Hg) NATO Litter vs. NATO Litter plus Orange AE Mattress (n = 32)

Position	Support Surface	Occiput	Buttocks	Right Heel	Left Heel
Supine	Litter	148 ± 9	95 ± 6	93 ± 11	102 ± 13
	Litter plus AE mattress	76 ± 4*	54 ± 4*	73 ± 6*	72 ± 6*
30° backrest elevation	Litter	97 ± 7	136 ± 10	181 ± 4	190 ± 9
	Litter plus AE mattress	57 ± 4*	93 ± 7*	98 ± 7*	99 ± 6*

*Significantly different from the NATO litter alone ($p < .001$).

In 2006, a product evaluation was conducted as part of the acquisition of a new AE mattress.[570] The evaluation was conducted in five healthy subjects, with skin interface pressure in the supine position measured for 2.5 minutes on seven mattresses. The standard (orange) AE mattress was the control. The mattress from Allen Medical demonstrated the best skin-interface pressure profile. For the occiput and sacrum, the interface pressure was significantly lower compared to the control (Table 18). There were no significant differences between the pressures on the right and left heels, thus they were combined for analysis; however, there was no significant difference in peak heel pressure between any of the mattresses.

Table 18. Skin Interface Pressure on the Allen Mattress Compared to a Standard AE Mattress

Support Surface	Occiput (mm Hg)	Sacrum (mm Hg)	Right Heel (mm Hg)	Left Heel (mm Hg)
Allen	38 ± 11*	32 ± 4†	49 ± 12	49 ± 3
Standard AE (control)	102 ± 16	54 ± 2	78 ± 30	82 ± 36

Compared to control: * $p < .05$; † $p < .001$.

Based on this product evaluation and airworthiness testing, in 2007 the USAF began using the Allen mattress (aka – black AE mattress; NSN 6530015480262 - Mattress Litter f/aeromedical patient transfer). The current standard of practice is that a black mattress is used during AE transport, if possible.
A study that evaluated the physiologic state of 48 severely injured casualties pre- and post-transport from Role II to Role III medical facilities in Afghanistan found that 27/39 (69%) patients with pre-transport labs and vital signs were hypoperfused (21 occult; 5 moderate/severe) at the time of transport.[571] In this study, the median flight time from Role II-III was 43 minutes (IQR 30 – 72). Although the skin interface pressure observed on the standard black AE mattress (Allen) should be low enough to not be a direct cause of pressure injury, the results of this study highlight the importance of recognizing that many of these casualties are hemodynamically unstable at the time of transport. In addition to immobility and friction, these patients have increased risk factors for the development of pressure injuries including hypotension, the use of vasopressors[572] and edema.[573]

Four subjects who participated in the evaluation of prototype AE mattresses completed additional data collection to evaluate the effect of the prototype occipital donut on skin interface pressure. Each subject was positioned supine on a NATO litter covered with an AE mattress. There were 2 female/2male, height: 69.5 ± 0.6 inches (range 68-72 inches), weight: 192 ± 46 lbs (range 140-247 lbs); BMI: 27.8 ± 5.8 (range 21-35). Peak interface pressures for each time point (five measurements – 50 second epochs) are summarized in Table 19.

Table 19. Skin Interface Pressure on Occiput (NATO Litter + AE Mattress + Prototype Donut)

Surface	Mean ± SD	Confidence Interval (mean ± 1.96 SE)	
Standard AE (2)1	98 ± 10	83	113
Standard AE (2)	102 ± 17	75	128
Standard AE (3)	107 ± 22	71	142
Standard AE + Donut (1)	67 ± 10	49	84
Standard AE + Donut (2)	75 ± 10	61	88

There was a significant ($p = .006$) difference in the average peak skin interface pressure on the occiput on the AE mattress (102 ± 16 mm Hg) compared to the average peak interface pressure on the AE mattress with the donut under the occiput (71 ± 7 mm Hg).

As demonstrated in the following graphics (Figure 20) the main concern with the AE prototype donut is the localized increase in pressure on the internal edges of the donut. The XSensor mat may have interfered with complete settling into the “donut hole”, which would increase peak pressures.

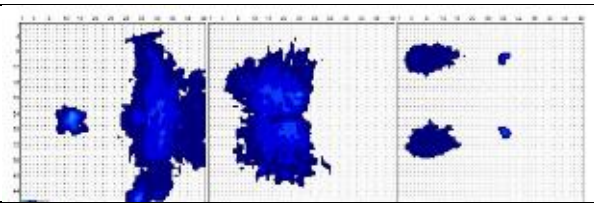
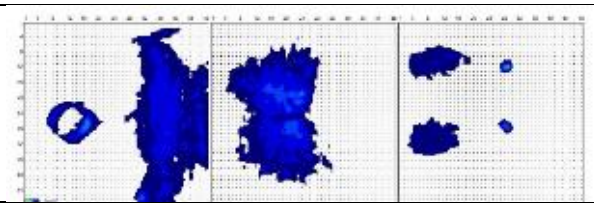
	
Skin Interface pressure on NATO litter + Allen mattress	Skin interface pressure on NATO litter + Allen mattress + cotton donut

Figure 20. Product evaluation – NATO litter with Allen Mattress with/without prototype head donut.

A recent study[431] evaluated the pressure mitigating effects of Mepilex (multilayered foam dressing on the sacrum/heels and LiquiCell (pad comprised of baffles of low viscosity fluid to decrease friction/shear/pressure positioned under the occiput/sacrum/heels) on skin interface pressure, tissue perfusion (transcutaneous tissue oxygen and tissue blood flow) and skin temperature on the sacrum under offloaded (sidelying) and loaded (supine/supine with 30-degree backrest elevation) and during post-loading reactive hyperemia. Forty healthy subjects were supine for 40 minutes on a NATO litter with an Allen mattress to simulate Role II-III transport. There were no group effects for the interface pressure, $TcPO_2$ or skin temperature. Peak interface pressures on the sacrum was ~ 43 mm Hg; heel ~50 mm Hg. Interface pressure on the occiput increased from 60-70 mm Hg in supine position and 46 to 54 mm Hg in the HOB elevated position. The sacral $TcPO_2$ was significantly different between unloaded/loaded conditions in flat (79 ± 16.5 mm Hg/57 ± 25.2 mm Hg, p = .000) and HOB elevated position (85.2 ± 13.6 mm Hg/66.7 ± 24.2 mm Hg, p = .000). The results were similar for the heels. Sacral skin temperature increased significantly across time (~1.0°C). Although the overall results found no significant difference in tissue perfusion, further evaluation of the LiquiCell under AE conditions may be warranted (vibration, ascent/descent) to evaluate a potential decrease in sliding, friction and shear and to determine its effectiveness under conditions where an AE mattress is not available. There are sufficient clinical data to recommend Mepilex in high risk patients undergoing prolonged evacuation. There is a need to develop a pressure injury prevention CPG, which extends across the continuum of care (see example from WRAMC-Bethesda[574]).

Gaps

- ***Extend evaluations of mitigating strategies to 2 hours (maximum time for supine position) under AE conditions***
- ***Evaluation of LiquiCell pads under AE conditions***
- ***Include microclimate (skin temperature/moisture) in evaluation of any device (e.g., Stryker, VSB) to identify strategies to mitigate pressure injuries***
- ***Validate pre-flight risk assessment for combat casualties undergoing AE***
- ***Identify en route care related risk factors for pressure injury development***
- ***Develop en route care specific care recommendations for pressure injury prevention (CPG)***

4.19 Pain/Pain Management

Several studies have been conducted to describe analgesia/sedation administered during the en route phase of care for less acutely and seriously injured patients (Appendix 5). Of interest are those studies that link en route care with patient outcomes.

Buckenmaier[575,576] surveyed patients post-transport (93% < 8 days since transport; 85% < 5 days) on their recall of pain, anxiety, distress and worry related to their injuries during transport. Patients were included in the survey if they suffered extremity trauma, were reporting pain and receiving analgesia. The average pain score during transport was 5.3 ± 2.3, and only 46% of casualties recalled pain relief greater than 50%. There was an association between pain, anxiety, and distress scores. Rupprecht[577] analyzed the open-ended questions: 1) Greatest concerns during transport as related to your injury and 2) what could have been better to control your pain after surgery. Specific to the transport phase of care, the major themes were "Concerns" for both self and others; "Communication of the unknown" wanting a sense of location, knowing what to expect, and being informed; "Fear" of injury, pain and helplessness; "Physiological Concerns," characterized by basic needs and symptom experiences; and, "Dignity" described by feelings of helplessness. Limitations of this study, which reflects care provided in 2007-2008, was a lack of information on en route pain management provided (occurred before implementation of epidural and en route continuous peripheral nerve block) and reliance on recall of pain. The study, which used a validated instrument, is important in demonstrating the need to explore and treat the multidimensional nature of pain (pain, distress, anxiety, worry).

Gentry[497] studied pain in combat casualties from the pre-flight phase (MTF) to their arrival at the aircraft (period of study: 2009-2010). The study used the preflight/inflight medical records, which were collected immediately post-flight at Ramstein/Landstuhl to avoid a loss of records. Overall there was a lack of pain documentation. Only 18/41 patients had a pain score documented upon arrival to the aircraft or upon ascent to altitude. Pain on arrival to aircraft (n = 12) 2.9 ± 2.5 (median = 1; range 0-8); pain at first assessment at altitude (n = 15) 3.9 ± 3.5 (median = 2.5; range 0-10) indicated a low level of pain. The results of this study support the findings of Buckenmaier's study of patients with extremity trauma.[575] An important finding in Gentry's study was that pain scores on arrival/1st inflight assessment were significantly higher for the nine casualties with external fixators (with 8.7 ± 1.1/without 2.8 ± 2.8, p = .012), but not for casualties with splints/casts. Pfennig[578] analyzed prospective, real-time survey data on pain intensity, acceptable level of pain, and en route pain management on 120 patients (BI/NBI/Dz) evacuated from Iraq to Germany (period of study: Nov 2006-Jan 2007). The patients were queried about their minimum and maximum level of pain (1-10) during the flight, and what level of pain they felt was "acceptable" to them. Twenty-seven percent of the patients reported a maximum pain score of 4-7 (moderate pain) and 11% reported a maximum pain score of 8-10 (severe pain). Among the subset of trauma/surgical patients (*n* = 65), 51% reported moderate pain and 9% reported severe pain.

An important aspect of pain management is the timing of the administration of the medications relative to the phases of transport (Table 20). In Gentry's study, the time from hospital departure to aircraft lift off ("wheels up") was 110 ± 42 minutes (range 56-240 minutes), and the four patients with severe pain all received an opioid approximately 1 hour before hospital departure. The timing of the preflight medication suggests inadequate analgesia during the extended period when the patients were being transported from the hospital to the aircraft and during takeoff and ascent to altitude.

Table 20. Transport Times

Phase	Bagram – LRMC[497]	LRMC – Andrews[579]
CASF (Ramstein) to arrival at aircraft		43 ± 46 (0-113)
MTF (Bagram) to takeoff	110 ± 42 (56-240)	--
Takeoff to cruising altitude		39 ± 33 (7-131)
Arrival at aircraft to altitude	39 ± 33	121 ± 52 (65-247)
Takeoff to touchdown		563 ± 42 (504-615)
Total transport time		643 ± 29 (600-680

***These data demonstrate the need to standardize the definitions of the phases of transport. (See Thompson[580] delineation of the Air Transport Minimum Data Set).**

A series of studies were conducted in 2013-2014 to describe pain and pain management in the en route (fixed wing) environment.[579,581-587] As outlined in Appendix 5, there were higher pain scores in trauma victims compared to those with a medical or psychiatric diagnosis. The percentage of patients on the AOR-LRMC had more analgesics administered by the AE crew compared to a higher rate of patients who self-administered on the Germany-CONUS missions. In addition, pain scores were often highest upon arrival to the aircraft or during the MTF to ascent to altitude phase of transport. This finding suggests a need to analyze this phase of care in terms of the timing of analgesics, factors related to the safe administration of analgesia during a period when the patient may have a lower level of monitoring or be required to ambulate, and strategies to gather accurate pain scores using various methods (VAS vs. FACES). In general, a lack of documentation limits the analysis of these patients. However, the collection or copying of medical records immediately post-flight supports the practice used by the CCATT Pilot Unit, to ensure that these records are not lost as the patient transits the continuum of care.

Hatzfeld[587] conducted an ethnographic observational study of 16 non-CCATT patients transported on eight missions from LRMC to Andrews. Observation of pre/post-flight preparation was observed in the sending and receiving ASFs, and pain assessment was performed using the FLACC tool starting when the patient arrived at the aircraft through disembarkation. Adequate pain control ($\leq$ 3/10) was observed in 12/16 patients upon arrival to the aircraft, in 5/14 (36%) for the entire flight, and during landing in 9/14 (64%) of patients. Communication was a key factor associated with en route pain management. One finding was that the patients limited interaction with the Flight Nurses/AETs if they were wearing headphones. An area for future research is the evaluation of noise damping headphones worn by the patients, which can plug into the crew headphones to facilitate communication.[588] In simulations, these headphones enhanced communication; however, they need to be evaluated with patients. Observation of the preflight preparation identified that preparatory guidance on pain management did not address the expected stressors of flight nor the timing of the flight (i.e., during ascent the Flight Nurses would not be available to administer analgesia)., which affected the patient's ability to anticipate their pain management needs. These findings are important as 58% of the patients on the AOR to LRMC[585] and 55% of the patients from Ramstein to Andrews[579] self-administered their medications. An additional finding from Hatzfeld's study was the need to further explore the implications of the en route psychological distress that was observed, as it relates to effective pain management.

Gallimore's study[582] was unique in the use of systems and human factors engineering principles to evaluate pain management in AE. The study involved multiple methods, including interviews with subject matter experts; team member roles, responsibilities, and task timing; perceptions/attitudes related to use of pain medication in a high-stress, high-workload environment; event reporting; and various measures of baseline indicators of system functionality. Preliminary results suggest that pain management might be improved by implementing enhanced information sharing practices, enhanced system monitoring and feedback loops, streamlining and redesign of paper artifacts, and expanding and supplementing procedures for patient flight preparation (Table 21). The recommendation for standardizing patient education is similar to a recommendation from Lamb from the British Air Force.[589] and reinforces the observation by Hatzfeld[587] on the limitations of preparatory guidance. Research gaps related to the priority areas identified by Gallimore should focus on the implementation and evaluation of strategies to address these gaps.

Table 21. Human Factors Engineering Recommendations Related to Pain Management in AE[582]

Research Focus	System Characteristics	Top Priority
Information Flow	Right information, right place, right time, right format	Develop patient education information tools
System Monitoring	Continuous monitoring of performance metrics	Develop a system monitoring plan
Feedback	Supporting users' situational awareness, system improvement	Identify the clinical outcomes expected for baseline AE system performance
Technology	User-friendly, easy to learn, easy to use interfaces	Provide opportunities for patient self-monitoring
Culture	Informal and formal, shared attitudes, goals, behaviors, "unspoken rules"	Gauge AE Personnel perceptions of pain management
Learning Management	Training, information storage and access, reducing reliance on memory	Incorporate opportunities for continuous access to skill and process training
Task Processes/Cognitive and Physical Workload	Risks for human error, miscommunication, incomplete tasks, fatigue, stress, multitasking	Evaluate techniques for locating controlled medicines on aircraft in >1 location

There are no studies that follow patients across the continuum of care (POI to rehabilitation). Cohen[590] studied 162 soldiers who presented to the pain clinics at WRAMC or LRMC. Their predominant cause of pain was NBI, with low back pain as the primary presenting complaint. A small subset (17%) of patients had pain related to a BI (missile or blast injury). Among these casualties, the most common complaint was complex regional pain syndrome II (causalgia) and phantom limb pain associated with blast trauma. After missile injuries, the most common diagnosis was soft tissue injury, complex regional pain syndrome II, or post-surgical pain syndrome. The most common treatments were NSAIDs (56%) and opioids (49%), with patients who received opioids reporting higher pain (6.2 ± 2.0 vs. 5.6 ± 1.7, $p = 0.05$). No information on time from injury/event, or acute pain management was reported. Gironda[591] studied 291 OEF/OIF veterans seeking care at the VA, with 55 patients (19.5%) with chronic pain attributed to an injury. Among these patients, 17.2% were related to soft tissue injury, 12.1% were associated with falls and 3% with motor vehicle crashes or other noncombat injuries (6%). None of these individuals suffered a blast or gunshot wound. These findings, which are similar to Cohen's, are important in emphasizing the need to study the en route care of all patients with pain (BI/NBI/Dz), as evidenced by the high prevalence of pain in the NBI patients seeking care. This study is limited by the narrow population (NBI), a lack of pain documentation, and no information on factors that may have contributed to the chronic pain state. Studies are needed to explore care across the continuum, to include early pain/pain management through long-term outcomes.

The 2017 JTT CPG: Management of Pain, Anxiety and Delirium in Injured Warfighters[592] provides only general technical recommendations for management of patient during AE, and the primary source document specific to en route pain management identified in the CPG is the Defense & Veterans Center for Integrative Pain Management. This web site has a page specifically related to Air & Ground Pain Casualty Evacuation (http://www.dvcipm.org/clinical-resources/aero-evacuation-resources); however, the most current documents available on the page are from 2005 and relate to the initial roll-out of the AMBIT Pain Pump. There are no specific pain management recommendations relative to en route care in the primary DoD source documents. The report from the Pain Management Task Force[593] from the Office of the Army Surgeon General reiterates the need for effective pain assessment and management through all phase of care, to include the use CPNB and regional analgesia, but does not provide specific guidance for the en route phase of care.

Carness[594] studied differences in demographics and opioid administration for 84 casualties with amputations who did/did not receive regional anesthesia during AE. The two major demographic differences between the groups with RA versus non-RA in morphine equivalents (RAL 5.19 ± 13.92 mg/flight; Non-RA 45.01 ± 100.45 mg/flight, p = .008) and intubation rates (RA 7 [16%], non-RA 39 [92.9%], p = .0041). Among the 42 patients with RA, 16 had the regional intervention removed; however, the indications for the removal were not identified. No pain data were provided due to lack of consistent documentation. This study is the first to describe outcomes for patients transported with regional anesthesia**. A prospective study, or quality improvement database is needed to capture decisions regarding the use of RA and the rationale for intubation. Other outcomes to explore include the incidence of PTSD in relation to heavy sedation and VAP rates associated with differential treatment. The lack of pain data reinforces the need for standardized documentation requirements and the use of a validated pain scale for intubated patients.**

Research into the use of routine prophylactic analgesia before transport of the patient to the aircraft should be explored and the development of a practice guideline outlining the selection and timing of analgesic administration to ensure adequate pain management during the transport phase from the CASF to the aircraft and during taxiing and takeoff needs to be undertaken. The TCCC Guidelines for Analgesia for Moderate to Severe Pain[552] may have application during periods of short-term transport (i.e., MTF to aircraft). Identification of analgesics that meet the requirements for ideal point of injury analgesics (rapid onset, do not promote hypotension or respiratory depression), such as transmucosal fentanyl,[595] should be considered for the MTF-aircraft phase of transport, as pain may be the most severe during this epoch. Analysis of task performance during this transport phase is needed, with consideration of implications for patient safety and monitoring the patients during this phase of en route care; a period when the CASF and flight crews are busy with the patient transfers and handoff. The summary document by Butler[596] recommending modifications to the TCCC analgesia guidelines may serve as a useful format for a similar exploration for en route care, with consideration given to the current evacuation environment as well as a potential A2/AD environment. The reports from Operation Just Cause (Panama) may provide a useful example to explore the requirements for the rapid treatment, staging and evacuation of casualties with limited resources.[597-599]

No research has been conducted on adherence to pain management guidelines in en route care. A recent study[600] in the pre-hospital setting found that only 35% of patients who had suffered a major injury and met TCCC criteria for analgesia received point of injury analgesia IAW TCCC guidelines. Additionally in three Role II hospitals in Iraq in 2015, only 50% of patients had a documented pain scores;[601] thus pre-transport pain scores cannot be assessed.

A recent study by Huntsberger[602] evaluated the potential risk of various medications during AE, using an tool developed by Prudhomme[603] for use in Army and Navy flight personnel. The original tool includes 70 medications most commonly prescribed to personnel on flight status and a calculation of the risk for side-effects and severity of side-effects was undertaken. In the AE study, a total of 48 medications were studied (eight analgesics: Ibuprofen, celecoxib, morphine, hydrocodone, oxycodone, acetaminophen, meperidine, Toradol). Among these analgesics, meperidine, morphine and hydrocodone, had side effects above the upper control limit (maximum tolerable side effect risk), and oxycodone was at the UCL. In the discussion of this article, the author noted that in vitro and in vivo research is ongoing to assess the integrity of the blood brain barrier at altitude, which may have implications for increased drug concentrations in the brain for analgesics commonly used in AE. Analysis of the actual occurrence of adverse events during en route phase of care for the high-risk medications may validate this instrument.

Gaps:

- ***Association between acute en route pain and chronic pain and pain burden(see Puntillo[604])***
- ***Establish/validate algorithm/standards for en route analgesia, along with specification of monitoring requirements during all phases of transport (i.e., MTF-aircraft, onboard aircraft, etc.)***
- ***Development/validation of en route pain management clinical practice guidelines; safety of integration of TCCC guidelines for periods of rapid transport (i.e., MTF/CASF to aircraft)***
- ***Analyze dosages ordered/received for analgesics/adjuvants compared to the MAARA recommendations and effectiveness of strategy adhering to MAARA guidelines,[605] controlling for previous opioid exposure***
- ***Validate Prudhomme's tool for medication risk against a series of patients transported in AE***

4.20 Anemia

AFI 48-307[108] specifies that all trauma, post-arrests, and post-operative patients will have a current hemoglobin and hematocrit. In addition, all patients with a low hemoglobin should have supplemental oxygen ordered., "Patients with hemoglobin below 8.0 mg (sic) may be transported if the condition is chronic and stable, and not related to bleeding. Patients with a hematocrit below 25% are not airlifted without concurrence of the Validating Flight Surgeon (VFS). Low flow O2 is used continuously on patients with extremely low hemoglobin or hematocrit levels, as in dialysis and chemotherapy patients. An altitude restriction below 5000 feet may be ordered by the VFS".

PATIENT'S CONDITION	IN-FLIGHT O2 REQUIREMENTS
Chronic low hemoglobin states	
8.5 – 10 7.0 – 8.5 Below 7.0	Oxygen Available Oxygen 2L for flight As directed by the AE Validating FS
Post-Operative low hemoglobin states	
9.0 - 10.0 8.0 – 9.0 Below 8.0	Oxygen Available Oxygen 2L for flight As directed by the AE Validating FS

Ingalls[107] analysis of 10 years (2001-2011) of CCATT found no significant differences in hematocrit between survivors (35.1% ±8.6) versus non-survivors (37.6 ± 12.1). The odds of mortality were not significant based on hematocrit or PRBCs received, but was significant for whole blood transfused (OR 1.9; 95% CI 1.03-1.16, p = .003). Four studies explored the association between hemoglobin values and post-flight outcomes. Hamilton[606] studied the association between Hgb $\leq$ 10 g/dL versus > 10 g/dL in 140 critically injured burn patients transported by CCATT. The patients with the lower Hgb had higher injury severity score (34±19.8 vs. 25 ± 16.9, P = 0.02) and additional trauma (50% vs. 25%, P = 0.04), but there were no differences in clinical outcomes (ARDS, sepsis, VAP, renal failure) ventilator, ICU or hospital days, or mortality. Similarly, in Mora's study of 1252 CCATT patients (Hgb >8 g/dl = 1,033 vs. Hgb < 8 g/dl = 215, no preflight Hgb= 57) there were no significant differences in adverse outcomes (e.g., pneumonia, sepsis, DVT, PE, infection) or 30-day discharge status/mortality. In Johannigman's[171,607] study of the walking wounded (ISS 8 ± 11), the mean pre-flight hemoglobin was 13.2 ± 3.5 g/dL (9.4-18 g/dL); thus, analysis of the effect of altered Hgb was not conducted. In Butler's study[59,324] of cabin altitude restriction, the mean Hgb in the CAR group (n = 35) was 10.3 ± 2.6 g/dL compared to 9.0 ± 1.7 g/dL in the non-CAR group (n = 33), p = .025. However, the study does not describe the rationale for prescribing CAR, the use of supplemental oxygen in patients with Hgb < 10 g/dL, or en route or post-flight complications in this patient population. Additional analysis of the data from Butler's study in conjunction with en route care records is needed, particularly as related to the relationship between Hgb and en route and post-flight complications after controlling for PaO_2/SpO_2 inflight.

Barnard[608] explored preflight variables that were associated with post-flight mechanical ventilation greater than 72 hours and 30 days mortality. For every one-unit increase in PRBCs received, there was a 4-5% increase in odds of requiring > 72 hours of mechanical ventilation and patients who received whole

blood had a 3x increase in 30-day mortality; however, no data were provided on the corresponding preflight Hct. There was no significant difference in preflight Hct and ventilation > 72 hours or mortality, however, the study was not designed to explore the relationship between a threshold value (i.e., Hct < 27%) and outcomes. This study is important as it provides the basis for the development of a pre-flight risk assessment. The data could be re-analyzed relative to en route care requirements and outcomes.

4.20.1 Blood Transfusions – En Route. There is limited information on en route blood transfusions and outcomes. A series of papers from Bebarta and Mora [609-611] address the transport of patients with a low Hgb (< 8g/dL). In 1,252 CCATT patients transported between 2007 – 2011, 219 had a Hgb < 8 g/dL, 1033 had a Hgb > 8, and 75 did not have a documented lab value. There was no association between preflight Hgb and post-flight adverse events (pneumonia, ARDS, kidney injury, infection, sepsis, shock, anemia, coagulopathy, DVT, PE, MI, complicated mechanical ventilation, hemodialysis, or transfusion) or disposition at 30 days. The shock index pre/post flight was different in patients who had post-flight complications (0.84; 95% CI 0.7-0.97) compared to patients without complications (0.72; 95% CI 0.61-0.85), but not different based on pre-flight Hgb. Blood was administered during flight in 11% of patients with a Hgb > 8.0 g/dL and 23% of patients with a Hgb < 8 g/dL ($p < .001$). A limitation of these papers is a lack of information on en route adverse events. As discussed below, the development of a model to predict en route care requirements (i.e., blood transfusions) and possible adverse events/clinical deterioration is needed. Similar to research related to the administration of blood during MEDEVAC/MERT,[612,613] a description of outcomes patients who met criteria but did/did not receive blood during regulated en route phase of care may be warranted.

4.20.2 En Route Monitoring – Anemia. Areas for future research include the integration of the monitoring technology, such as that used in previous research[171,614] (Masimo Rad-57 or Masimo Rainbow Set), which provide SpO2 and Hgb to allow for the calculation of oxygen capacity and provide a more integrated analysis of the patient's physiologic status. Similarly, integration of continuous skeletal tissue/muscle oxygenation[571] (StO2/SmO2) or other indicators of physiologic status/oxygenation, may provide insight into differences in physiologic response state based on Hgb level. A limitation of these studies was the lack of information on en route care, to include the administration of blood or supplemental oxygen, and en route adverse events. Additionally, none of the studies explored the relationship between other preflight factors in conjunction with Hgb on en route adverse events or care requirements (including the need for blood transfusions). **The development of a preflight risk assessment that includes not only hemoglobin, but other indicators of physiological stability and risk for en route deterioration is needed,** as there may be a bias associated with the decision to transport/not transport a patient based on factors in addition to Hgb level. Several studies reported on models to predict the need for blood transfusions during MEDEVAC[615] or during first three hours in hospital.[616] These models may be relevant to the prediction of need for blood transfusions during en route care for patients who are still stabilizing. The study by Mora (reported by Bebarta at MHSRS)[609-611] also presents a standardized method for post-flight outcome variables. Similar standardization for en route outcome variables is needed.

Gap:

- ***Preflight threshold for transport based on Hgb and physiologic indicators of stability (i.e., shock index) with en route adverse events/outcomes on longer term outcomes.***
- ***Studies need to include en route data (vital signs, interventions – blood transfusions, supplemental oxygen; and adverse events) and cabin altitude restriction***
- ***Integrate other physiologic measures (continuous hemoglobin, StO2/SmO2)***

4.21 En Route Monitoring

This section of the gap analysis focuses on those technologies/monitoring methods that have been evaluated in the regulated en route care environment or are designed for en route monitoring. A discussion of technologies identified for pre-hospital and MEDEVAC settings,[398,617] is outside of the scope of this analysis, but consideration of the translation of these technologies/methods to the en route care setting may be appropriate. In considering en route monitoring, in a presentation at a NATO conference, Shackelford[616] provided a broad view of technology and strategies to bridge the gap between field and hospital care. One area Dr Shackelford challenged the audience was to consider the major technology successes of the past ten years – simple solutions (tourniquet) along with education and systems of care. Consideration of en route monitoring can balance the success of these simpler solutions and the need for advanced technologies (data capture, data interpretation) within the framework of new care settings, such as A2/AD.

4.21.1 Auscultation. The ability to auscultate chest/abdomen is limited in the en route environment. Frequency spectrum analysis demonstrates an overlap between lung and heart sounds and the noise from a jet turbine engine,[618] although similar analysis has not been conducted for fixed wing military aircraft. The traditional stethoscope has the ability to auscultate up to 80-85 dB.[619,620] Under sound conditions consistent with UH-60 helicopter, the heart beat is not discernible above 85 dB using a passive acoustic stethoscope. One solution to this problem has been the development of a stethoscope with an adequate signal to noise ratio, that discriminates critical pathologic conditions under noisy conditions.

4.21.1.1 Noise Immune Stethoscope. A series of studies have evaluated a noise immune stethoscope (NIS). The NIS has both electronical acoustic mode (passive) isolation technology and an ultrasound Doppler (active) mode that transmits a 2.3 MHz signal into the body, which allows for detection of sound normally insensitive to the human ear (Figure 21).[619,621-625] Of note, using the Doppler component of this technology requires the clinician to relearn normal heart (ta-dá-da versus lub-dub) and breath sounds (bronchial breath sounds or course friction rub). In bench studies the acoustic mode maintained an adequate signal to noise ratio up to 90 dBA for heart sounds and 100 dB for breath sounds.[620 622] Clinicians rate the usefulness of the acoustic signal at least "fair" at 70 dB and 90 dB for heart and breath sounds. The Doppler mode was able to maintain a signal to noise ratio of approximately 20 dB up to 110 dBA and was rate at least fair at 70 dB, 90 dB and 110 dB under lab conditions. Of note, an Army fact sheet reports the noise level on the C-130 between 80-100 dB and on a Falcon 50 (corporate jet – French) the noise level was 77 dB.[626-628]

Figure 21. Noise immune stethoscope.

The NIS was evaluated in an animal model.[629] While the acoustic mode was able to detect esophageal intubation and progressive development of a pneumothorax, the results for hemo-pneumothorax were inconclusive and not consistent with clinical expectations (i.e., unilateral hemopneumothorax with bilateral alterations in breath sounds). The Doppler mode failed in all experiments. Of note, this study was conducted in a laboratory and not evaluated under noise/vibration conditions consistent with AE. The NIS was also evaluated in a clinical setting by four clinicians.[630] Compared to the standard stethoscope, respondents reported similar ability to auscultate respirations in patients with normal pulmonary physiology and in those with known hemo or pneumothorax. The clinicians reported greater confidence in assessing pulmonary and cardiac sounds in the acoustic compared to the Doppler mode and overall the device was moderately helpful in making clinical diagnosis and decisions compared to a traditional stethoscope under quiet conditions. The ability of the NIS to detect potential pathology (e.g.,

pneumothorax, hemothorax, thoracic trauma, pneumonia, arrhythmias, valvulopathy, heart failure, endotracheal tube misplacement) was also evaluated in the medical operations of Navy aircraft carrier (ambient noise 71.9-84.2 dBA).[625] Under these conditions the ability to auscultate for bilateral lungs sounds after intubation and confidence in diagnosis was higher in the acoustic mode compared to the Doppler mode. The acoustic mode was rated as moderately helpful and the Doppler as not helpful in two conditions (intubation, heart/lung sounds). This series of studies demonstrates potential utility of the acoustic NIS in cases of pneumothorax and intubation. The NIS (A-SCOPE) was recently evaluated in a simulated C-130 environment.[631] The 10 AE medical crew members evaluated the stethoscope based on their ability to hear heart and lung sounds in two healthy subjects, ease of use and cleaning and applicability to AE. In contrast with previous research, the Doppler mode was rated significantly higher than the acoustic mode for cardiac auscultation. Further evaluation is needed in preflight area and onboard military aircraft used for AE to include auscultation of critical conditions likely to occur during en route care.

An evaluation was conducted of the noise signature onboard a Sikorsky UH-60 helicopter and the effect on auscultation using the 3M Littman Model 3200 electronic stethoscope.[632] Onboard the UH-60, both noise and vibration interfered with auscultation. Current strategies, including a reference microphone and adaptive noise cancellation would not be effective in this environment. The authors suggest that using a reference accelerometer may be more effective. It is not known if similar results would be found onboard the C-130, C-17 or other fixed wing aircraft.

The Navy conducted a study[633] in 2000 on research on sound-cancelling (COTS) stethoscopes under conditions consistent with a field-hospital 100 kilowatt generator, inside the medical area of a soft-top Humvee, and the interior of a C-130. The experienced providers listened to normal or abnormal heart and lung sounds under the three environmental conditions. Under conditions consistent with a C-130 (simulated 104 dB SPL at the stretcher with a large noise component at lower frequencies and a large amount of energy in the 6-kHz region) the maximal detectable heart/lung sounds were 85.8 ± 0.9 dB SPL, which was lower than the generator and the Humvee. The uses of COTS stethoscopes with sound cancelling were all better than a standard stethoscope for the C-130 environment, with one stethoscope (Smart Med stethoscope) performing better for both heart and lung sounds. The devices were further evaluated under field conditions, which may provide an example for future usage and design questionnaires. In field tests on the C-130 (> 100 dB) the participants were unable to detect even *normal* heart or lung sounds with any of the stethoscopes since it was well out of the intended operating range of these compact devices. The participants also recommend further evaluation on blood pressure measurement, under conditions where automated cuffs are not available. In the pre-flight staging area located behind the C-130 (70-80 dBA) the Sonar Sound stethoscope could detect blood pressure and normal lung and heart sounds.

4.21.1.2 Littman Electronic Stethoscope. Another series of studies using simulation and clinical application were conducted by French investigators onboard the C135 (strategic refueler) or the Falcon 50 (corporate jet configured for medical transport). A standard Littman Cardiology III stethoscope were compared to several versions of the Littman electronic stethoscope (Littman 3100).[626,634] A simulation study conducted onboard a C135 aircraft (ambient noise 85dB) evaluated the Littman Electronic Stethoscope Model 2000 compared to a conventional stethoscope (Littman Cardiology III) on ability to accurately detect cardiac and pulmonary abnormalities (22-30 dB). Five experienced flight providers (nurse anesthetist /intensivist) were unable to accurately detect cardiac abnormalities (systolic, diastolic, Austin-Flint murmur) using electronic stethoscope (4/15 auscultations) or conventional (0/15 auscultations). For simulated lung sounds (crackles, wheezes, one-sided lung silence) there was a significant difference in accurate diagnosis with the electronic (18/20 auscultations) compared to the standard stethoscope (10/20 auscultations). Onboard a C-135 (French strategic refueler – ambient noise88 dB) the quality of auscultation for cardiac and lung sounds in patients was 53 ± 24/100 for the traditional

stethoscope (3M Littman Cardiology) compared to 85 ± 11/100 (3M Littman Stethoscope 3000).[628] A similar study was conducted on the Falcon 50. For cardiac auscultation, the quality was 5.8 ± 1.5 and 6.4 ± 1.9, respectively, for the traditional and amplified stethoscope (P = .018). For lung sounds, quality of auscultation was estimated at 3.3 ± 2.4 for traditional stethoscope and at 3.7 ± 2.9 for amplified stethoscope (P = .15). These studies are important, as they are generalizable to US fixed wing aircraft.

Gap

- ***What are the physical assessment requirements during AE – what technologies are appropriate and most accurate/sensitive for use for cardiac and pulmonary assessment (e.g., auscultation, ultrasound, blood pressure measurement) for potential pathologies (*(e.g., pneumothorax, hemothorax, thoracic trauma, pneumonia, arrhythmias, valvulopathy, heart failure, endotracheal tube misplacement, tamponade). Add blood pressure auscultation.***
- ***Use of reference accelerometer versus active noise cancellation techniques (controlling for noise and vibration)***
- ***Describe noise conditions in pre-flight area (en route patient staging facilities) adjacent to the flight line (for both land based runways and onboard Navy ships).***
- ***Methods for evaluating accuracy/use of devices in en route area (simulation fidelity)***
- ***Standardize methods for evaluation of usage and design, performance,***
- ***Characterize clinical implications of physical assessment (auscultation) on patient outcomes***

4.21.2 Pulse Oximetry (SpO2). SpO_2 monitoring may be a challenge in the en route care environment, particularly in patients with altered perfusion or lack of accessible monitoring sites (i.e., burns, edema). The en route environment may also affect SpO_2 measurements, as mediated through thermoregulatory and hemodynamic vasoconstriction. As discussed in the section on thermal stress, onboard the C-17 the temperature in the front and back of the aircraft was less than 60F within 30-45 minutes of takeoff. Onboard the C-141, which had a similar thermal environment, the skin temperature and skin temperature gradient (indicator of thermoregulatory vasoconstriction) were correlated with the ambient temperature. This importance of these environmental condition on SpO2 monitoring was demonstrated in a series of studies in healthy subjects exposed to an environmental temperature of 58°F - 62°F with their SpO2 rapidly adjusted between 100% and 70%. Compared to radial artery (lag time 10.7 ± 7.6 seconds), the mean lag times to detect changes in the SpO_2 was significantly longer for the sensors on the ears (25.6 ± 8.5 sec, $p < .001$) and fingers (77.5 ± 28.4 sec, $p < .001$), but not on the forehead (10.1 ± 5.4 seconds). In a second study, in 68% of the observations, the lag times between the forehead and finger sensors were between 60 to 120 seconds for both desaturation and re-saturation.[635,636] These findings were replicated in a study[637] where the core temperature of healthy subjects was decreased to 35-36°C and they were exposed to a hypoxia challenge (FiO2 100% to 11%). Under these conditions the nadir ABG was reached at approximately 60 seconds after initiation of the challenge. The finger response time increased from 130 under to normothermia to 215 seconds with hypothermia. In contrast, core hypothermia did not affect the lag times for the ear or forehead sensors.

The finding of the effect of vasoconstriction on pulse oximetry performance is not new. What is unique is the consideration of the additional effect of the AE environment on the ability to detect acute hypoxic events. The differences or interaction in response time for thermoregulatory vasoconstriction and reflex vasoconstriction under conditions of trauma has not been studied. The ability and time lag to detect a slow deterioration in SpO_2 under AE conditions has not been studied. Use of alternative monitoring sites, such as forehead oximetry[638] may be relevant to en route monitoring.

Johannigman's[171] study, which detected a high incidence of hypoxemia in non-critical combat casualties, needs to be replicated with the inclusion of patient demographics and en route observation (i.e., were the patients sleeping and slumped over versus awake). This study also identified the need to explore portable, continuous SpO2 monitoring for a larger number of patients, including those sitting. Two studies are ongoing to evaluate the portable ViSi monitor (CSTARS – Cincinnati and 711 HPW – USAFSAM) and a prototype miniaturized SpO2 monitor[639] is under development to identify physiologic and cognitive decline in combat soldiers at altitude. A recent study[640] evaluated a prototype oximeter for use on alternate body locations in healthy subjects undergoing a hypoxia challenge (100% to 70%). Compared to a standard measurement of accuracy (ARMS – root mean square difference < 3.5% compared to radial arterial blood gas) the following ARMS data were observed: calf 1.7% (n = 26); bicep 3.1% (n = 12); forearm 3.4% (n = 11); pectoral 2.9% (n = 42); sternum 2.9% (n = 13), suggesting the potential feasibility of this new device. These various devices may have application for en route monitoring, but need to be evaluate under conditions associated with peripheral vasoconstriction.

4.21.3 Buccal Oximetry. De Jong[641] described the accuracy and precision of buccal pulse oximetry (SbpO2) compared to arterial O2 saturation (SaO2) and finger oximetry (SpO2) in 53 healthy adults exposed to hypoxemic conditions created using the Reduced Oxygen Breathing Device 2 (ROBD 2). The buccal oximeter using a veterinary oximeter (Nellcor VETSAT). Using the ROBD, the inspired oxygen was decreased until the subject's SPO_2 was 90% ± 1%, at which time an arterial blood gas and simultaneous SbpO2, Spo2 measurements were obtained. The procedure was repeated with the subjects SpO2 at 80% and 70%. Upon completion of the 70% phase, the subject received 100% oxygen. At all levels, the SbpO2 was higher than the SaO2. During the desaturation phase of the study, the mean bias between the SbPO2 and SaO2 was 1.8 ± 1.6% (normoxia), but was less accurate and precise under hypoxemic conditions: 0.3 ± 2.5% (90%), 2.4 ± 2.2% (80%), and 2.6 ± 3.0% (70%). During desaturation, the finger oximeter lagged the buccal oximeter 21.8 seconds, and during re-saturation from 70% (administration of 100% O2), the $SbPO_2$ reached 80% 21.8 ± 9.5 seconds faster than the finger oximeter and 18.4 ± 11.4 seconds faster to 90%. These data demonstrate a lack of accuracy and precision of the buccal oximeter, but also the limitation of finger oximetry to rapidly respond to acute changes in oxygenation. A recent study by Amini[642] evaluated a new near infrared spectroscopy probe and laser doppler flow measurements on the buccal mucosa in six healthy subjects exposed to altitude (Ground – 16,000 feet). The buccal and finger SpO_2 decreased with altitude, with the mean difference between the two measurements increasing with altitude (1.8% at 2000 feet to 11.4% at 16,000 feet), which is consistent with the findings from DeJong's study. An interesting finding was that using the NIRS technology, the buccal SpO2 was reflected in the first and third spectra and blood flow was detected in the middle segments, which allowed for the simultaneous measurement oxygenation and flow. In addition to the changes in SpO2, there was a decrease in blood flow at higher altitudes.

Gap

- **Utility of buccal oximetry under 85% - 100% SpO2 range (consistent with studies in previous range) – particularly in casualties with severe vasoconstriction or inability to use standard sensor sites**
- **Integration of oximetry and flow measurements**

4.21.4 Ultrasound. Several review papers have outlined the potential for the use of ultrasound during helicopter transport. Wagner[643] summarized the current literature and potential applications for ultrasound in space and Libert[644] discussed the potential use of cerebral echography during transport combat casualties patients with neurological injuries (no data). Two studies demonstrated the ability of hospital emergency personnel who are not experienced in ultrasound to detect pneumothorax during transport.[645,646] These studies present possible readiness training strategies to support the performance of ultrasound in en route care. Murthi[647] studied six critically injured civilian trauma patients. A focused

echocardiographic evaluation (FREE) at time 0 (within first two hours of resuscitation) found that 3/6 patients were volume replete, while the remaining three patients did not achieve volume repletion until approximately 18 hours of treatment. The results indicated that in 40-50% of the cases, a fluid bolus may not have been beneficial (i.e., bolus caused a 10-15% increase in SV). This pilot study demonstrates a possible non-invasive strategy to assess cardiac functional status to inform fluid resuscitation. A recent larger study by Murthi[648] further refined the use of echocardiography in surgical/trauma patients. Analysis of the subset of the trauma patients would be useful to determine its utility in pre-transport and en route care environment. **No studies have been published or discuss the use of ultrasound during AE.**

Gaps

- **Requirement for en route performance of ultrasound**
- **Diagnostic accuracy of en route ultrasound (consider experience level of providers), effect of en route stresses of flight on performance and changes in diagnostic criteria**

4.21.5 Blood Pressure Monitoring. A majority of CCATT patients are transported with invasive arterial blood pressure monitoring, with over 80% of trauma patients with arterial lines.[90,92,649] These monitoring systems can be affected by altitude (gas expansion) and aircraft vibration. A bench study[650,651] (altitude chamber, vibration table, C-17) analyzed the effect of microbubbles and vibration on the dynamic response characteristics of the fluid-filled pressure monitoring system. There were significant main effects from the line type (straight line, straight line plus VAMP device) and air volume (5 μL). There was no main vibration effect during the bench study. In the field study on the C-17: there was an Altitude and Altitude*Air Volume effect, with a worsening of the dynamic response characteristics (decreased Fn) due to microbubble expansion at altitude. There was also a significant increase in underdamped systems with engines on (? vibration effect). There was no interaction between aircraft Off/On and line type or air volume. To mitigate the effects of the microbubbles, precise line preparation, including removal of all microbubbles using a Rocket Flush (rapid injection of saline through the system to remove microbubbles) resulted in a significant improvement in dynamic response characteristics. These results were integrated into a line preparation protocol for CCATT. (Note – it is not clear if this protocol is currently in use).

Previous research has demonstrated that arterial and non-invasive SBP measurements are not the same, and should not be compared. Optimizing the dynamic response characteristics and correct referencing of the system are required to ensure accurate arterial BP measurements. Similarly, optimizing the performance of the noninvasive measurements is essential to the accuracy.[652] A recent study,[653] which compared invasive arterial BP and non-invasive BP measurements confirmed these results during ground-based measurements and during rotary wing transport. Integration of these research findings and the practice implications (including line preparation as described by Bridges) are a basic part of ICU education and should be integrated into the education and training for en route providers.

As discussed in the cardiac section, the position of the transducer relative to the body may be associated with an artifactual variation in blood pressure during acceleration and deceleration.[406] This finding needs to be confirmed during aeromedical transport, particularly in patients with a potentially altered cardiovascular response or those who may be affected by blood pressure variability. Areas for future research – integration of closed-loop arterial blood pressure control in trauma patients during the en route phase of care.[654] and further description of hemodynamic responses to phases of transport (see Ehlers[405]).

4.21.6 Shock Index. Three studies used changes in the shock index (HR/SBP) as an indicator of stability across transport. Two studies evaluate pre-post transport SI in the pre-hospital setting. The study by Gross[612] analyzed the pre-post transport SI for casualties who met criteria to receive en route blood products. There was a significant improvement in the SI in those casualties who met criteria for a blood

transfusion and received a transfusion (1.56 to 0.95; median decrease 0.31; IQR 0.04-0.74) compared to casualties who did not receive a transfusion (1.17 to 1.09; median decrease 0.16; IQR 0.07-0.49). No other data were provided on en route care or vital signs during transport. Apodaca's study[655] use SI to evaluate outcomes based on the type of transport (MERT, PEDRO, DUSTOFF), controlling for injury severity. For casualties with an ISS $\geq$ 26, the SI improved (1.39 ± 0.62 to 1.09 ± 0.42) only for MERT transports. The casualties with an ISS (10-25), the SI improved for both the MERT and PEDRO transports, but not DUSTOFF. For the least severely injured (ISS 1-9) the SI improved for all groups. No data on transport times or en route interventions or other vital signs were provided. Bridges[571,656,657] studied SI, StO2, lactate, base deficit and vital signs pre-post Role II-III 48 transports supported by En Route Critical Care Nurses and in six POI to Role II transports, vital signs and StO2 were measured pre-post MEDEVAC. For the ECCN transports (Phase 2) the mean StO_2 was lower, but not significantly different, in patients with abnormal vital signs (76 ± 15) compared to patients with normal vital signs (83 ± 11). Only 14 patients had pre-transport laboratory values to assess perfusion status. Among these patients, an abnormal StO2 had a positive predictive value of 80% and a negative predictive value of 64% for hypoperfusion. Patients with an abnormal StO_2 were four times more likely to have concurrent hypoperfusion than patients with normal StO_2. En route: The average transport time was 54 ± 29 minutes (median 45, IQR = 42). A majority (n = 32) of the patients were ventilated during transport. Crystalloids were administered to 29 patients, with 75% receiving less than 250 ml. The three patients with overt hypoperfusion at the time of transport received between 250 and 600 ml of crystalloid and two received norepinephrine. In contrast, the five patients with occult hypoperfusion, received between 0 and 200 ml of crystalloid. Upon arrival, among the patients with pre-transport hypoperfusion, three had hypoperfusion (2 severe and 1 mild); however, labs were not obtained on four patients (taken to a non-US facility). Post-transport: Vital signs were recorded on 44 patients (SBP < 90 = 1; HR > 120 = 12) and the shock index was > 0.60 in 35 patients (mild shock = 27; moderate shock = 7; severe shock = 1). Twenty-one patients had post-transport labs (14 obtained within 100 minutes of arrival). Among these 14 patients, nine had abnormal perfusion (overt hypoperfusion = 1; occult = 8) and the StO2 was lower, but not significantly different) in the patients with hypoperfusion (72 ± 11) compared to patients with normal perfusion (80 ± 15). The change in perfusion status (pre-post transport) was analyzed for the seven patients with complete data sets. In the five patients who continued to have alterations in perfusion, the StO2 decreased (↓4 ± 10), but there were insufficient data to evaluate patients with normal or improved perfusion (Tables 22 and 23).

Table 22. Shock Index (Pre/Post-Transport)

Shock	Pre-Transport	Post-Transport
No shock (SI < 0.6)	13 (28%)	9 (19%)
Mild shock (SI 0.6 to < 1)	26 (55%)	25 (53%)
Moderate shock (SI 1 to < 1.4)	2 (4%)	2 (4%)
Severe shock (SI $\geq$ 1.4)	1 (2%)	1 (2%)
Missing	5 (5%)	10 (21%)

Table 23. Pre-Post Transport: Change in StO2 Based on SI (< 0.8 or ≥ 0.8) (n=40)

Pre-Post Perfusion Status	n	ΔStO2	Percent ΔStO2
Continued normal (SI < 0.8)	20	↑ 2 ± 5	↑ 3 ± 7
SI $\geq$ 0.8 (shock) to SI < 0.8 (normal)	1	↓ 42 (see case)	--
SI < 0.8 (normal) to SI $\geq$ 0.8 (shock)	4	↑ 1 ± 10	↑ 1 ± 15
Continued shock (SI $\geq$ 0.8)	15	↓ 2 ± 13	↑ 0 ± 25

Post-transport, 20% of the patients had indications of hypoperfusion (based on available labs). When using a shock index $\geq$ 0.8 as the indicator of hypoperfusion, pre-transport 18/47 (38%) and post-transport 20/43 (47%) were in shock. The perfusion status deteriorated in 5/9 (56%) patients based on pre-post transport vital signs and labs and in 19/40 (48%) patients based on SI. Only 14 patients had a clear delineation of their perfusion state at the time of transport (defined as measurement of base deficit, lactate or acid-base status within approximately 2 hours of transport) along with vital signs. Nineteen (48%) patients demonstrated a deterioration in their perfusion state (n = 4) or unresolved hypoperfusion (n = 15) during this epoch of care. These findings in conjunction with the post-transport perfusion state (estimate 20% to 47% of these patients were hypoperfused) indicates the need for a real-time method to rapidly assess perfusion state pre-transport and during transport. Although abnormal StO_2 values (< 75% or > 90%) were intermittently useful in identifying patients requiring additional evaluation, in the Role II transport setting the StO_2 was not a reliable indicator of altered perfusion. The analysis of the StO_2 as a supplement to standard monitoring was limited by the absence of simultaneous lab values (base deficit or lactate) to confirm the perfusion state. In the ECCN transports, which lasted a median of 45 minutes, there was limited documentation of en route vital signs and care activities (fluids, vasopressors). Further description of en route care provided during critical care transports, particularly for patients with or at risk for hypoperfusion. A key question is whether these shorter transport periods are focused only on transport or whether they are treatment periods.

4.21.7 Functional Hemodynamics. There is limited research on the use of advanced hemodynamic monitoring (i.e., functional hemodynamics) to identify occult deterioration or to guide volume resuscitation during the en route phase of care. Two animal studies using a hemorrhage model under conditions consistent with en route care[650,651] and a prospective observational study of combat casualties from entry into the emergency department through surgery or ICU have been conducted.[658] In the study[658] of 25 severely injured combat casualties (ISS 21 ± 10; ventilated), functional hemodynamic indicators (arterial line – systolic pressure variation and pulse pressure variation; noninvasive pleth variability index) were monitored from time of admission through the first six hours of care (ED, OR, ICU). This study compared the invasive and non-invasive indicators of fluid response status and described the changes in the patient's hemodynamic status over the initial six hours of care. Overall, there was a poor correlation between PVI and arterial functional indicators during operative period; however, the changes in PVI were more consistent with macrohemodynamic changes and interventions (i.e., blood, vasopressors). A subset analysis was conducted in 15 patients with > 60 minutes of ICU care (average monitoring 141 ± 48 minutes). In these patients, there was a strong correlation between PVI and SPV. Independent of ventilator tidal volume, a PVI > 15.5 discriminated fluid response status for SPV% and PPV. There was a significant difference in PVI values for responder versus non-responders. Seven of 25 patients had a > 20% dropout (6/7 with hemodynamic instability, receiving vasopressors, massive transfusion, "cold extremities" 1/7 in ICU -all others in OR). A limitation of this study was that it was conducted at two Level III hospitals (Bagram, Kandahar), thus, many of the casualties received initial resuscitation at another facility prior to arrival. Evaluation of the patient's physiological state (including continuous Hb) during emergent management and transport post-damage control resuscitation is needed. An area for further research is the temporal relationship between changes in the functional hemodynamics and clinical deterioration and assessment of the adequacy of volume resuscitation (Figure 22). In these two cases, the functional hemodynamic indicators (indicative of fluid response status as a surrogate for hemorrhage or fluid resuscitation) preceded macrohemodynamic changes (HR, BP) and reflected the response to volume resuscitation.

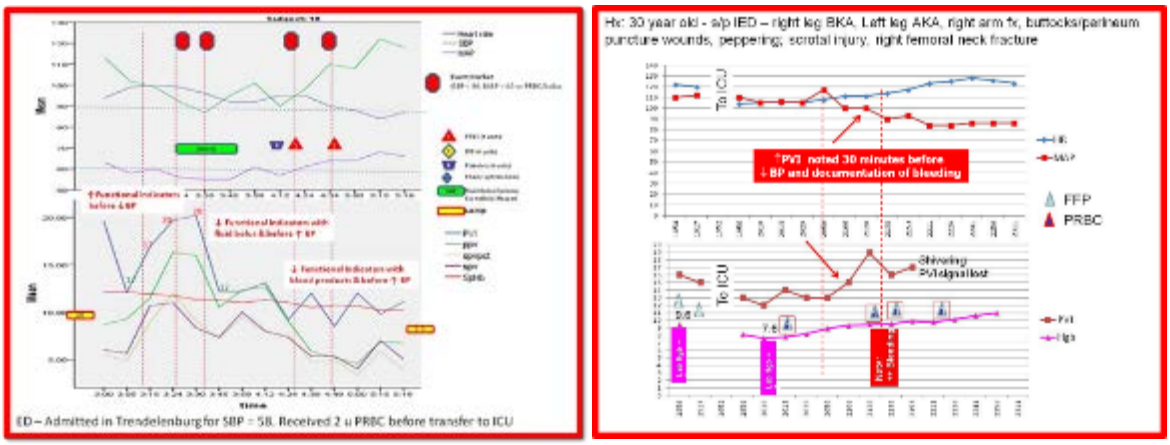


Figure 22. Exemplar cases of changes in macrohemodynamic (HR, SBP, MAP) and functional hemodynamic indicators in combat casualties. Case 1. Casualty transferred to ICU for stabilization before surgery. The case demonstrates the correlation between the pleth variability index (noninvasive) and invasive (SPV and PPV) functional indicators. Of note are the acute increases in the functional indicators before a clinically significant decrease in MAP and the response to fluid/blood administration. The continuous Hgb progressively decreased across the period of monitoring despite the administration of two units of blood. **Case 2** is a critically injured casualty who was coagulopathic. The patient was transferred to the ICU for stabilization before surgery. There was an acute increase in the PVI approximately 30 minutes before the BP decreased and it was noted that the patient was bleeding from the amputation (dressing completely saturated and dripping in the bed). Of note, the continuous Hgb had minimal change with the rapid administration of three units of blood.

Dubost[659] presented a study on the use of bioreactance hemodynamic monitoring in 18 combat casualties evacuated from Afghanistan. Measurements were feasible (no signal loss) in 16/18 (two excluded due to severe thoracoabdominal trauma, which precluded the placement of the monitoring pads). Compared to baseline, the CI decreased during the first 10 minutes of flight, with a significant decrease noted for minutes 4-10. There was no change of HR during this period. The CI continued to decrease at minutes 10/30/50, but the CI was not significantly different from baseline at Minute 70. There was no difference between the CI 10 minutes before landing and the landing values. This paper presented a case where the patient with multiple gunshot wounds to the abdomen, with a vertebral hematoma. Shortly after takeoff the patient deteriorated (CI decreased 15%, BP decreased to 89/49, with an increase in SVV). The patient responded to a 250-ml colloid bolus with an increase in CI and BP. As noted by the author, this case demonstrates the integration of SV and SVV monitoring in a differential diagnosis and management. This study is limited by the small number of patients. Comparison of the characteristics of the patients in this study with those transported by CCATT would be useful in identifying the requirement for this level of monitoring.

Gaps

- **Integration of functional hemodynamic indicators during en route care – determine ability to detect occult deterioration before macrohemodynamic changes**
- **Use functional hemodynamic monitoring to describe cardiovascular response to phases of transport (takeoff/landing)**

4.21.8 Continuous Hemoglobin. There is a large body of research related to noninvasive continuous hemoglobin. A recent meta-analysis[660] of 32 studies found an overall mean difference (noninvasive – central laboratory) of 0.10 ± 1.37 g/dL (-2.59 to 2.8 g/dL), and in the subset of five ICU studies the mean difference was -0.51 ± 1.59 (-3.63 to 2.62 g/dL). No studies have been conducted using continuous hemoglobin during en route care. Bridges[614,661,662] studied continuous hemoglobin in 23 combat casualties

(ISS 20 ± 9.8; age 29 ± 9 years; male 97%; 100% intubated). Ten subjects were direct admits (median time from injury 82 minutes) and remaining patients were transferred to the Role III facility (median time from injury 11.2 hours). Overall the bias was 0.3 +/- 1.6 g/dL (95% LOA -2.4, 3.4 g/dL). The SpHb-Hb difference < ± 1 g/dL in 37% of pairs and 86% of the pairs changed in similar direction. An important finding was the error introduced by the iStat compared to the central laboratory Hb, which may have increased the bias and imprecision of the SpHb. In four cases, Hb samples were run on both the iStat and the Coulter. The Coulter Hb was significantly higher than the iStat Hb (1.38 ± 0.3 g/dL; 95% CI 1.87, 0.88, P=0.003). An area for further study is the ability of continuous monitoring to detect occult hemorrhage. As demonstrated in the following case (Figure 23), the continuous Hb demonstrated the rapid changes in Hb associated with massive hemorrhage and resuscitation, that would not be as well characterized by intermittent Hgb measurements.

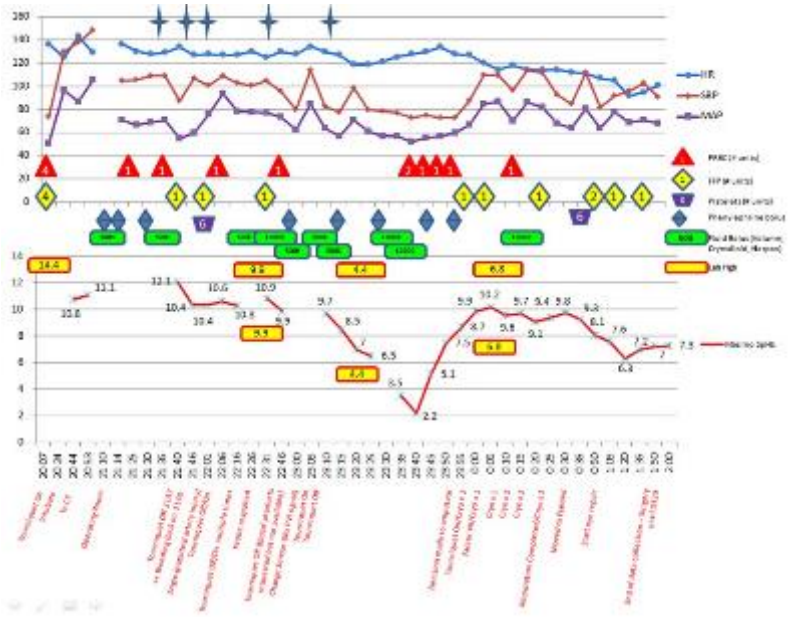


Figure 23. Case study of combat casualty with hemorrhage and massive transfusion. Case: Combat casualty who suffered a mounted IED blast injury. Injuries: left globe injury, open tibia/fibula fracture, facial lacerations, fractured mandible, wounds to left elbow, tourniquet on lower extremity). Injury Severity Score: 25. A tourniquet was in place on the lower extremity. The data collection, which started 80 minutes after the injury, began in the Emergency Department and continued through surgery. During surgery, there were multiple attempts made to re-vascularize the lower extremity, with release of the tourniquet. During the monitoring period, the patient received a massive transfusion (14 units of PRBCs, 14 units of FFP, 12 units of platelets, 8 units of cryoprecipitate) and a dose of recombinant Factor VII in addition to 6000 ml of crystalloid, 1000 ml of Hetastarch, and multiple doses of phenylephrine. The laboratory Hb was obtained in the ED (Hb = 14.4 g/dL) and three times during surgery, with a nadir of 4 g/dL. The SpHb was monitored continuously, with three drop out periods. The median perfusion index (PI) was 0.9 (IQR 1.8). Over a 30-minute period during the final attempt to re-vascularize the leg, the SpHb decreased from 9.7 g/dL to 2.2 g/dL followed by an acute increase to 10.2 g/dL associated with the rapid administration of five units of PRBCs. The case demonstrates the ability of SpHb to trend with the laboratory Hgb and to capture changes in SpHb associated with acute blood loss and massive resuscitation despite a low perfusion state.

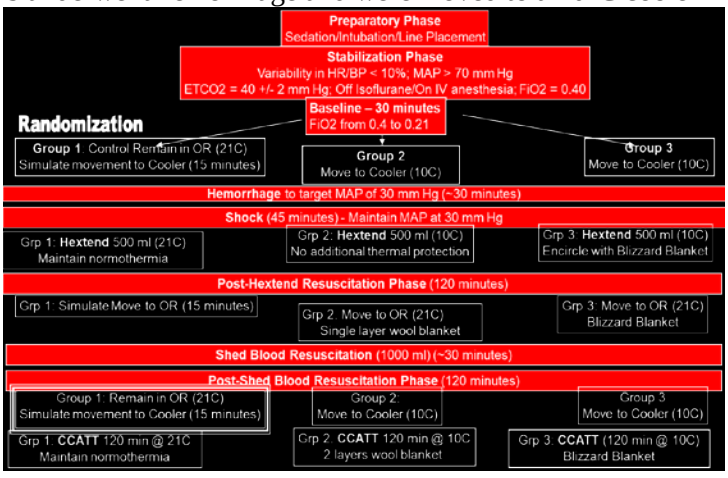
A study[663] was conducted in healthy subjects to evaluate the effect of oxygenation status on the accuracy of SpHb measurements compared to laboratory Hb.[663] At baseline, the SpHb was on average 3 g/dL lower than the lab Hgb. Of note, this bias is considerably larger than observed in Kim's[660] meta-analysis, which suggests a potential calibration error. There was no difference in the SpHb with ascent to altitude (14K feet) or at 14K feet + 100% O2 or return to baseline. However, at 14K, there was a loss of measurement

in 49% of cases, which may reflect internal recalibration to the acute change in SpO_2 (87%). A recent study[664] using the Pronto-7 (Masimo) found no significant change in the bias between 21% (1.1 g/dL) and 100% FiO2 (1.0 g/dL; however, this study was conducted in an operating room with an unspecified time to increase the FiO2. A gap is how the monitor would respond during less acute changes in SpO_2 (consistent with changes observed in AE), and the clinical significance of the SpHb signal dropout.

Gaps

- **Currently no validated method for en route continuous Hgb monitoring (see above for lack of accuracy for iStat)**
- **Continuous Hgb (and other indicators of perfusion) during post-damage control transport**
- **Effect of slower changes in SpO2 on SpHb accuracy and precision**
- **Effect of single preflight calibration[665,666] (based on initial Hb-SpHb difference) on en route values and need for recalibration under dynamic conditions**
- **Integration of continuous Hgb into Butler's[322] research related to prediction of oxygen deliver in patients with/without CAR**

4.21.9 StO2/SmO2. There is limited research related to the use of skeletal tissue/muscle oxygenation during en route care. Studies in combat casualties at a field hospital focused on the use of StO2 to predict LSIs, blood transfusions, and mortality[667,668] Experimental studies have demonstrated the ability of SmO_2 to identify hypovolemia created by lower body negative pressure before changes in StO2.[669] A swine model[670,671] of hemorrhagic shock was used to describe the perfusion status during combat resuscitation and evaluate the effect of core temperature on StO2 compared to femoral venous O2 and central venous O2 and other indicators of perfusion. Animals underwent hemorrhage and were moved to a 10°C cooler to simulate field conditions. Animals were provided various levels of thermal protection (simulates uniform only and wool blankets in field hospital) or a Blizzard Blanket. Following resuscitation in a simulated field hospital (21C) the animals were moved back to 10C environment to simulate AE (temperature consistent with the back-litter position on a C-17). The various thermal conditions created three groups based on core temperature (Group 1: 38 ± 1C; Group 2: 31.9 ± 1.6 – nadir; Group 3: 33.2 ± 1.8C). There was no significant difference in the SfvO2-StO2 based on core temperature. The StO2 trended with other O2 indices, but overestimated the SfvO2 at all points (mean bias -14% ± 16%, mean limits of agreement -1, 45%) with increased bias during shock (baseline -9% ± 11%, 40% hemorrhage -35 ± 16%). The StO2 probe failed repeatedly at 10°C. Systemic O_2 indices decreased rapidly during hemorrhage with nadir at 50% hemorrhage (Baseline DO_2 1123 ± 362 ml/min; nadir = 417 ± 180 ml/min; Baseline SvO_2 64 ± 7%; nadir 25 ± 10%; Baseline $SfvO_2$ = 72 ± 9%; nadir 29 ± 15%; Baseline StO_2 83 ± 8%; nadir 51 ± 29%). Lactate/BE response lagged behind other O_2 indices (Baseline Lactate 0.9 ± 0.3 mmol/L; max 5.1 ± 3.1 mmol/L at post-Hextend 500 ml; Baseline BE 8.7 ± 2.1; nadir 1.2 ± 4.6 post-Hextend 250 ml). Indices returned to levels indicating adequate perfusion at the following points: MAP > 60 mm Hg (post-Hextend 500 ml); HR < 120 beats/min (post-Hextend 75 min); SvO_2 > 50% (10% shed blood); BE < 2 below baseline (post-shed blood 60 min) and Lactate < 2.5 mmol/L (post-shed blood 120 min) (Figure 24).



Gaps: The noninvasive StO_2 probe failed under field/military AE conditions and was not an accurate indicator of tissue or systemic O_2. StO_2 cannot be used to guide operational trauma resuscitation. Occult hypoperfusion lasted 120- 240 minutes and occurred before arrival at the simulated field hospital, indicating the need to study other methods to detect occult hypoperfusion under field conditions and during en route phase of care.

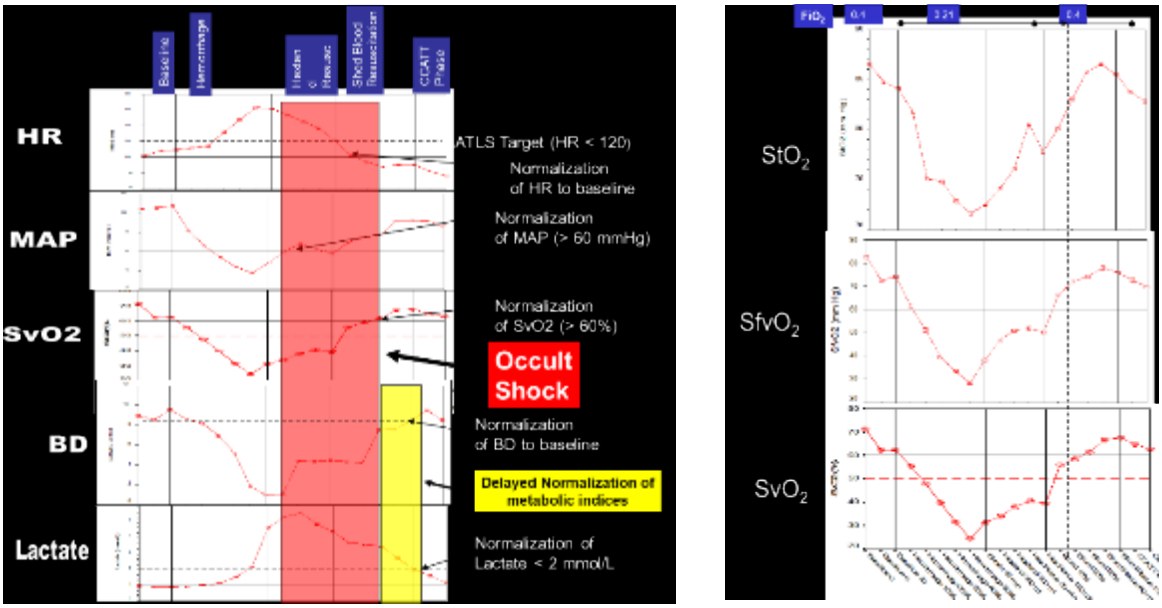


Figure 24. Perfusion state during hemorrhagic shock and resuscitation.

Only one study has evaluated the use of StO_2 in the en route care environment. As previously described (see Shock Index section) in the Role II-III transport of severely and critically injured/ill patients[571,656,657] did not find the StO_2 to be a reliable indicator of altered perfusion. An area for further research is to determine if abnormally elevated StO2 (? Shunt or hyperdynamic state) is associated with hypoperfusion and adverse outcomes.

A report from a feasibility study outlines the methods to evaluate the utility of lactate and tissue oximetry for the early detection and treatment of circulatory shock during pre-hospital en route care.[672] In this study an occlusion StO_2 was performed to evaluate tissue metabolic needs and perfusion state (recovery time after release of occlusion). Preliminary results related to the performance of occlusion StO2 by flight crew in healthy subjects demonstrated reliability in performance. The report indicated a study was to be conducted on the use of these monitoring methods during transport to a trauma center, however, no final report could be located. These results would be more applicable to pre-hospital care or during the transport of unstable patients.

4.22 En Route Nutrition

There is minimal information on nutritional support during en route care. Until 2005, the administration of enteral nutrition was not allowed in AE, at which time a policy letter from AMC authorized enteral feeding during AE transport from EUCOM to CONUS. The safety of this practice was monitored through the JTTS. In April 2007, glutamine supplements were added to the nutritional guidelines. Dorlac[673] reported on the administration of en route nutrition following the guideline implementation. Using data from the JTTR and CCATT, records for 486 patients transported from LRMC to CONUS in 2006 were analyzed. During this period, there were 486 CCATT patients. Among the 210 nonintubated patients, 133

records were reviewed (90 trauma dx). All of these patients had documentation of enteral access or oral feeds. There were 276 intubated patients (237 trauma, ISS 21.5 ± 12.8). Records were reviewed for 207 patients (177 trauma diagnosis). Among these patients 199 had documentation of enteral access and nutrition. The time of tube placement at LRMC was available for 127 records, with 61% of the patients with enteral access within 24 hours (average time 23 hours). No data were available on time to transport, time from injury to placement of enteral nutrition, percentage of patients with enteral tubes placed before transport from AOR, en route care management issues.

AF1 48-307 provides general guidance on en route nutrition, including the continuation of total peripheral nutrition (TPN) during flight (f the TPN runs out during flight, it should be replaced with D10). A review of AFI 48-307 regarding enteral tube management identified a need to update the AFI based on current literature. Areas are those related to the confirmation of tube placement (i.e., auscultation following air insertion is no longer recommended) and the performance of residual checks and holding enteral nutrition based on residual volumes.

The JTS CPG: Nutritional Support Using Enteral and Parenteral Methods (CPG ID: 33)[674]
Specifies: 1) gastric feeds are not recommended during transport to CONUS, 2) enteral nutrition (past ligament of Treitz) does not need to be stopped for CCATT/AE. However, additional clarification is also provided:

> When a patient is transferred from one level of care to the next in a rapid fashion (e.g., Forward Operating Base (FOB) to Role 3 to Role 4 (e.g., Landstuhl Regional Medical Center (LRMC)), it is difficult to monitor feeding tolerance during AE or Critical Care Air Transport Team (CCATT) evacuation. It may be best to hold initiation of feeds until patient will be at one location for at least 24 hours. The risk of aspiration in an awake patient or intolerance in an intubated patient is real and necessitates appropriate repeated examinations until feeding tolerance is well established prior to any flights.

Two papers[675,676] from the British CCAST program comment on the risk for microaspiration during AE due to gravitational forces, head flat position, and variations in endotracheal tube cuff inflation with changes in altitude. Prevention of microaspiration and strategies to enhance en route nutrition were identified as high priorities for the CCAST program.[677] The summary[676] of a proposed research study to evaluate the incidence of microaspiration during CCAST is outlined, however, no reports have been published summarizing this work. A 2014 review[678] also commented on the risk for microaspiration during AE, but presented no recommendations for en route nutritional support.

Gaps

- **Adherence to guidelines for nutritional therapy in trauma patients and effect of transport on adherence to guidelines (e.g., time to initiation of nutrition, calories/type of nutritional support provided during AE)**
- **Describe nutritional support during en route phase of care for CCATT and AE patients (expand analysis conducted by Dorlac[673])**
- **Incidence of microaspiration during en route phase of care (see Turner[676])**
- **Incidence of ventilator associated pneumonia in patients transported with/without enteral nutrition**

4.23 Noncompressible Junctional/Torso Hemorrhage – REBOA/Junctional Tourniquets

There is increased emphasis on the application of solutions (e.g., REBOA and junctional tourniquets) for noncompressible junctional/torso hemorrhage under pre-hospital conditions.[679] The implication for en route care is the potential requirement for longer distance transport these patients, with the devices in place or the potential to place these devices during the en route phase of care.

4.23.1 REBOA. The 2014 JTS CPG: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for Hemorrhagic Shock[680] outlines the indications and considerations for the use of REBOA in a surgically capable field facility. In summer 2017, a series of papers related to the far forward use of REBOA were published.[681,682] A case series[683] reported on the successful use of ER-REBOA in four casualties under A2/AD conditions. The casualties were transported less than 10 minutes to a far forward casualty collection point where REBOA was performed and the casualties underwent damage control surgery and resuscitation before evacuation to a Role II facility. The duration of occlusion ranged from 20 to 65 minutes, with the sheath removed before evacuation. All patients survived the 2-hour transport and were hemodynamically stable upon arrival (no details of en route care).

Only one study has explored the placement of REBOA in the field and during MEDEVAC. The study was conducted during the 2016 military medical exercise at the Kirov Military Medical Academy, St Petersburg with transport on a Mil Mi-8 helicopter.[684] During the MEDEVAC evaluation, successful sheath placement was accomplished at 12 minutes (30 minutes from initial injury). Challenges noted included inability to place the access wire on the first attempt and difficult lighting and vessel visualization. The animal survived the 14-minute flight. **No studies have been published on long distance transport or en route care of patients with a REBOA catheter in place. Research is needed to evaluate the stresses of flight on REBOA function and en route monitoring requirements and care are needed. Additional outcomes are also needed on the effects of prolonged balloon inflation, including the feasibility of en route transport with partial REBOA.[685-688]**

4.23.2 Junctional Hemorrhage Control. Kotwal[689] published a summary article on the four junctional tourniquets evaluated by the DoD. In the recommendation from the 2011 Defense Health Board to include the Combat Ready Clamp (CRoC) in the TCCC guideline, it was noted that the stability of the device during transport or exacerbate an existing pelvic fracture was not known. Only two case reports[690,691] are available on the MEDEVAC transport of patients with a junctional tourniquet. Both cases suggest that the devices remained stable and functional during transport; however, no systematic evaluation has been completed on the use of these devices during any phase of transport (including AE). The US Army recommends the use of the SAM Junctional Tourniquet (SJT) and the 2017 TCCC guidelines[552] state only that a TCCC recommended junctional tourniquet be used. A British study[692] evaluated the Abdominal Aortic Tourniquet (AAT), which is a circumferential device placed around the abdomen. Compression is applied with a windlass mechanism and an inflatable bladder to compress the aorta. No studies have been conducted using this device during air evacuation. An area for research is the effect of altitude changes during transport on the compression applied. An area for further research is the use of these devices during prolonged transport, as an animal model demonstrated extensive muscle necrosis after a 2-hour umbilical application of the CRoC. In contrast, with a 2-hour inguinal application of the CRoC there was extremity ischemia, but limb function was regained after several days.[693]

Gaps

- **Effects of stresses of flight (MEDEVAC/AE) on REBOA system function**
- **Ability to place REBOA catheter on AE aircraft (see Reva[684] study)**

- **Adverse outcomes [694] under field conditions (blind placement, placement in aircraft, long-distance transport with balloon inflated)**
- **Transport of patient with junctional tourniquet**
- **Effects of altitude on compression applied for devices (AAT) with inflatable bladder**
- **Maximum time for application of the junctional tourniquet (implications for prolonged transport of casualty under conditions where pre-transport damage control surgery not possible)**

4.24 Care Across Continuum

Except for a few case studies, no research was found that addresses a systematic analysis of patients as they move across the continuum of care. The newly developed Aeromedical Evacuation Registry (AER), is designed to track individual patients, aircraft missions, AE related to major operations and across epochs of time, should facilitate this analysis.

A case is presented as an example of the capability of the AER to support the analysis of an individual as they move across the continuum of care (Table 24). Case: A male patient who was critically injured on 15 February at 0400 (date adjusted for privacy) underwent initial damage control surgery at a field hospital. Approximately 15 hours after the injury the patient was transported by CCATT to the theater trauma hospital where they underwent a second surgery to washout and finalize surgical repairs. Approximately 48 hours after the injury the patient was transported from the AOR to Germany on a 6-hour flight. Upon arrival, they underwent an additional surgery. On Day 4, the patient completed an 8-hour flight to a military medical facility in the US. The time from of injury to arrival in the US was approximately 111 hours (just over 4 days); during which the patient was evacuated from the battlefield, received a massive transfusion, underwent three surgeries and three flights (total flight time 15 hours), and traveled over 7,000 miles. In the second phase of the development of the AER, en route medical care information will be integrated to provide a more complete description of the patient status and the care they received as they move across the continuum of care.

Table 24. Example of Individual Level Data from AER

History (report from Field Hospital): Male presented post improvised explosive device blast with near traumatic bilateral amputations (injury 0400 on 15 February). Hemodynamically unstable (palpable femoral and radial pulses, HR 150s) on arrival. He responded appropriately to blood products. Intubated – taken to CT scan (small liver laceration, sacral fracture, retroperitoneal hemorrhage. Spine precautions maintained. Head normal (GCS ~15 on arrival although obscured by pain), face notable for facial fractures. In OR – right knee amputation, left below knee amputation (BKA), right elbow washout, cleaned and closed facial lacerations, right thigh fasciotomies (likely from pelvic hematoma), pelvic external fixator. Post-operative – no vasopressors, on propofol/fentanyl. Ventilated. PO_2 123 mm Hg; pH 7.45; Base excess -3. Hgb 8.8 g/dL No planned return to OR before evacuation. Totals so far: PRBC (14 units), FFP (14 units), Platelets (2 packs), Cryoprecipitate (2 units), Factor VIIa (2 vials)							
Origin	**Departure Date**	**Departure Time (Z)**	**Destination**	**Arrival Date**	**Arrival Time (Z)**	**Flight Time (min)**	**Theater Route**
AOR Field Hospital	15 Feb	20:00	AOR Trauma Hospital	15 Feb	21:07	67	AOR-AOR
Remain overnight (15/16 Feb – Trauma Hospital). History: Injury on 15 Feb. Initially treated at field hospital on morning of 15 Feb. Underwent massive transfusion. Injuries include right above knee amputation, left BKA, sacral fractures, Grade 2 liver/spleen lacerations, 6-8 rib fractures, C7 chip fracture (patient in a hard collar), fractured right elbow, soft tissue injuries left arm. To OR on 15 Feb for washout. Extubated post-op and received 2 units PRBCs. Currently on face mask 8LPM. Pain is well controlled.							
AOR Trauma Hospital	17 Feb	06:51	Germany– US Military MTF	17 Feb	12:45	354	AOR-Germany
Remain overnight 17/18 February (Germany). History: Arrived at US Medical Center (Germany) on 17 Feb. Diagnosis: I & D left BKA stump, right knee disarticulation stump and right thigh fasciotomy wound, left open elbow joint and left epicondyle fracture, and left medial elbow wound with delayed primary closure. Zygomatic arch fracture – plate to injury. External fixation to pelvic fractures. TBI – mild with symptoms. Pain: PCA pump.							
Germany - US MTF	19 Feb	11:34	US Military MTF	19 Feb	19:43	489	Germany-CONUS

AOR – Area of responsibility (e.g., Afghanistan, Iraq), CONUS – continental United States, Z -Zulu – refers to Greenwich Mean Time, to allow for time standardization across multiple time zones; MTF -Military Treatment Facility

4.25 ERPSS

With the exception of the report from Vermillion[597] on the set up of the MASF during Operation Just Cause, no reports were found on en route preparation/receiving patients from the en route care system.

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Appendix 1: High Performance Team Gap Analysis

HPT Gap Analysis	Research Specific to En Route Care
What is the effect of hypothermia in making neurological determination	Pre-transport
Identification of predictive biomarkers or physiological parameter for TBI)	
Measure biomarkers in flight on AE patients	Need to breakout by specific injury – integrated literature review
Examine the effects of flight on the biomarkers clinical utility	
Improve the ability to differentiate TBI from ischemic stroke and to allow measurement in serum rather than cerebral spinal fluid	Outside scope of review
What is the effect of vibration on TBI	Limited research – primarily related to spinal cord injury
What is the effect of acceleration on TBI	Johannigman[166]
What is the effect of altitude on TBI	
What is the effect of variation of temperature on TBI	Incidence of fever -
When is the right time to move a patient	
What is the incidence of complication of TBI patients	See Dukes[105,120,121,137,138]
Gain understanding of enormous gaps (data/clarity) during patient transport	Not a specific gap -
Evaluate if there is a best practice for sedation analgesia en route?	No studies
What is the effect of oxygenation and ventilation on TBI	See Skovira, Scultetus
What is the cumulative effect of stress of air flight on TBI	No studies related to cumulative effects
What is the compliance rate for Clinical Practice Guideline (CPG) of head injury movement during transport	See civilian study as example – no studies on military adherence with guidelines
Evaluate what is the ideal treatment of TBI management during transport	No studies – see comments relative to adherence to TBI bundle
Evaluate role of End Tidal Carbon Dioxide (ETCO2) in Management of TBI patients	No studies related to en route care

Summary of questions presented at XXX. (organize table by topical area)++ +

Question	Comments
• Does AE worsen outcomes after TBI	•
• Is the negative impact of AE caused by hypobaria?	•
• Are different forms of TBI affected differently by hypobaria?	•
• Does hypobaria elevate intracranial pressure (ICP) and reduce brain oxygenation?	• See
• Can time of AE optimize outcome?	• Not specific questions
• What level of inspired O2 during hypobaria results in best outcome?	• Only research done with 21%, 28% and 100%. Hyperoxia associated with worse outcomes. No studies r/t O2 levels routinely used during flight (40-60%)
• Can outcome after TBI and hypobaria be improved by anti-inflammatory interventions	• Outside scope of this review
• Can neurohistopathologic outcomes and behavioral outcomes after TBI and hypobaria be improved by administration of a PARP inhibitor o Compare outcomes after initial flight using two different does of PJ34 to those using drug vehicle administered at 2 hours after LFP	• No report found
• How does AE-associated hypobaria affect intracranial pressure and brain tissue oxygenation o Measure ICP during and after 6-hour flight starting 1 day after TBI o Measure brain tissue O2 during and after 6 hour flight starting 1 day after TBI o Compare to measurements made at same times after TBI using sham hypobaria	• See
• Additional TBI models (e.g., free-field blast exposure, polytrauma)	• *Ongoing Study: Effects of AE relevant hypobaria on polytrauma patients (animal models)*[697]
• Additional AE factors (e.g., vibration)	• *Ongoing study: Vibration and normobaric hypoxia – effect on systemic and cerebral inflammatory response to TBI*[698]
• Magnetic resonance imaging and spectroscopy	• Outside scope of review
• Molecular effects of hypobaria on the injured brain	•
• Combination therapies (e.g., targeting energy metabolism and inflammation)	• Outside scope of review
• Translation to clinical studies using measurements of ICP, PtO2, MRI/MRS, serum biomarkers and neurologic outcomes	• *Ongoing study: Biomarker profiles and the timing of treatment strategies.*[699]
• Optimization of neurologic outcome after TBI for warfighter and civilian TBI victims	Not a research gap – overall goal of program

Appendix 2: Search Strategy

PubMed – Search

Search #1: ("afghan campaign 2001-"[MeSH Terms] OR ("afghan"[All Fields] AND "campaign"[All Fields] AND "2001-"[All Fields]) OR "afghan campaign 2001-"[All Fields] OR "afghan campaign 2001"[All Fields]) AND air ambulances[All Fields] AND ("humans"[MeSH Terms] OR "humans"[All Fields]) AND ("iraq war, 2003-2011"[MeSH Terms] OR ("iraq"[All Fields] AND "war"[All Fields] AND "2003-2011"[All Fields]) OR "2003-2011 iraq war"[All Fields] OR "iraq war, 2003"[All Fields]) AND military medicine[All Fields] AND wounds and injuries/classification[All Fields]
Result: **262 articles** – after scanning title 68 articles (with 65 after 2002), primarily related to critical care air transport.

Search #2: 209 articles – after scanning titles: 15 articles

- Accidental Falls/statistics & numerical data
- Adolescent
- Adult
- Afghan Campaign 2001-
- Air Ambulances/statistics & numerical data*
- Athletic Injuries/epidemiology
- Female
- Humans
- Iraq War, 2003-2011
- Male
- Middle Aged
- Military Medicine/statistics & numerical data*
- Military Personnel/education
- Military Personnel/statistics & numerical data*
- Motor Vehicles/statistics & numerical data
- Physical Education and Training/statistics & numerical data
- Population Surveillance
- United States/epidemiology
- Wounds and Injuries/epidemiology*
- Young Adult

Search #3: Air Ambulances OR Air Transport AND Military Medicine: 249 articles; after scanning 146

Search #4: Air evacuation and Military: 258 articles; after scanning 157 articles

Search #5: Aeromedical evacuation response: 287 articles/after scanning 99 articles

Search #6: En route care AND military: 42 articles/after scanning: 20 articles

Search #7: 991 articles/After scanning titles: 204
Publication Types

- Case Reports

MeSH Terms

- Aerospace Medicine/organization & administration*
- Air Ambulances
- Attitude of Health Personnel*
- Humans
- Iraq War, 2003-2011
- Male
- Military Nursing/organization & administration*
- Military Personnel
- Negative-Pressure Wound Therapy
- Nurse Clinicians/organization & administration
- Nurse Clinicians/psychology
- Nurse's Role/psychology*
- Surgery, Plastic/nursing*
- Transportation of Patients/organization & administration*
- United States

Search #8: Aerospace medicine AND Transportation of Patients AND Military: 86 articles/title scan: 60 articles

Search #9 (related citations search): 97 articles/title search 20 articles
Chapter 3 innovations in the en route care of combat casualties.
Hatzfeld JJ, Dukes S, Bridges E. Annu Rev Nurs Res. 2014;32(1):41-62. doi: 10.1891/0739-6686.32.41. PMID: 25222537 [PubMed - in process] Related citations

Search #10: 325 articles/title search: 109 articles
MeSH Terms

- Afghanistan
- Air Ambulances/organization & administration*
- Altitude
- Continuity of Patient Care/organization & administration*
- Critical Care/organization & administration*
- Equipment and Supplies
- Forecasting
- Health Facility Environment/organization & administration*
- Health Services Needs and Demand
- Humans
- Iraq
- Iraq War, 2003-2011
- Light/adverse effects
- Military Medicine/organization & administration*
- Noise/adverse effects
- Resuscitation/methods
- Time Factors
- Transportation of Patients/organization & administration*
- United States
- Vibration/adverse effects

Search #11: ((("Air Ambulances"[MAJR]) AND "Iraq War, 2003-2011"[MeSH Terms]) AND "Military Medicine"[MAJR]) AND "United States"[MeSH Terms]: 8 articles/title search: 8 articles

Military Medicine – search (MHSRS)
August 2014 (Proceedings of the 2012 Military Health System Research Symposium)
Safety[695]
Communication – Task Saturation [696]
Safety – Using reference list from McNeill[695]
-Similar references: 96 articles/title search: 19 articles
-Reference list: Additional references:

- Guerdan BR: United States Air Force aeromedical evacuation: a critical disaster response resource. Am J Clin Med, 2011; 8(3), 153-6 (found online – not in PubMed)[40]

Disaster
Lezama (2011) [72] Similar references: 155/title search: 58

- Air Ambulances*
- Cyclonic Storms*
- Disasters*
- Earthquakes*
- Haiti
- Humans
- Military Medicine*
- Practice Guidelines as Topic
- Transportation of Patients/standards
- United States

USAISR Publications (2000 through 2011) http://www.usaisr.amedd.army.mil/publications.html

DTIC oif OR oef aeromedical AND evacuation (493 documents/title search:

- aeromedical evacuation
- oif oef
- medical evacuation
- operation enduring freedom oef
- operation iraqi freedom oif
- oif operation
- aero medical evacuation
- army aeromedical research laboratory
- casualty evacuation
- evacuation medevac

Appendix 3: Gap List Summary*

Topic Area	Gaps
Epidemiology	• There is a need to integrate evidence related to the effect/timing of AE on inflammation for a given injury type and possible association with long-term outcomes. • Inclusion of information on en route care, including days since event, and outcomes (beyond return to duty rates). • Inclusion of all diagnosis, not just primary diagnosis. • Inclusion of information on pre-existing condition. • Integration of data on AE during high-operational tempo actions (e.g., Battle of Fallujah, Somalia) is needed to develop flight profiles. • Any future epidemiologic studies specific to this patient population should be designed to link en route care medical records with existing databases to explore contemporaneous outcomes (e.g., within the first seven days post-evacuation) or longer-term outcomes. • Integrate epidemiologic data (see AER) and patient flow data in models for planning (see recommendation from Rand Corporation on STEP approach to planning[1,2] • Incidence of hypothermia or hyperthermia during the acute phase of care and transport • Relationship between en route complications (decreased blood pressure or oxygen saturation or need for supplemental oxygen above what is predicted) and preflight hemoglobin • Neurological Casualties o Physiological profile (BP, ICP, CPP, temperature, oxygen saturation) during flight o Incidence of events associated with secondary brain injury (hypotension, hypoxia, hyperglycemia, hyperthermia or hypothermia, hypocapnia, or acidosis) • Blast Injury Casualties – Blast lung injury o Review the preflight medical records for indications of pulmonary blast injury (PaO2/FiO2, chest radiograph characteristics and the presence of bronchopleural fistula) and other factors strongly associated with pulmonary blast injury (skull fracture, burns > 10% body surface area or penetrating injuries to the head or torso) o En route cardiopulmonary status and care requirements (e.g., increase in supplemental oxygen or changes in ventilator parameters) o Acute outcomes en route or post-transport indicative of worsening pulmonary status (e.g., pneumothorax, desaturation, or increased supplemental oxygen) • Soft Tissue Trauma o Relationship between altitude induced hypoxemia, hypothermia, and wound complications • Acute Coronary Syndrome

	○ Demographic characteristics to include status (Active Duty, Guard, Reserve, civilian) and prevalence of risk factors • Incidence of inflight complications and the relationship between the occurrence of en route complications and the time since the initial event and stabilization of signs and symptoms • Gaps in this analysis included information on the number of flights for the patient, time from injury/event, timing (which flight) of adverse events, adverse events by injury/disease type, preflight/post flight vital signs, no short term (post-transport) outcomes. The characterization of the en route adverse events may allow for standardization of definitions for the analysis of other populations. • Cardiac - specific demographics (e.g., ACS vs. cardiac arrhythmia as diagnosis), time to transport since stabilization, en route adverse events, post-flight diagnostics (i.e., MI vs rule-out MI), preflight state (vital signs/labs) predictive of en route adverse events or post-flight status. • Use data from MEDEVAC missions to identify gaps related to the en route care requirements/effect of en route care on patients who are stabilizing/stabilized acutely post-injury and inform gap identification for potential A2AD scenarios.
Humanitarian/Disaster	• A gap is the ability to rapidly collect required data during a large-scale humanitarian response. Consideration of module in TRAC2ES or an appropriate registry that could be used to facilitate standardized data collection for disaster response). Another limitation is the lack of a central repository for after action reports. Consistent with the principles of a learning health care system,[3] a central repository for after action reports and a systematic and rapid process for the integration of lessons learned (as appropriate) is needed. • Create profiles of casualty flow from different disaster response scenarios (based on disaster type, location, military, military-civilian response) – start with summary of extant literature. Modeling. • TRACE^{2}ES – for AE disaster response • Reanalyze composite data sets (confirm coding) for trends across time – See Galvagno[4] • Identification of patients with occult pulmonary blast injury

Time to Transport	• A recent review[5] of military medical doctrine noted that beyond MEDEVAC there is a lack of guidance on time to transport to a specified level of care. The report also noted inconsistencies in allied joint medical planning documents. • Limited findings related to time to transport – need to integrate data into all registries and documentation records • Expand research from pre-hospital/Role I to transport times Role 2-3 and 3-5 • Use data to explore en route care requirements for casualties who have undergone prolonged field care • Provision of prolonged field care in en route setting • Include in doctrine • Effects of time to transport on morbidity, mortality and long-term outcomes • Describe transport times for entire population (CCATT and AE)
TBI	• No data were provided on the time from injury to detection of the vasospasm or information about the timing of the evacuation flights or en route care considerations. These data could be reanalyzed to add in the en route phase of care (AOR-LRMC) and LRMC-CONUS to explore any relationship between outcomes (including traumatic cerebral vasospasm) and GOS at discharge. • the need for both isolated and polytrauma models of TBI reflecting these mechanisms of injury, in addition to current blast-related injuries. • No studies have been conducted to evaluate the prevalence of tympanic membrane rupture in AE patients, with a focus on concurrent neurologic injury or communication of potential risk. The • Mild TBI - need for studies to evaluate strategies to mitigate deterioration (e.g., avoidance of hypobaria induced-hypoxia) and further analysis of time to transport. • A gap is whether transport of patients whose injury occurred at high altitude has different outcomes compared to those whose injury occurred at lower altitudes. Evaluation of the penetrating injury model in a manner similar to the blunt blast trauma models may be appropriate. • The implications for transporting a patient with pre-transport secondary insults has not been described. • Update analysis of TBI using definitions consistent with updated 2015 ICD definitions (concussion/mild TBI, moderate TBI and penetrating TBI or open head injury) • Effect of en route care on cerebral oxygenation (see Scultetus[6]) • Effects of supplemental oxygen consistent with clinical use vs experimental protocol (100%) – analysis controlling for FiO2 and SpO2 (see Skovira[7])

	• Models demonstrate blast effect – need model of complex injury (e.g., type of TBI with/without polytrauma) - see Donovan[8] for description of patients • Standardization of models (type of injury), timing and duration of hypobaria/hypoxia exposure • Integrate results from ground based research – see Track-TBI study for long-term outcomes (http://www.brainandspinalinjury.org/research.php?id=189 • Adherence to TBI guidelines during en route phase of care and association with acute and long-term outcomes (use civilian examples[9-11] for examples from civilian setting) • Integrate implementation dates of TBI CPGs and Directive Type Memorandum (mTBI – DTM 09-033, Jun 2010) on outcome evaluation (consider effect on in-theater en route care) • Development of a Living Systematic Review[12,13] process – see example (https://www.center-tbi.eu/) • Validation of a prognostic model (similar to IMPACT) that includes military relevant characteristics, including en route care[14,15] • Integrate data sets (TRAC2ES, DVBIC, etc.) to clearly define population for various operations and epochs of time (evaluate changes in practice on outcomes) • Integrate common data elements for TBI into database[16] • Specific criteria to identify complications proximally attributed to en route phase of care, including identification of en route care quality indicators • Pre-flight risk assessment tool (particularly for patients with mild TBI) • Standardize terminology/assessment methods for mTBI research[17] • Identify timing of first and second AE flights (See Proctor, Scultetus, Skovira)[6,7,18] • Based on Johannigman[19] study, evaluate effect of hypobaria/hypoxia on outcomes mTBI • Cabin altitude restriction (see Butler[20] CAR study – evaluate subset with TBI) Gaps previously identified in the Defense Centers of Excellence review[21,22] • Identify risks, benefits, intervention strategies and outcomes associated with military AE transport of TBI patients (identify ideal time to fly) and develop risk profiles and injury protocols to address the timing and use of interventions. (initial research has been conducted to address this gap)

	• Document the effects of altitude exposure on mild TBI (mTBI) and blast-induced neurotrauma. (initial research has been conducted to address this gap) • Determine what, if any health risk or performance effects might occur among post-TBI/post-concussion military personnel who return to high altitudes (not in scope of this review). • Investigate the efficacy of pharmacotherapeutic interventions for the prevention of altitude-related and secondary brain injuries Pneumocephalus • Effect of rate of ascent/descent on ICP and cerebral oxygenation • Validation of Andersson's calculations in animal model (effect of physiologic compensation response to maintain ICP) – establish guidelines/threshold/clinical condition associated with risk for tension pneumocephalus en route • Preflight/inflight therapy – administration of supplemental oxygen on pneumocephalus resorption (is there a beneficial effect with lower FiO2 versus 100%) • Incidence of altitude associated complications due to pneumocephalus during recovery phase and long term– association with injury type (e.g., presence of fistula, history of CSF leak post-repair). (see civilian articles) • Is cabin altitude restriction applied IAW recommendations Flight Surgeon's checklist? • Variations in response based on type of head injury (e.g., closed head injury, GSW, post-craniotomy)
Spinal Cord Injury	• En route management/care of patients with spinal injury (with/without VSB requirement) • En route stresses of flight (hypoxemia, altered glycemic control) – factors potentially associated with long term outcomes • Number of patients evacuated with spinal precautions (adjudication of actual requirement) • Standardization of statistical methods to calculate rates[23] • Compliance rate for CPG during transport in patients with spinal injury (from AFMS gap analysis) • CCATT outcomes of movement of casualties with thoracic and/or lumbar spinal fractures utilizing the Vacuum Spine Board • CCATT outcomes of movement of casualties with thoracic and/or lumbar spinal fractures between (What AOR/what timeframe) • Effect of vibration studied in ground vehicles and MEDEVAC helicopters – no studies conducted on fixed wing aircraft or ground transport vehicles used to transport patients to aircraft (K-loader, ambus) • Effect of en route hypoxemia on neurologic outcomes Vacuum Spine Board

	• Case-control study to identify risk factors for pressure ulcer development (extension of Thomas study to include cases), with control for factors known to be associated with increased risk of pressure ulcers (e.g., vasoactive medication) • Mitigating strategies (pressure, shear) used in conjunction with VSB or other spinal immobilization devices • Adherence to standard pressure ulcer strategies (lateral rotation – offloading)
Pulmonary	• A case study involving patients with similar injury/transport characteristics who did/did not experience inflight complications (pulmonary) may be warranted to inform the development of a preflight risk profile. For example, among the casualties on the USS Cole who suffered blast trauma, describe their location (above or below decks and distance from explosion), presence of secondary, tertiary and quaternary blast injuries, and preflight state (vital signs, SpO2, oxygen requirements), medications (including narcotics or sedatives). Johannigman's study similarly identifies the need for more sensitive indicators of sub-clinical pulmonary blast injury, and further analysis of potential effects of narcotic-induced respiratory depression (no data provided in paper to support this assertion except for the lack of dyspnea) or fatigue/sleep deprivation. • Future research should consider use of $P_{ET}CO_2$ or a similar indicator of ventilation to explore the relationship between narcotic/sleep-induced hypoventilation on hypoxemia during en route care (? effect of sitting in Evans seat). • No studies were found on the effects of hypoxia on the circadian pattern of coagulation, although as discussed in the VTE section there is limited evidence that hypoxia directly affects coagulation activation. Changes in the circadian patterns in coagulation activation may have implications for ACS and VTE risk. Additionally, no studies have evaluated the interaction between transmeridian flights and hypobaric hypoxia (and other stresses of flight) in ill/injured patients on these biomarkers**.** Data from the Glue Grant: Inflammation and the Host Response to Injury • Effect of variations in respiratory rate/depth on pulse-dosed oxygen delivery (FDO_2) in spontaneously breathing individuals using pulmonary parameters consistent with casualties during AE (e.g., previous studies by Alkins[24] and Johannigman[19] report no dyspnea documented) Mechanical ventilation: • These data need to be linked to the electronic health record to evaluate pre-event/post-event state. The study is also useful in describing the potential O2 requirement during a disaster evacuation, when a larger number of ventilator patients are simultaneously transported.

	• Areas not addressed by this study were the rationale for preflight intubation (physiological requirement, en route safety, need for additional surgeries), timing of blood administration (when preflight). There was no multivariate analysis (i.e., is mechanical ventilation a surrogate for injury severity). The study focused on post-flight outcomes, but did not address en route events. The timing of events (risk factors) was not delineated. The study does have Implications for post-flight resource requirements. • Areas for further research include the accuracy of the VT at lower FiO2 (0.28-0.60). A description of the frequency of use of different ventilators for CCATT (versus ALeRT) or Burn team and the incidence of adverse events associated with specific ventilators is needed. Integrating this research on ventilator performance with the research on closed loop systems is needed to evaluate the ability of the closed loop controller to function given the altitude-induced changes in ventilator performance. Of note, Johannigman's study[25] used the Eagle Uni-Vent 754 Transport Ventilator as a part of the closed loop system. Analysis using the current CCATT ventilators is needed. These studies also highlight the importance of accurate and continuous monitoring of SpO2 under en route conditions. As discussed Maddry's study,[26,27] the ability of the closed system to provide lung protective ventilation during en route care is also needed. Models with different lung compliance and airway resistance developed by to test portable transport ventilators are warranted.[28-30] • No reports are available on en route issues related to HMEs, to include the loss of an airway or en route care requirements to mitigate the effects of low humidity on airway status. • Describe characteristics of AE patients at increased risk for en route hypoxemia • Describe incidence of inflight desaturation controlling for pre-flight acclimatization; possible occult blast injury, in-flight care – narcotics, sleep state, and complete vital signs (HR, RR, SpO2) • Replicate effect of hypobaria c/w AE on SaO_2 and StO_2/SmO2 in healthy subjects/ill-injured controlling for ground SaO2 • Validate Muhm's logistic predictive model[31] using data from combat casualties (implications for Flight Surgeon pre-flight assessment) • Effect of vibration consistent with fixed wing transport on oxygen requirements (only studied in rotary wing)[32] and ability to monitor • Standardize animal model to simulate AE post-combat trauma – effect of varying time to fly • Characterize critical tissue oxygenation (StO_2/SmO_2) level for various outcomes (bacterial growth, cytokines, wound healing • Incidence of en route intubation

	• Control other factors potentially associated with wound infections (interaction with hypoxia, hypobaric environment; glucose, core/local temperature • Effect of negative wound pressure therapy (interaction effect) • Preflight predictors of risk for en route adverse events • Interaction between closed loop control of oxygenation and ventilation at altitude • Incidence of humidification related adverse events (i.e., loss of airway, mitigating care strategies)
ECMO	• Need to describe the en route care requirements, patient's physiological status, adverse events, short and long-term outcomes. • Description of patients at risk for pulmonary deterioration (see Edens[33])/patients who required advanced pulmonary support (timing of deterioration, time to implement advanced support, outcomes) • Capability for prone position transport • Outcomes based on mode of ECLS support (PECLA, ECMO) -for example with TBI patient. Separate outcomes for medical versus trauma patients (see Swol[34]) • Description of alternative advanced therapies implemented) (proning, epoprostenol) and feasibility and en route care capabilities/requirements • Description of burn transport team support of patients requiring advanced lung support • Timeline for activation and initiation of teams (ALeRT, SAMCC ECMO team) • En route care of patients (care requirements, adverse events, acute outcomes), pre-post physiological status • Comparison of outcomes related to current civilian ECMO transport programs • Evaluation of sustainment training programs • Theater implementation of ECMO in preparation for transport (requirements, implications of time delay to initiation of therapy)
CAR	• Relationship between en route DO2 (establish safe threshold) and post-flight outcomes. Pneumothorax • Describe incidence/outcomes for patients transported with small pneumothorax unrelieved by a chest tube. • Effect of time since resolution of the pneumothorax or discontinuation of the tube thoracostomy before transport. • Effect of needle decompression versus tube thoracostomy on relief of pneumothorax under hypobaric conditions. Describe need for placement of tube thoracostomy during extended flight.

	• No studies related to the use of a vented chest seal under hypobaric conditions (including prolonged flight). Compare with needle thoracostomy, and under conditions with assisted ventilation where the development of a tension pneumothorax may be more severe compared to spontaneous ventilation.[35] • Efficacy of needle decompression versus tube thoracostomy in relieving hemo-pneumothorax[36] under hypobaric en route conditions, • Safety of placing a tube thoracostomy in the en route setting. • A potential research gap consideration is that procedures now performed by TCCC and MEDEVAC may need to be provided during urgent evacuation on fixed wing aircraft under A2AD conditions. Ocular • Further research is needed to describe the acute effects of en route care in combat casualties, controlling for rate of ascent consistent with military transport. No reports or studies were found for military population on pre=transport care, the incidence of adverse events related to en trapped air or the incidence of cabin altitude restriction due to ocular injury. Additionally, no data are available on the time to transport post-injury or surgery. Description of current medical management to mitigate intraocular air is also needed. Integration of the data from the Walter Reed Ocular Trauma Database (WROTD) with the DoDTR and the AER is needed to provide a more comprehensive analysis of care across the continuum Abdomen • Description of complications in post-abdominal surgery/damage control surgery • Bladder pressure monitoring during AE • Negative pressure wound therapy on open abdomen
Cardiology	• There is a need for a standardized set of definitions for en route and post-flight[37] complications to allow for comparison across studies • Need for analysis of en route complications based on time to transport, pre-flight physiologic state (complicated/uncomplicated) and preflight care (e.g., thrombolytics). • Physiological stress of the catapult launch, and identifies a gap related to consideration for the evacuation of other critically ill/injured patients from a ship • CPR = A similar study, describing required care related tasks and the ability to perform these tasks based on litter separation may be warranted for en route care, with consideration to conditions requiring the transport of a larger number of patients (i.e., what is

	the minimum space between litters/maximum number of litter patients). • Although there is research on the effects of airline travel and critical illness on circadian rhythms (cardiovascular, endocrine, immune), there are no studies on the effects of long-distance transport on ill/injured casualties. • This finding of artifactual variation in blood pressure versus physiologic response needs to be confirmed during transport, particularly in patient with potentially altered cardiovascular response or who may be affected by blood pressure variability. • Characteristics (low/moderate/high risk for ACS/MI – see AE Cardiac Tool developed by Steinkraus)[38] and outcomes (initial diagnosis/confirmed diagnosis) for patients evacuated for circulatory disorders (e.g. ACS/MI and cardiac arrhythmias) • En route care (care provided, complications/adverse events – See Saenger[39]) o Preflight order for supplemental oxygen adjusted for altitude – incidence of en route hypoxemia requiring supplemental oxygen greater than anticipated/ordered o Factors (stresses of flight, preflight preparation) associated with adverse events (e.g., failure to order supplemental oxygen in an at-risk patient) • Describe acceleration forces during standard ascent/descent and combat maneuvers and cardiovascular response
Infections/Infection Prevention	• No studies have been conducted to evaluate adherence to the adherence to the JTTS CPGs or AFI 48-307. • VAP: A limitation of this study is that no information on en route care (including adherence to VAP prevention guidelines), the timing of the diagnosis of pneumonia/VAP relative to transport, and the continuation of intubation for transport were not reported. Thus, exploration of the relationship between time to transport, en route care and the occurrence of pneumonia is not possible. • An area for research is to explore the use of en route supplemental oxygen (adherence with the guideline recommendation), the relationship between en route SpO2 and wound infections for both CCATT and AE patients, controlling for time from injury. Extension of Lloyd's study[40] on adherence to antibiotic guidelines during the en route phase of care is required (continuation, timing of medications). Further updates to these guidelines should address en route care considerations. There is limited research on the relationship between en route care and short and long-term outcomes. Integration of data from the Trauma Infectious Disease Outcomes Study (TIDOS)[41-43] and collaboration with the Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study Group

	(https://intranet.idcrp.org/public/research/trauma-infections) may address this gap. • Correlate en route SpO_2 and wound infections • Integrate en route care data with outcomes data from TIDOS (The Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study[44]) • Mechanism – TBI-Pneumonia • Integration of en route care variables (time to transport, en route adverse events, adherence to standards and guidelines), timing of diagnosis of infection relative to transport (i.e., within 48-72 hours) • Infection transmission in en route care
Infectious Disease	• A model[45,46] could be used to evaluate the risk for en route motion sickness. Inclusion of pre-screening for motion sickness should be documented in TRAC^{2}ES (no description exists on the incidence of motion sickness during en route care), with an analysis of administration of antiemetics in low versus high-risk patients. • Exploration of the use of an ethical model and vignettes related to ethical dilemmas experienced during the transport of these high-risk patients, to include limitations on care provided, is warranted. • Description of care provided en route for patients with highly contagious disease • Ethical dilemmas experienced and use of standardized ethical approach to establish policy and inform pre-deployment preparation; translation of ethical lessons learned in ground-based facilities to en route care • Code TRAC^{2}ES for infectious disease transports (see Lang[47]) • Incidence of en route motion sickness; delineation of high-low risk patients, use of anti-emetics (see Lucertini[48]) • Analysis of current policies/regulations specific to infection control – adherence for infection prevention (e.g., MDRO transmission) • Description of aircraft risk environment (airflow, humidity) • Preflight screening (adherence)
VTE	• Lack of detailed medical records related to VTE • All these studies related to prolonged immobilization in civilian literature refer to a seated position. Thus, generalizability of these results to AE can be applied only to those less seriously injured individuals able to sit during AE.
• Soft Tissue Trauma	• An identified gap was the need for case-control (patients who did/did not require delayed fasciotomy) or patients who did/did not develop ECS (early or delayed). • Further exploration may include a trauma model (versus exsanguination) with ongoing volume resuscitation under hypobaric hypoxia or hypobaria with supplemental oxygen and

	measurement of cytokines including ROS, and vascular permeability in the extremity.
	• This study suggests a need to standardize documentation/assessment requirements for patients at risk for compartment syndrome and further medical record review
	• Included all patients with extremity trauma (not based on severity) – need to differentiate monitoring requirements and outcomes for CCATT vs. AE
	• Inadequate documentation related to patients at increased risk for compartment syndrome to facilitate continuity of care (evaluate critical information to communicate/standardize)
	• Effects of hypobaric environment on compartment syndrome (continue focus area – integrating multiple stresses of flight)
	• Correlation design (regression) to identify risk factors
	• Describe time frame for complications (when occurred, en route care)
	• En route compliance with established CPGs/standards
	  • Enroute care (research reflective of transport environment, variable timing from injury, phase of care)
	  • Mitigating interventions (en route focus – preflight/inflight interventions)
	
	Gaps - ECS:
	  • Effect of hypoxic hypobaria versus normoxic hypobaria on ECS[49,50] versus outcomes associated with supplemental oxygen administration (inflammatory markers)[51]
	  • Control for threshold effect (case-control – casualties with prolonged unrelieved ischemic injury compared to < 6 hour resolution) followed by aeromedical evacuation (control for preflight care – e.g., MEDEVAC and volume resuscitation).
	  • Effect of hypobaria at a later point post-injury (e.g., > 14 hours) on ECS – using variable time to transport
	  • Is there a serial biomarker or physiologic indicator (e.g., StO_2) associated with progressive development of ECS, or a threshold indicator of increased risk for ECS?
	  • ECS model[50,52] with crush injury (current animal model does not create a crush injury), primary blast injury or penetrating trauma controlling for en route volume resuscitation
	  • Do altitude related stressors (hypobaria, hypoxia, vibration, humidity) and immobility have a differential effect on coagulation under conditions of extremity trauma?[53,54] and is there a variable effect in cases with/without ECS
	  • Need to control for humidity during experiments related to coagulation response to be consistent with en route conditions[54,55]

	• Different study design (case-control) similar injury distribution and severity of casualties who did and did not undergo fasciotomies at LRMC – identify risk factors, acuity (isolated extremity injury versus polytrauma), pre-flight status, en route care/events. Determine if there are any pre-flight or inflight indicators. • Pre-flight assessment – should there be a targeted preflight assessment (needs description – does this include noninvasive StO2 assessment or intracompartmental pressure assessment for patients at risk for compartment syndrome (RN vs MD documentation/assessment).[56,57] – need to delineate normal hyperoxic response to injury versus indicators of ECS For soft tissue trauma research, consider partnering with CDMRP sponsored program – Major Trauma Extremity Research Consortium (METRC.org). METRC currently has one study by Schmidt: "Predicting Acute Compartment Syndrome using Optimized Clinical Assessment, Continuous Pressure Monitoring, and Continuous Tissue Oximetry (PACS Study)", which may apply to en route care. Negative Pressure Wound Therapy • The study documents did not include details on time post-injury for the hypobaric exposure. In addition to exploring mechanisms of variation in the macrophage response, further study of timing post-injury and the effects of supplemental oxygen to offset hypobaria are needed. • Timing post-injury on effects of hypobaric exposure on altered inflammatory response • Effect of supplemental oxygen to offset hypobaria effect • Effect of hyperoxia -SpO2 > 95% on bacterial growth • Association between hypoxia and clinical presence of infection versus wound contamination <u>Gaps – Negative Pressure Wound Therapy</u> • Use of negative pressure wound therapy for temporary closure of abdominal wounds – safety in the en route care environment and effect on inflammatory markers/infection (i.e., reduction in sepsis or wound infection) • Use over closed wounds – safety, effect on tissue edema, post-transport care modification (e.g., wound debridement, amputation management) Medical Maggots • Requirement for use of medical maggots during transport • Use of model simulating human body (temperature, humidity) during transport

	• Effect of combined effect of stresses of flight during prolonged transport • Case-control outcomes for patients treated with/without medical maggots • Delineation of policies and procedures for approval and the evaluation of biologic therapies onboard aeromedical evacuation aircraft is needed.
• Renal	• A gap in these studies is a description of the specific timing of the onset of rhabdomyolysis or AKI, time to transport, en route care requirements and adverse events and outcomes and discussion of any need for en route advanced treatment. • No description of timeline for onset of AKI and rhabdomyolysis (is there a safe time to transport before onset) • En route care requirements/treatment strategies for patients with AKI and/or rhabdomyolysis • Requirements for disaster nephrology[58] (e.g., earthquake crush injuries)
• Thermal Stress	• Evaluate strategies to mitigate the effects of the thermal environment onboard aircraft used for AE. • Study effects of low humidity on physiological parameters sensitive to this dry environment (fluid loss – particularly in patients with altered skin integrity) and airway maintenance/humidification • Evaluation of currently used HPMK over extended period (6 hours) in trauma model (simulate rapid evacuation of unstable/stabilizing casualty • Evaluate uptake of clinical practice changes (use translational science evaluation) • Evaluate HPMK in physiological model of hemorrhage at altitude (c/w long distance transport – See results of McKeague[59] – effect of hypoxic environment on function of Ready Heat) • Evaluate adherence in en route environment to JTS CPG and TCCC guidelines related to hypothermia prevention
• Fever	• Incidence of fever in patients with isolated TBI (mild[60] to severe) and TBI with polytrauma • Timing of fever (compare to civilian control group without transport) – larger sample size (studies currently report median) • Association between fever and longer-term outcomes (re-analyze Bell's[61] data with integration of early secondary insults and en route care) • Description of patient population who may benefit from prophylactic hypothermia (hematoma evacuation) with consideration of generalizability to TBI with polytrauma • Monitoring brain temperature versus systemic temperature – implications for management • Recommendations for fever management during en route care

• Pressure Injuries	• Extend evaluations of mitigating strategies to 2 hours (maximum time for supine position) under AE conditions • Evaluation of LiquiCell pads under AE conditions • Include microclimate (skin temperature/moisture) in evaluation of any device (e.g., Stryker, VSB) to identify strategies to mitigate pressure injuries • Validate pre-flight risk assessment for combat casualties undergoing AE • Identify en route care related risk factors for pressure injury development • Develop en route care specific care recommendations for pressure injury prevention (CPG)
• Pain	• Standardize the definitions of the phases of transport • Association between acute en route pain and chronic pain and pain burden(see Puntillo[62]) • Establish/validate algorithm/standards for en route analgesia, along with specification of monitoring requirements during all phases of transport (i.e., MTF-aircraft, onboard aircraft, etc.) • Development/validation of en route pain management clinical practice guidelines; safety of integration of TCCC guidelines for periods of rapid transport (i.e., MTF/CASF to aircraft) • Analyze dosages ordered/received for analgesics/adjuvants compared to the MAARA recommendations and effectiveness of strategy adhering to MAARA guidelines,[63] controlling for previous opioid exposure • Validate Prudhomme's tool for medication risk against a series of patients transported in AE Regional Anesthesia • A prospective study, or quality improvement database is needed to capture decisions regarding the use of RA and the rationale for intubation. • Other outcomes to explore include the incidence of PTSD in relation to heavy sedation and VAP rates associated with differential treatment. • The lack of pain data reinforces the need for standardized documentation requirements and the use of a validated pain scale for intubated patients.
• Blood Product Administration	• The development of a preflight risk assessment that includes not only hemoglobin, but other indicators of physiological stability and risk for en route deterioration is needed, • Preflight threshold for transport based on Hgb and physiologic indicators of stability (i.e., shock index) with en route adverse events/outcomes on longer term outcomes.

	• Studies need to include en route data (vital signs, interventions – blood transfusions, supplemental oxygen; and adverse events) and cabin altitude restriction • Integrate other physiologic measures (continuous hemoglobin, StO2/SmO2)
• Monitoring	• What are the physical assessment requirements during AE – what technologies are appropriate and most accurate/sensitive for use for cardiac and pulmonary assessment (e.g., auscultation, ultrasound, blood pressure measurement) for potential pathologies ((e.g., pneumothorax, hemothorax, thoracic trauma, pneumonia, arrhythmias, valvulopathy, heart failure, endotracheal tube misplacement, tamponade). Add blood pressure auscultation. • Use of reference accelerometer versus active noise cancellation techniques (controlling for noise and vibration) • Describe noise conditions in pre-flight area (en route patient staging facilities) adjacent to the flight line (for both land based runways and onboard Navy ships). • Methods for evaluating accuracy/use of devices in en route area (simulation fidelity) • Standardize methods for evaluation of usage and design, performance, • Characterize clinical implications of physical assessment (auscultation) on patient outcomes • Utility of buccal oximetry under 85% - 100% SpO2 range (consistent with studies in previous range) – particularly in casualties with severe vasoconstriction or inability to use standard sensor sites • Integration of oximetry and flow measurements • No studies have been published or discuss the use of ultrasound during AE. • Requirement for en route performance of ultrasound • Diagnostic accuracy of en route ultrasound (consider experience level of providers), effect of en route stresses of flight on performance and changes in diagnostic criteria • Integration of functional hemodynamic indicators during en route care – determine ability to detect occult deterioration before macrohemodynamic changes • Use functional hemodynamic monitoring to describe cardiovascular response to phases of transport (takeoff/landing) • Currently no validated method for en route continuous Hgb monitoring (see above for lack of accuracy for iStat) • Continuous Hgb (and other indicators of perfusion) during post-damage control transport • Effect of slower changes in SpO2 on SpHb accuracy and precision

	• Effect of single preflight calibration[64,65] (based on initial Hgb-SpHb difference) on en route values and need for recalibration under dynamic conditions • Integration of continuous Hgb into Butler's[66] research related to prediction of oxygen deliver in patients with/without CAR • The noninvasive StO_2 probe failed under field/military AE conditions and was not an accurate indicator of tissue or systemic O_2. StO_2 cannot be used to guide operational trauma resuscitation. Occult hypoperfusion lasted 120- 240 minutes and occurred before arrival at the simulated field hospital, indicating the need to study other methods to detect occult hypoperfusion under field conditions and during en route phase of care
• Nutrition	• Adherence to guidelines for nutritional therapy in trauma patients and effect of transport on adherence to guidelines (e.g., time to initiation of nutrition, calories/type of nutritional support provided during AE) • Describe nutritional support during en route phase of care for CCATT and AE patients (expand analysis conducted by Dorlac[67]) • Incidence of microaspiration during en route phase of care (see Turner[68]) • Incidence of ventilator associated pneumonia in patients transported with/without enteral nutrition
• Abdominal	• Association between en route hypoxia (or hypobaria) and irritable bowel disease and inflammatory biomarkers (analyze biomarkers specific to gut function). • Is there an alteration in the gut microbiome with hypoxia/hypobaria exposure?
• REBOA	• No studies have been published on long distance transport or en route care of patients with a REBOA catheter in place. Research is needed to evaluate the stresses of flight on REBOA function and en route monitoring requirements and care are needed. Additional outcomes are also needed on the effects of prolonged balloon inflation, including the feasibility of en route transport with partial REBOA.[69-72] • Effects of stresses of flight (MEDEVAC/AE) on REBOA system function • Ability to place REBOA catheter on AE aircraft (see Reva[73] study) • Adverse outcomes [74] under field conditions (blind placement, placement in aircraft, long-distance transport with balloon inflated) • Transport of patient with junctional tourniquet • Effects of altitude on compression applied for devices (AAT) with inflatable bladder

	• Maximum time for application of the junctional tourniquet (implications for prolonged transport of casualty under conditions where pre-transport damage control surgery not possible)
• Other	• Integrate case scenarios developed for the CBA CCATT[75] for traditional (i.e., states employing recognized military capabilities/forces in well-understood forms of military competition /conflict), irregular (i.e., come from those employing "unconventional" methods to counter traditional advantages of stronger opponents), catastrophic (i.e., acquisition, possession, and use of WMD or methods producing WMD-like effects , and disruptive (i.e., may come from adversaries who develop and use breakthrough technologies to negate current US advantages in key operational domains) situations

*Based on Gap Analysis – List not prioritized

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Appendix 4: 2012 J-ERC Topics[20]

1. Impact of movement environment on patient physiology
2. Life saving interventions for ERC and preparation/transition for movement
3. across all levels of evacuation
4. Non-Invasive methods for patient monitoring during patient transport
5. Skill level/training of ERC medical personnel
6. Patient safety
7. Patient immobilization during transport
8. Joint documentation ERC
9. Medical personnel human factors
10. Standard equipment/supplies for ERC
11. Medical equipment test standards
12. Autonomous control equipment/remote monitoring

Appendix 5: En Route Pain/Pain Management Studies

Study	Phase Studied	Aims	Findings
Gentry[497]	MTF-Aircraft & AOR-LRMC (Apr-Jun 2009)	Describe the pre-evacuation/en route pain management of trauma patients evacuated by AE from Craig Joint Theater Hospital (CJTH), Bagram Air Field, Afghanistan to Landstuhl. • Type/timing of analgesic medications/adjuvant administered before transport • Patient's pre-transport/initial pain score upon arrival at the aircraft • Relationship between patient's pre-transport analgesic/adjuvant administration and their initial pain upon arrival at the aircraft and en route.	41 patients with BI/NBI (9 with CJTH only records/32 with CJTH & en route documentation) • Typical preflight medication profile: Percocet 1-2 tabs po q 4-6 hrs prn pain; morphine 2-4 mg IV q 2 hr prn pain; zofran 4mg IV q 6 hr prn nausea; Tylenol 500 mg po/pr/pt q 4 hrs prn. Two patients on PCA/1 on routine analgesia – all others receiving prn analgesia. • Only 3 records with predeparture pain assessment documented. • Time from departing hospital–wheels up (n = 17) 110 ± 42 minutes (range 56-240 minutes). • Only 18/41 patients had a pain score documented upon arrival to the aircraft or upon ascent to altitude. Pain on arrival to aircraft (n = 12) = 2.9 ± 2.5 (median = 1; range 0-8); pain at 1st assessment at altitude (n = 15) 3.9 ± 3.5 (median = 2.5; range 0-10). o These 18 patients were stratified based on first pain score: 8/18 (44%) had no/minimal pain, 8/18 (33%) had moderate pain (pain score 4-7) and 4/18 (22%) had severe pain (pain score 8-10), and 3/4 of those with severe pain had an external fixator. • Of those whose initial assessment indicated severe pain (n = 4) all had been receiving narcotics (dilaudid, morphine and/or Percocet) and all had received a dose approximately 1 hour before departure from the hospital. • Severity of pain at first assessment not associated with aircraft type. • Pain scores on arrival/1st inflight assessment were significantly higher for 9 casualties with external fixators (with 8.7 ± 1.1/without 2.8 ± 2.8, p = .012) but not for casualties with splints/casts. • There was insufficient documentation to evaluate the timing of medications preflight.
En Route Pain Study (Phase 1)[584,585]	AOR-LRMC	Describe pain management to trauma patients evacuated by AE from Bagram Air Field to LRMC. • What are the types/timing of analgesia and adjuvant therapies administered before and during transport by AE? • What are the patient's pain scores pre-transport, upon arrival at the aircraft, and en route? • What percentage of patients has analgesics ordered consistent with the current Joint Theater Trauma System CPG's.	Retrospective medical record review. Convenience sample of 50 patients on 14 flights from AOR-Germany and 130 patients on 22 flights from Germany-Andrews AFB (14 flights) or San Antonio, TX (8 flights). *(records collected immediately upon departure from aircraft to aid in record retention)* • Male (88%), age 28 ± 8 years; 67% suffered an injury: BI (n = 48; 27%) or NBI (n = 72; 40%). Psychiatric (n = 40; 22%), medical (n = 20; 11%). • Median number of days from injury to transport was 4 (IQR 6). • Pain scores recorded for 41/50 (82%) AOR patients and 129/130 (99%) of Germany patients. • Average pain scores were 1.3 ± 1.8 for AOR patients and 1.5 ± 1.5 for Germany patients. • Worst pain scores were primarily $\leq$ 3, but 10 (24%) AOR patients and 47 (36%) Germany patients had a score of $\geq$ 4. • Significantly higher pain scores for patients with injuries versus those with medical or psychiatric diagnosis, those admitted to Landstuhl (inpatient) versus the CASF (outpatient), and patients transported to Andrews versus San Antonio. • Analgesics administered to 107 patients (59%). Percocet and IV morphine were the most common analgesics ordered. • Only 34 patients had pre- and post-analgesia pain scores documented. Among patients with any pre-analgesia pain score greater than 4 (n = 33/34), 6 (18%) had pain scores greater than 4 post-analgesia, and in all cases the absolute pain score decreased.
Buckenmaier[575,576]	AOR-LRMC	Determine the severity of pain and extent to which pain affected emotional status in soldiers who were evacuated to and treated at LRMC, Germany (Jul 2007-Feb 2008).	110 wounded soldiers evacuated from AOR-LRMC (93% hospitalized < 8 days at LRMC; 85% within 5 days) – patients being with major injury requiring analgesia • Used standardized data collection instrument • Avg pain relief during transport 45 ± 27% • Avg pain/worst pain negatively correlated with % pain relief during transport • Greater worry during transport and worst pain scores explained 71% of variance in average pain levels during transport • No patients transported with CPNB

Study	Phase Studied	Aims	Findings
Rupprecht[577]	AOR-LRMC	Analyze qualitative responses on survey (See Buckenmaier): 1) Greatest concerns during transport as related to your injury and 2) what could have been better to control your pain after surgery?	Major themes: • "Concerns" for both self and others • "Communication of the unknown" • "Fear" of injury, pain and helplessness • "Physiological Concerns" • "Dignity" described by feelings of helplessness
Lamb[589]	AOR-UK	1: Investigate Flight Nurses experiences in managing patients' pain during AE phase of transfer to UK medical facility. 2. (concurrent with study 1) Establish the completeness of pain management documentation during AE missions. 3. Study 2 audit repeated - evaluate training program	3 Studies • Study 1: Have you ever experienced an AE flight during which you felt unable to adequately control a patient's pain: Yes 13%/No 87%; Do you feel limited when caring for patients in pain during a flight because you do not have a clearly defined pain algorithm to follow? Yes 27%/No 73%. Identified need for patient information booklet, standardize pain documentation • Study 2: Audited 140 flights: 44% with analgesic with documentation; 42% without documentation of pain management in notes, despite 71% with prescribed analgesic. CCAST – 100% documentation. Of patients with pain documented 33% with pain score $\leq$ 3/10; 11% with pain >3; 42% no documentation • Study 3: Audited 283 flights (BI (24%). Analgesia ordered (56%), documented pain scores (73%). % BI patients with pain documents (93%), NBI (72%); psych (38%)
Pfennig[578]	AOR-LRMC	Describe pain management for casualties undergoing aeromedical evacuation (AE) from Iraq/Afghanistan to Germany in support of OEF/OIF (Period of Study: Nov 06-Jan 07).	N = 120 (71 (59%) injury/surgical diagnosis/49 (41%) medical • Mean acceptable pain score was 3.5 ± 2.4; max pain (3.7 ± 2.6); min pain (1.5 ± 1.8). • Maximum pain rating: < 4 (no pain-mild pain): 61%; 4-7 (moderate pain): 27% and > 7 (severe pain): 11%. 45% patients experienced pain more severe than acceptable and 22% had maximum pain = acceptable pain. • 52 patients whose maximum pain > acceptable, 73% (n = 38) had a surgical diagnosis. • 100/121 patients had pain medications ordered. • Narcotics and NSAIDs were the most common types of medications (percocet -55 patients; morphine -33 patients or ibuprofen -25 patients) ordered most frequently. • 66% of the medications were ordered as PRN, 22% routine, 6% continuous (AmBIT pain pump) and 2% nerve block. • No significant difference in the number of patients with maximum pain > acceptable level of pain based on the frequency (e.g., prn, continuous) of medication
Ervin[96]	AOR-LRMC	Descriptive analysis of trauma patients evacuated by Critical Care Air Transport out of combat theater (2007-2013)	N = 1128; Blast (767; 68%), penetrating (197; 17%), Burn (21, 2%) ISS 24 ± 13 • Inflight analgesia: Parenteral (1044; 93%), oral opioid (39; 3%), sedation (730; 65%), Ketamine (51; 5%), PCA (236; 21%), Epidural (90; 8%), regional block (5; 1%), • Paralytic (50; 4%) • Complications during flight: Hyperthermia (532; 47%), respiratory (460; 41%), hemodynamic (209; 19%), Hemoglobin < 8 g/dl (200; 18%), HR (161; 14%), Decrease UOP (87; 8%); Increased ICP (52; 5%), bleeding (9; 1%), Neurologic (8; 1%), medication reaction (2, < 1%), cardiac arrest (0; 0%) • No discussion of pain management adequacy, adverse events, timing of analgesia or sedation

Study	Phase Studied	Aims	Findings
Mora[700]	AOR-LRMC	Describe analgesics used by CCATTs for nonintubated, critically ill patients during evacuation from a combat setting (2007-2012)	N = 381/1128 CCATT patients (non-ventilated & received analgesic – AOR to LRMC) • 97% trauma (70% blast, 17% penetrating, 11% blunt, 3% burn); ISS 19 ± 9 • 98% received opioids (51% morphine, 39% hydromorphone, 15% fentanyl, 5% ketamine) • PCA (63%), bolus IV (32%), epidural (24%), continuous infusion (21%), oral (9%) • No difference in route of administration and complications (inflight/post-flight) – established standardized list of complications • Patients with epidural or nerve block received lower dose opioids • Limited documentation of pain scores; 18% with missing dose information • No preflight/inflight pain scores
Pain Study (Phase 2)[579,586]	LRMC-CONUS	Describe en route pain management during AE from LRMC to CONUS military treatment facilities (MTFs) (Dec 2012/May 2013). • Describe the types/timing of analgesia and adjuvant therapies administered before and during transport by AE. • • Describe the patient's self-reported pain scores for the phases of transport and patients' satisfaction with en route pain management. • Analyze differences in pain scores based on pain control, satisfaction/quality, injury type and pain management strategies.	N = 114 less severely ill/injured on 12 flights (10 ± 4 patients studied/flight) • Battle injuries (31% of trauma patients), median time to transport was 4 days (IQR = 3), 92% transported within 6 days of injury. • NBI (59% of trauma patients); median time to transport: 10 days (IQR =18 days), 32% transported within 7 days of the injury • Analgesics administered (same or combination): 1 (32%), 2 (43%),3 (18%), 4 (7%) 5 (1%) • Documentation of 114 medications being administered: 22 preflight (i.e., before leaving the medical treatment facility), 12 during the period from aircraft takeoff (wheels-up) to ascent to altitude, and 80 during flight (i.e., after reaching cruising altitude and before descent). • No significant difference in pain intensity preflight (3.2 ± 1.7 versus 2.5 + 1.7, p = 0.09) or on arrival to the aircraft (5.2 ±1.7 versus 4.1 ± 2.4, p = 0.07) for those who did or did not receive preflight analgesics/adjuvants. • Preflight medications were opioids (oxycodone/acetaminophen = 15 doses; hydromorphone = 1 dose, morphine = 1 dose), with 73% of the medications taken within 60 minutes of the aircraft taxiing for takeoff • During AE transport, 75% of patients reported at least one pain score > 4. The worst pain was reported for the phase: CASF to Aircraft Arrival, with 65% of the patients with a worst pain score > 4 during this phase • > 47% of patients experienced pain that exceeded their acceptable intensity level, but of those patients with pain that was more severe than acceptable, only 10% rated their satisfaction with their pain management as poor or fair.

<table>
<tr><th>Study</th><th>Phase Studied</th><th>Aims</th><th>Findings</th></tr>
<tr><td>En Route Pain Study (Phase 3)[581]</td><td>LRMC-CONUS</td><td>Describe the environmental factors and social context that impact pain management in the AE setting from LRMC to CONUS MTFs
• What environmental factors influenced pain?
• What were the interactions between the patient and the crew with respect to pain management?</td><td>Ethnographic study to describe the environmental factors and social context that impact pain management in AE (8 missions/16 patients).
• FLACC - adequate pain control (< 3/10) - On arrival to aircraft 12/16 (75%); For entire flight 5/14 (36%), During landing 9/14 (64%).
• Key themes: Communication was a key problem noted in the interaction between the AE crew and patients. The reasons were multi-factorial and primarily related to aircraft noise. However, additional factors negatively impacted communication, including the reluctance of patients to speak with crew members while they were wearing headsets and the limited time between boarding and take-off to adequately assess for pain and provide patient education.
• Preparatory guidance on pain management in the aeromedical staging facility did not appear to address the stressors of flight or transportation phases, which made it difficult for patients to adequately anticipate pain management needs, particularly for those who were self-medicating.
• Seating and litters provide limited options for repositioning and appeared to be uncomfortable for both ambulatory and litter patients.
• Another compounding factor noted was the psychological distress, particularly among those leaving a combat zone before the anticipated end of a deployment.
• Military culture of independence and stoicism were evident.</td></tr>
<tr><td>En Route Pain Study (Phase 4)[582]</td><td>LRMC-CONUS</td><td>Describe the AE system and human factors engineering issues as they affect pain management of AE patients, and make recommendations for process improvements.
• Identify pain management and patient safety issues during AE
• Perform system and human factors engineering analysis of AE pain management process.</td><td><table><tr><td>Information Flow</td><td>Right information, right place, right time, right format</td></tr><tr><td>System Monitoring</td><td>Continuous monitoring of performance metrics</td></tr><tr><td>Feedback</td><td>Supporting users' situational awareness, system improvement</td></tr><tr><td>Technology</td><td>User-friendly, easy to learn, easy to use interfaces</td></tr><tr><td>Culture</td><td>Informal and formal, shared attitudes, goals, behaviors, "unspoken rules"</td></tr><tr><td>Learning Management</td><td>Training, information storage and access, reducing reliance on memory</td></tr><tr><td>Task Processes/Cognitive and Physical Workload-</td><td>Risks for human error, miscommunication, incomplete tasks, fatigue, stress, multitasking</td></tr></table></td></tr>
</table>

LIST OF ABBREVIATIONS AND ACRONYMS

A2AD	Anti-access area denial
ACS	Acute coronary syndrome
AE	Aeromedical evacuation
AER	Aeromedical Evacuation Registry
AFI	Air Force Instruction
AFMS	Air Force Medical Services
AKI	Acute kidney injury
ALeRT	Acute Lung Rescue Team
AOR	Area of responsibility
BKA	Below the knee amputation
CAR	Cabin altitude restriction
CASF	Contingency aeromedical staging facility
CBA	Capabilities based assessment
CCATT	Critical Care Air Transport Team
CDMRP	Congressionally Directed Medical Research Programs
CONUS	Continental United States
CPG	Clinical practice guidelines
DCoE	Defense Centers of Excellence
DO2	Oxygen delivery
DoDTR	Department of Defense Trauma Registry
DVBIC	Defense Veterans Brain Injury Center
ECMO	Extracorporeal membrane oxygenator
ECS	Extremity compartment syndrome
ERPSS	En route patient staging system
FiO2	Fraction inspired oxygen
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GSW	Gunshot wound
Hgb	Hemoglobin
Hct	Hematocrit
HME	Heat and moisture exchanger
HR	Heart rate
I & D	Incision and drainage

IED	Improvised explosive device
J-ERC	Joint En Route Care
JTS	Joint Trauma System
JTTR	Joint Theater Trauma Registry (now DoDTR)
LRMC	Landstuhl Regional Medical Center
MAARA	Military Advanced Regional Anesthesia and Analgesia
MD	Medical doctor
MEDEVAC	Medical evacuation
METRC	Major Trauma Extremity Research Consortium
MI	Myocardial infarction
MTF	Military treatment facility
O2	Oxygen
PECLA	Pumpless extracorporeal lung assist
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
RN	Registered nurse
RR	Respiratory rate
SBP	Systolic blood pressure
SI	Shock index
SAMCC	San Antonio Military Medical Center
SmO2	Skeletal muscle oxygen
SpO2	Peripheral oxygen saturation
STEP	Stabilize, triage and treat, and evacuate (from RAND)
StO2	Skeletal tissue oxygen
TBI	Traumatic brain injury
TCCC	Tactical Combat Casualty Care
TCV	Traumatic cerebral vasospasm
TIDOS	Trauma Infectious Disease Outcomes Study
TRAC2ES	TRANSCOM Regulating and Command and Control Evacuation System
USAF	United States Air Force
VAP	Ventilator associated pneumonia
VSB	Vacuum spine board
VT	Tidal volume
VTE	Venous thromboembolism
WBGT	Wet bulb globe thermometer
Z	Zulu (Greenwich Mean Time)