Resuscitation and Evacuation from Low Earth Orbit: A Systematic Review

Craig D. Nowadly, MD;[1,2] Brandon D. Trapp, MD;[2] Stephen K. Robinson, PhD, MS;[3] John R. Richards, MD[2]

1. Department of Emergency Medicine, David Grant United States Air Force Medical Center, Travis Air Force Base, California USA
2. Department of Emergency Medicine, University of California at Davis, Medical Center, Sacramento, California USA
3. Department of Mechanical and Aerospace Engineering, University of California, Davis, Davis, California USA

Correspondence:
Craig D. Nowadly, MD
Department of Emergency Medicine
PSSB 2100, U.C. Davis Medical Center
4150 V Street
Sacramento, California 95817 USA
E-mail: cdnowadly@ucdavis.edu

Conflicts of interest/disclaimer: The authors have no conflicts of interest to declare. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, or the US Government.

Keywords: Advanced Life Support; astronaut; critical care; emergency medicine; evacuation; International Space Station; low Earth orbit; resuscitation; space ambulance

Abbreviations:
ACRV: Assured Crew Return Vehicle
CMO: Crew Medical Officer
CPR: cardiopulmonary resuscitation
DMCF: definitive medical care facility
EMU: Extravehicular Mobility Unit
EVA: extravehicular activity
HMS: Health Maintenance System
IMM: Integrated Medical Model
ISS: International Space Station
LEO: low Earth orbit
NASA: National Aeronautics and Space Administration

Received: February 2, 2019
Revised: April 15, 2019
Accepted: May 9, 2019

doi:10.1017/S1049023X19004734

Abstract

Introduction: Provision of critical care and resuscitation was not practical during early missions into space. Given likely advancements in commercial spaceflight and increased human presence in low Earth orbit (LEO) in the coming decades, development of these capabilities should be considered as the likelihood of emergent medical evacuation increases.

Methods: PubMed, Web of Science, Google Scholar, National Aeronautics and Space Administration (NASA) Technical Server, and Defense Technical Information Center were searched from inception to December 2018. Articles specifically addressing critical care and resuscitation during emergency medical evacuation from LEO were selected. Evidence was graded using Oxford Centre for Evidence-Based Medicine guidelines.

Results: The search resulted in 109 articles included in the review with a total of 2,177 subjects. There were two Level I systematic reviews, 33 Level II prospective studies with 647 subjects, seven Level III retrospective studies with 1,455 subjects, and two Level IV case series with four subjects. There were two Level V case reports and 63 pertinent review articles.

Discussion: The development of a medical evacuation capability is an important consideration for future missions. This review revealed potential hurdles in the design of a dedicated LEO evacuation spacecraft. The ability to provide critical care and resuscitation during transport is likely to be limited by mass, volume, cost, and re-entry forces. Stabilization and treatment of the patient should be performed prior to departure, if possible, and emphasis should be on a rapid and safe return to Earth for definitive care.

Nowadly CD, Trapp BD, Robinson SK, Richards JR. Resuscitation and evacuation from low Earth orbit: a systematic review. *Prehosp Disaster Med.* 2019;34(5):521–531.

Introduction

In recent decades, advancements by the National Aeronautics and Space Administration (NASA; Washington, DC USA) and its international partners have allowed for the continuous human habitation of the International Space Station (ISS). The health and safety of astronauts and cosmonauts during the ISS program has been exemplary. There has been no medical evacuation, fatality, or long-term sequelae from a treatable medical or traumatic injury. This was made possible by strict astronaut medical selection and mission safety standards. These standards were first implemented during early missions into space when the on-board medical capabilities were primitive and focused on treating minor medical conditions commonly encountered during spaceflight, such as nausea, vertigo, or insomnia.[1] Due to limitations in mass and volume, crew medical training, mission duration, and poor prognosis if a severe medical event did take place, provision of critical care and resuscitation abilities was not practical.

As missions lengthen and cumulative man-years in space increase, the risk of an unpredictable medical or traumatic incident rises. Thus, NASA and international partner agencies undergo rigorous evaluation of risk, safety, and cost effectiveness to balance mission requirements with available resources. However, there is a paucity of publicly available research and on-orbit technology dedicated to resuscitation and medical evacuation, due in part to the safety record of the ISS program. Given terrestrial advancements in emergency and austere care, as well as the potential for an increase in human presence in low Earth orbit (LEO) due to commercial spaceflight, it may be timely to re-visit the available capabilities and challenges of providing emergency care during medical evacuation.

In this systematic review, the pertinent literature regarding the past, present, and future of medical evacuation from LEO is contextualized and analyzed. The unique physiologic and technical challenges of prehospital care in space are also discussed, with a focus on situations where resuscitation and medical evacuation would be required, rather than on low-acuity interventions or maintenance health care. This discussion of higher acuity situations pushes the boundaries of today's capabilities and lays a foundation for advancements in the decades to come.

Methods

All human studies, case series, case reports, or reviews were considered in the literature search. Data were abstracted systematically from a query of PubMed (National Center for Biotechnology Information, National Institutes of Health; Bethesda, Maryland USA); Web of Science (Thomson Reuters; New York, New York USA); Google Scholar (Google Inc.; Mountain View, California USA); NASA Technical Server (NASA Langley Research Center; Hampton, Virginia USA); and Defense Technical Information Center (Fort Belvoir, Virginia USA) from inception to August 2018. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[2] Studies published in a language other than English without available translation and articles not specifically addressing critical care and resuscitation during evacuation from LEO were discarded. The search strategy included free-text words (TW) and controlled vocabulary terms using medical subject headings (MeSH) for these topics, their synonyms, abbreviations, and alternate spellings. The search string included: ("Life Support Systems"[Mesh] OR "Space Flight"[Mesh] OR "Astronauts"[Mesh] OR "Spacecraft"[Mesh] OR "Weightlessness"[Mesh] OR "Weightlessness Simulation"[Mesh]) AND ("Trauma"[TW] OR "Injury"[TW] OR "Ambulance"[TW] OR "Emergency"[TW] OR "Evacuation"[TW] or "Surgery"[TW]).

References in each selected publication were also carefully screened for any additional reports having relevance. All references are cited in appropriate context. A grey literature search was also performed using OpenGrey (INIST-CNRS – Institut de l'Information Scientifique et Technique; Paris, France) and Google. All four authors were independently involved in the search process and in the review of the identified articles. Articles were graded using the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence.[3] These levels are defined as: I = properly powered and conducted randomized clinical trial, systematic review, or meta-analysis; II = well-designed controlled trial without randomization, prospective comparative cohort; III = case-control studies, retrospective cohort studies; IV = case series with or without intervention, cross-sectional studies; and V = opinion of authorities, case reports.

Results

The initial search identified 757 articles, and 38 additional articles were obtained through hand-searching. These records were screened for eligibility after duplicates were removed, and 396 were excluded from review of title and/or abstract contents. Of the remaining 207 publications, 98 addressed issues outside the scope of this systematic review. The remaining 109 articles were included in the review (Figure 1). Literature obtained included human and animal studies, case studies, technical reports, white papers, and review articles. A total of 2,177 study subjects were associated with the included articles. There were two Level I systematic reviews,[4,5] 33 Level II prospective studies with 647 subjects,[6–38] seven Level III retrospective studies with 1,455 subjects,[39–45] and two Level IV case series with four subjects.[46,47] There were two Level V case reports[48,49] and 63 pertinent review articles.[50–112] The included articles were further sub-divided into five categories: Airway, Anesthesia, Critical Care, Equipment, and Transport (Supplementary Table 1; available online only).

Discussion

Is There a Risk?

There have been 21 fatalities from five tragic incidents in the American and Russian space programs.[80] The majority of these fatalities were caused by a failure of the spacecraft resulting in catastrophic injuries which modern medical interventions could not have treated. Medical interventions were required for 17 non-fatal, severe medical events between 1961 and 1999.[80] While many of these were treated utilizing on-board resources, four Russian cosmonaut medical evacuations have occurred when these resources were exceeded.[80,108]

The incidence of medical emergencies for the general terrestrial population is approximately 0.06 events per person-year.[80] Estimated projections have placed the risk of emergent medical evacuation from LEO as low as 0.01 events per person-year to as high as 0.17 events per person-year.[75,80] The reduced risk compared to the general population may be explained by the rigorous medical selection standards for astronauts and the microgravity environment, which reduces the risk of traumatic injury. These frequencies represent a low-risk of severe injury or illness given the current ISS crew complement of three to six individuals. In the event of a larger presence in LEO of commercial crewmembers who may receive less medical screening or training than astronauts, a severe injury or illness requiring advanced medical treatment becomes inevitable.

Recent work has been performed to model medical emergencies during spaceflight. The most notable is NASA's Integrated Medical Model (IMM).[42,45] The IMM is a Monte Carlo simulation which uses probabilistic techniques to estimate the risk of medical and traumatic emergencies, the rate of medical evacuation, and the impact of illness on crew performance. In addition, NASA has published a list of 100 medical conditions included in IMM simulations.[45] These conditions represent a wide spectrum of pathologies, 47 of which have previously occurred. The additional 53 represent theoretical pathologies during spaceflight, such as chest trauma. As shown in Table 1, 37% of these conditions have the potential to require prehospital resuscitation and evacuation.

Equipment and Training

The Health Maintenance System (HMS) on the ISS represents the most robust LEO medical capability in use to date. There is a focus on commonly-used medications and equipment, such as anti-inflammatories and sleep aids.[107] However, the HMS contains a selection of up to 190 pharmaceuticals in addition to emergency medical equipment such as an ultrasound, backboard, defibrillator, interosseous access kits, intubation equipment, and a ventilator.[78,107,112] United States Pharmacopeia (North Bethesda, Maryland USA) standards apply aboard the ISS; medications that are re-packaged for the microgravity environment have decreased shelf-lives, requiring complex re-supply logistics to keep medications stocked and updated.[113,114]

In the event of a medical emergency on the ISS, initial resuscitation would be performed by a pre-selected Crew Medical Officer (CMO). The CMO receives approximately 40 hours of medical training during mission preparation on topics such as basic medical diagnostics and therapeutics.[86,115] While this model of care is

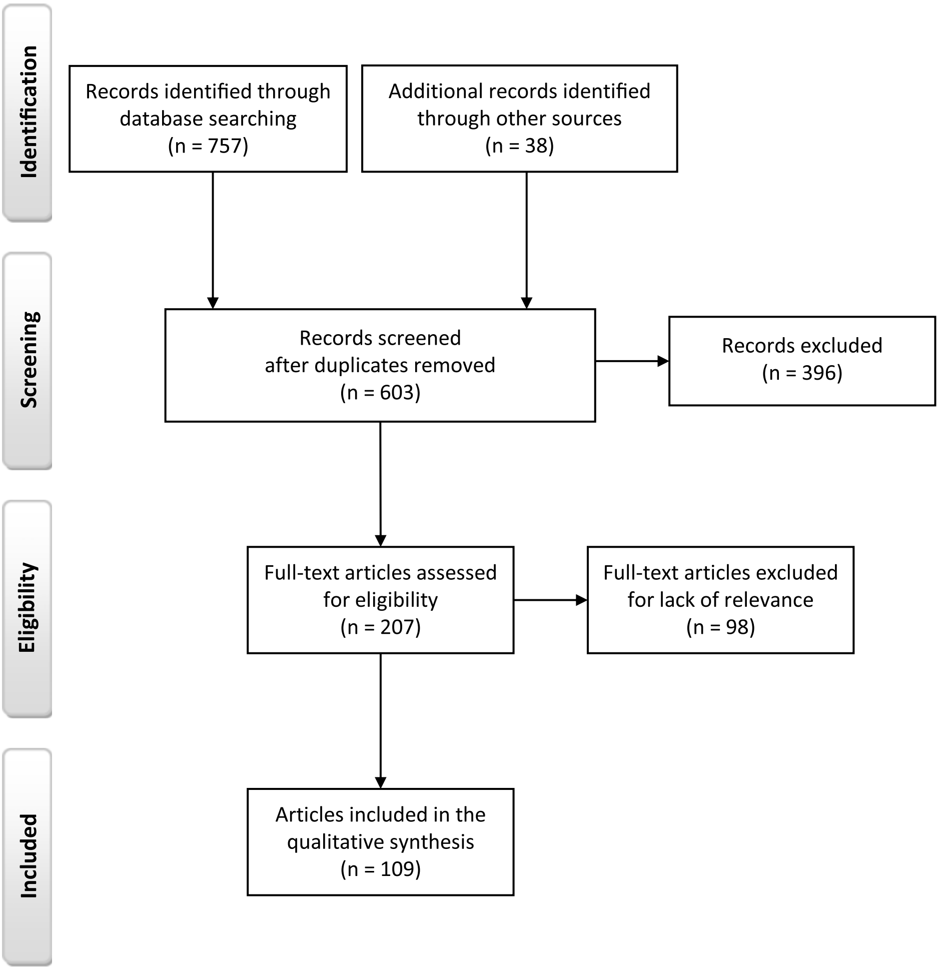

Figure 1. PRISMA Flow Diagram of Publications Reporting on Topics Specific to Emergency Medical Evacuation from Low Earth Orbit.

flexible and does not require exhaustive pre-mission training, there are limitations. Most CMOs are not physicians and receive limited clinical training prior to spaceflight. There are no examples in terrestrial health care where individuals with such limited medical training are expected to independently provide advanced prehospital interventions.[76] Additionally, only one or two CMOs are designated per ISS contingent.[86] This represents a single point failure if the CMO themselves becomes incapacitated from injury or illness.

Telemedicine may partially offset a CMO's lack of clinical experience. If a medical emergency took place, NASA flight surgeons would provide real-time advice to the CMO.[76,91] Under such supervision, the CMO may be capable of medical decision making beyond their training. This assumes video and audio communication capability is available, which may not be the case if the spacecraft has been damaged or is in poor orbital alignment. Russia provides continuous on-console physician staffing, and NASA flight surgeons are present during all high-risk operations. However, given the unpredictability of medical emergencies, the CMO may be required to operate independently. Practical skills such as intubation or chest tube insertion will remain challenging despite telemedical oversight.

Transport Considerations

Given the limitations of the current ISS medical capability, it may appear logical to immediately evacuate an ill or injured crewmember for care at a definitive medical care facility (DMCF). This philosophy, known as "scoop and run," is common in terrestrial Emergency Medical Systems (EMS) but has inherent risks if applied to spaceflight.[76] Once medical evacuation is initiated and the crew departs the ISS, CMOs cannot access additional medical resources on either the ISS or Earth for several hours until re-entry is completed. Even under ideal circumstances, a CMO may be unable to maintain communication with flight surgeons and/or access the patient's body due to ergonomic and gravitational restraints. The CMO is likely to develop neurovestibular symptoms and may be unable to move their head without the development of vertigo, nausea, and vomiting.[37,39] Given the large working area of the ISS and available medical and crew resources of the HMS, a short period of resuscitation and stabilization of a casualty would preferably occur on-station prior to evacuation. This may not be possible in the event of a simultaneous technical or structural emergency, when rapid evacuation is imperative for crew safety. While a "stay and play" strategy is not advised, an initial period of stabilization or treatment would be beneficial to ensure the patient is as stable as possible prior to the stress of LEO evacuation.

A crewmember would ideally be returned using a spacecraft optimized for medical evacuation, such as an Assured Crew Return Vehicle (ACRV). Spacecraft capable of medical evacuation were first proposed in the 1970's and 1980's.[51,60,65] Also, NASA proposed

Abdominal Injury
Abdominal Wall Hernia
Acute Cholecystitis/Biliary Colic
Acute Compartment Syndrome
Acute Diverticulitis
Acute Closed Angle Glaucoma
Acute Pancreatitis
Acute Prostatitis
Acute Radiation Syndrome
Angina/Myocardial Infarction
Anaphylaxis
Appendicitis
Atrial Fibrillation/Flutter
Burns [a]
Cardiac Dysrhythmia [a]
Cardiogenic Shock
Chest Injury
Choking/Obstructed Airway
Decompression Sickness
Epistaxis
Eye Chemical Burn
Head Injury
Headache
Hypovolemic Shock
Lumbar Spine Fracture
Nephrolithiasis [a]
Neurogenic Shock
Pelvis/Femur Fracture
Pneumonitis [a]
Respiratory Infection
Sepsis [a]
Small Bowel Obstruction
Smoke Inhalation
Stroke
Sudden Cardiac Arrest
Toxic Exposure
Urinary Retention [a]

Table 1. Integrated Medical Model Conditions with Potential to Require Critical Care Medical Evacuation

[a] Indicates documented spaceflight medical events which have occurred.[80]

technical restrictions such as limits on acceleration (no greater than 4g in the ± Gx, 1g in the ± Gy, and 0.5g in the ± Gz direction), spin stability, and impact acceleration which could affect medical outcomes in a deconditioned and injured crewmember.[21] The original plan for the ACRV was to interface with the space station's medical equipment and facilitate the delivery of Advanced Life Support during evacuation.[65] The NASA guidelines specified that a crewmember arrive at a DMCF within a maximum of 24 hours, with transit time from ISS separation until arrival at a DMCF of less than six hours.[65] These requirements balanced the need for rapid evacuation with mission planning, spacecraft preparation, and orbit alignment.

Figure 2. Space Limitations Inside the Soyuz Spacecraft. Source: National Aeronautics and Space Administration (NASA), images are in the public domain: CC0 1.0. https://www.nasa.gov/sites/default/files/thumbnails/image/inside-soyuz.jpg.

"Space Ambulance" Design

There were numerous proposals for ACRV design, including lifting bodies, capsules, and even single passenger escape pods.[60,62] Over the last several decades, the ACRV program underwent multiple iterations and different spacecraft were considered, including the Station Crew Return Alternative Module, HL-20, X-38, and The Orbital Space Plane.[108] Due to budget restrictions, the program was terminated in 2002.[116] At that time, the Space Shuttle and Soyuz descent module were deemed sufficient alternatives for LEO evacuation, despite restrictions on rapidly mobilizing the Space Shuttle during a medical emergency and the Soyuz descent module's limited ability to evacuate critically injured passengers.

Since the Space Shuttle's retirement, the Soyuz descent module is the only available manned spacecraft capable of travel to and from LEO. Unfortunately, the Soyuz descent module is not an ideal platform for medical evacuation.[76] It is small, with a volume of four square meters for a crew of three.[117] As seen in Figure 2, this environment provides minimal additional room for basic medical equipment and is incapable of supporting critical care equipment. During re-entry and descent, crewmembers wearing a Sokol spacesuit are restrained in a seated position. This limits a CMO's access to a patient and is sub-optimal for trauma patients who may require supine positioning. The module flies a moderate re-entry profile (~4g) and typically lands in the steppes of Kazakhstan, hundreds of miles from the nearest DMCF. While alternative landing sites have been proposed for use during a medical emergency, this has never been simulated.[76] During the rare ballistic re-entry, crewmembers are subjected to a steep re-entry profile (up to 9g) and the module can land up to 1,200 miles off course, drastically increasing the time required to reach the nearest DMCF.[80,108] The module impacts the ground with instantaneous g-force in excess of 17g.[27] These landing conditions occasionally injure healthy astronauts returning from space.[27] Although medical evacuation with this module may be satisfactory for a patient with a non-critical pathology, it could worsen or prove fatal for a critically ill or injured patient.[25,74]

Given the restrictions of the Soyuz descent module, recent work has been performed to revive the ACRV concept by designing a

Mission Requirement	Recommended Capability
Crew Capacity	Vehicle and systems can support 3+ passengers
Mission Duration	Return transit time 3 hours or less
Shirt-Sleeve Environment	Space suits not required by crew or patient during re-entry
Supine Passenger	Vehicle may accommodate 1 supine passenger
Patient Access	CMO has access to patient at all times
In-Flight Medical Care	CMO able to deliver ALS level care while in transit
Critical Care Equipment	Vehicle directly interfaces with ISS critical care equipment
Piloted Capability	Vehicle operable by an in-situ backup pilot
On-Station Duration	Vehicle to remain berthed to ISS for up to 2 years
Crew Extraction	Isolation suits not required by ground support crew upon landing
Landing Capability	Landing sites not limited to military runways
Communications	Uninterrupted relay of live medical information during re-entry
Low-g Force Re-Entry	Re-entry forces do not exceed 2.0g

Table 2. Proposed Mission Capabilities for a Medical Evacuation Capable Spacecraft
Abbreviations: ALS, Advanced Life Support; CMO, Crew Medical Officer; ISS, International Space Station.

dedicated medical evacuation spacecraft. One proposal adapts the United States Air Force's X-37B, an unmanned classified spacecraft, for use as a "space ambulance."[108] The X-37B has proven capable of long-duration spaceflight and flies a low-g re-entry profile due to its lifting body design. The interior is large enough to hold a crewed pressure vessel, can accommodate a supine patient, and is capable of accurate landings at pre-determined terrestrial runways with a nearby DMCF. Such an adapted craft would exceed NASA's original proposed ACRV criteria and provide an environment optimized for medical resuscitation and treatment. While the X-37B remains a classified military asset and these proposed changes would require significant modifications, the revival of the ACRV would fundamentally alter how medical care is provided during LEO evacuation.

Broad criteria for a "space ambulance" are presented in Table 2. While these criteria represent only minimum technical and medical necessities, they highlight unique challenges of LEO evacuation. Such a spacecraft could be designed solely for use as a dedicated "space ambulance" with an environment optimized for prehospital care, patient and crew safety, and rapid evacuation. It could also be designed to provide a rapidly configurable environment optimized for medical evacuation; a feature common to military transport aircraft. These criteria, and the implications for design, cost, safety, and operational capability, should be considered as new manned spacecraft become operational in the coming years, such as the SpaceX Dragon or Boeing CST-100.

Airway Management

The first step in the resuscitation of a critically ill or injured patient is establishing airway control, which may be complicated by the microgravity environment. Airway access becomes difficult if a patient is wearing a spacesuit, known as the Extravehicular Mobility Unit (EMU). The EMU requires significant time and assistance to don and doff and precludes access to the patient's head and neck.[72] Furthermore, the EMU is made of layers of durable materials such as Kevlar, contains fluid and electronics components, and has metal and composite struts surrounding the head and neck.[104]

One study examined medical care for an injured subject wearing a high-altitude pressure suit similar in configuration to the ISS EMU for a skydiving record attempt. In ground-based simulations of medical treatment, it was found that three to five minutes was required for a team of four rescuers to remove the pressure suit and initiate medical care.[104] This timeline would be further compromised if an astronaut sustained an injury during extravehicular activity (EVA), as additional time is required to ingress through an airlock. Fortunately, during EVA, astronauts are breathing 100% oxygen, which extends physiologic oxygen reserves.[72] No available research has been published that addresses the impacts of space suit design or astronaut size on the feasibility of and time required to gain access to the airway and upper chest, initiate bag-valve-mask ventilation, perform intubation, or the impacts on maintaining cervical spine alignment. These limitations need to be considered during design of future space suits.

Once the patient's head and neck are exposed, the airway can be temporarily controlled with bag-valve-mask ventilation. Physiologic changes of spaceflight complicate this effort. In LEO, fluid shifts occur within the human body which cause facial, sinus, and neck edema.[1,115] This may make bag-valve-mask ventilation more difficult. Airway adjuncts are already available on the ISS, such as a nasal trumpet or oropharyngeal airway.[107]

Endotracheal Intubation and Alternatives

Since early in the space program, researchers recognized the challenges of endotracheal intubation in microgravity.[53] Microgravity does not facilitate clearance of secretions, which can complicate visualization of vocal cords during a difficult intubation, such as a burned or bloodied airway.[53] Additionally, the force required to adequately visualize the vocal cords with a laryngoscope causes paradoxical movement of the patient and the operator in microgravity.[17,53,77] Some of these difficulties have been mitigated by the Crew Medical Restraint System, a backboard, harness, and head restraint.

A CMO typically has either limited or no clinical experience intubating.[17,77] It has been shown that intubation success rates in austere environments by operators with limited training is approximately 50%.[77] Studies show that even after 80 intubations, 18% of first-year anesthesia residents were unable to secure a patient's airway without additional assistance in optimal operating room conditions.[77] Such outcomes are unacceptable during emergency resuscitation on-orbit.

Despite the inherent challenges of airway control in microgravity, there are proposed techniques to improve success. The odds of successful intubation can be improved by restraining both the patient and operator to the deck of the spacecraft, such as the ISS's Crew Medical Restraint System, thus limiting movement in microgravity.[17] In the event that the patient cannot be restrained, there are other techniques to limit movement between the operator and patient, such as grasping the patient's head between the operator's knees.[23] However, these techniques had poor success rates in untrained personnel when performed in simulated microgravity.[23]

Some experts argue that the use of a supraglottic device is superior to an endotracheal tube.[17,24,77,84] Debate remains over which supraglottic device is optimal in the austere LEO environment.[24,84] For instance, NASA literature documented a success rate for placement of supraglottic device at nearly 99%, even for an operator with limited skill and expertise.[92] A supraglottic device does not represent a definitively secured airway and may be sub-optimal if a patient requires mechanical ventilation or paralytics. The ISS HMS has both supraglottic laryngeal mask airway and endotracheal tubes available.[107] If a physician-astronaut is on-board, placement of an endotracheal tube should be attempted; however, if a non-physician CMO is available, a laryngeal mask airway would be preferred during an emergency until NASA Flight Surgeons can provide additional recommendations. Notably, no studies assessed the use of video laryngoscopy in microgravity, which may significantly improve intubation success compared to direct laryngoscopy. The inclusion of video laryngoscopy on-orbit should be considered during future missions, especially if a physician-astronaut with experience in anesthesia, emergency medicine, or critical care is not available.

It is unclear how microgravity and re-entry would impact a supraglottic device or an endotracheal tube after placement. Movement or mispositioning of either device, which may occur during sustained g-loading, could prove fatal if not rapidly identified and corrected by a CMO. Even minor changes in pressure may impact an airway device's seal within the oropharynx or trachea. If pressure fluctuated during evacuation, this would proportionally impact the airway's cuff size, causing either cuff leaks or damage to local structures if under- or over-inflated. This issue is frequently encountered during US Air Force medical evacuation flights, despite pressurized cabins, and requires continuous reassessment.[15] Filling an airway cuff with a fluid has shown to create pressures which can cause damage to local airway structures and is not recommended.[118]

Ventilation and Oxygenation

Microgravity affects respiratory physiology in multiple ways, including increased pulmonary blood flow, decreased strength of chest wall musculature, and increased ventilation-perfusion mismatch.[78] There are also changes in lung volumes, such as decreased residual volume and functional residual capacity.[78] Standard terrestrial resuscitation oxygenation includes 15L per minute of oxygen delivered via non-rebreather facemask, a capability currently available on the ISS.[107] If the same 15L per minute were required throughout a six-hour medical evacuation, access to large oxygen tanks would be required, a difficult engineering challenge given on-orbit mass and volume limitations.

Oxygen delivered by non-rebreather facemask would leak into the confined evacuation spacecraft, changing the pressure and oxygen concentration of its small volume. Without environmental systems capable of controlling for these changes, there is a risk of fire or over-pressurization of the cabin. A patient could receive 100% oxygen if wearing a face seal aviator mask or re-entry space suit during evacuation, but this limits access to the patient by the CMO and may not be possible after injury. Overcoming these challenges may require unconventional medical and engineering solutions, such as prophylactically intubating any patient requiring significant oxygenation in order to create a closed respiratory system.

The ISS HMS currently stocks an Autovent 2000 pneumatic ventilator (Allied Healthcare; St. Louis, Missouri USA), a reliable albeit limited device.[78,107] Compared to the features of austere ventilators used on military medical evacuation flights, the Autovent 2000 lacks standard critical care features.[26,87] While capable of changes in tidal volume and rate, this ventilator is not capable of assist ventilation modes, positive end expiratory pressure, continuous positive airway pressure, or adjustments in inspiratory times and delivered oxygen concentration.[78] Given the short duration of evacuation, some advanced ventilator features may not provide additional clinical benefit.

Ventilators are complex medical devices and can be difficult to manage in a controlled terrestrial setting. Although ventilator function has been tested in microgravity, there is limited literature detailing how the re-entry environment may impact an intubated patient or the function of the ventilator.[18] Data from experiments involving intubated animal models on parabolic flights describe largely normal ventilator function between alternating periods of zero-g, one-g, and two-g.[18] However, these studies did not assess respiratory status or ventilator function as primary outcomes. Small variations in ventilator function or respiratory physiology can have significant clinical impact. Given the complexity of these devices, knowledge required for safe operation, and difficulty of managing a patient in space, some researchers have proposed closed-loop decision making with regard to ventilator management.[78] Closed-loop strategies include ventilators capable of adjustments in response to physiologic inputs remotely controlled by terrestrial flight surgeons, and more recently, artificial intelligence completing autonomous management decisions.[78,119]

Cardiopulmonary Resuscitation

Techniques for performing cardiopulmonary resuscitation (CPR) have been studied during simulated microgravity and in LEO.[6,19,20,22,30,35] Cardiopulmonary resuscitation is problematic in microgravity as the force required to provide chest compressions is tiring and causes reciprocal movement of the patient and operator. There were concerns that chest compression may not produce the required intra-thoracic pressure to ensure end organ perfusion, even if performed to the correct depth.[19] Fortunately, research confirmed that end-tidal CO_2 levels, a marker of normal physiologic perfusion, were adequate while testing different CPR techniques in simulated microgravity.[20]

A variety of novel CPR techniques have been studied, including for both a restrained or free-floating patient.[29] For example, the Evetts-Russomano method involves the operator diagonally straddling a free-floating patient's chest while providing compressions.[33] The Handstand Maneuver, by comparison, involves the operator standing on the "ceiling" of the spacecraft, above their patient, and providing compressions with straight arms against the patient on the floor.[22] While it is believed that the Handstand Maneuver produces the best cardiac output, variables that impact effectiveness of each method include airway access, patient and operator size, number of operators available, and the volume of the vehicular compartment.[4,30] Testing of mechanical CPR devices for use on-orbit has been limited.[19,28] In the event of emergent medical evacuation, these devices likely represent the only way CPR can be performed and sustained in the restricted volume of the spacecraft. There are mixed data on the impact of these devices on neurologically-intact survival in terrestrial literature.[120] The prognosis and outcome of patients on whom CPR is performed during evacuation from LEO would likely remain grim.

Anesthesia and Sedation

No human has yet required anesthesia or sedation during spaceflight, evacuation from LEO, or immediately after returning to Earth.[5] Researchers sent two primates to LEO for 14 days and administered an anesthetic immediately upon return to Earth. Despite close monitoring and care, one animal died and the other experienced anesthesia-related complications.[73] The authors of this study stressed that anesthesia and sedation should only be performed in extreme circumstances. For a critically ill or injured crewmember, anesthesia would be required prior to interventions such as intubation or chest tube placement.[5] Volatile gas anesthetics are contraindicated during spaceflight as there is a high-risk of exposing other crewmembers within an enclosed environment.[5]

Ketamine has been suggested as the primary medication for general anesthesia while in space.[5,98,106] Ketamine is considered safe, has favorable hemodynamic effects, can be delivered intramuscularly and intravenously, has an extended shelf life, and has been used extensively by military and civilian providers in austere environments.[121–123] Ketamine has already been approved for spaceflight and is included in the ISS HMS for procedural sedation.[107] Despite a favorable side effect profile, it is important that sufficient doses be given during medical evacuation to prevent emergence phenomena, as the associated agitation carries an additional risk of injury to the crewmember and CMO in an enclosed environment.

Ketamine provides dissociative anesthesia while maintaining protective airway reflexes.[122] This is beneficial as minor procedures and short-term sedation can be achieved without additional airway protection. If intubation was required, however, ketamine monotherapy may not be sufficient, and a paralytic agent would be required to overcome airway reflexes and facilitate endotracheal tube or laryngeal mask airway placement. Due to hypothetical changes in the neuromuscular junction in microgravity, succinylcholine is contraindicated during spaceflight.[5] Rocuronium has been proposed as an acceptable alternative.[5] No paralytics are currently included in the ISS HMS as of 2016, severely limiting the value of on-board intubation equipment.[107] Paralytics will need to be considered in future medical evacuation spacecraft if critical care capability is desired.

Surgical Intervention

The literature regarding anesthetic use during spaceflight focuses on facilitating surgical care during exploration class missions to the Moon and Mars. However, LEO evacuation should be possible within 24 hours, thus simplifying the role of anesthetics, as complex surgical care will be deferred until after return to Earth. Advanced techniques such as regional anesthesia have little to no role during emergent evacuation as they are complex, require additional training, risk damage to local structures, and provide minimal benefit over temporary sedation with ketamine.[98]

Like anesthesia, the majority of literature regarding surgicaland traumatic interventions in space focus on long-duration exploration class missions during which medical evacuation may be impossible.[102,103,110] Parabolic experiments simulating simple surgical procedures in microgravity led to the development of patient and operator restraints to facilitate positioning, as well as sterile surgical chambers to control bodily fluids.[10,11,64,68] Proper suctioning equipment is essential to control bodily fluids in microgravity, although such equipment is not available on the ISS.[107] Standard sterile surgical preparation and draping have been shown to be effective in simulated microgravity.[10] During the 1998 Space Shuttle STS-90 mission, surgical procedures, such as caesarian section and laminectomy, were successfully completed on animal models.[103]

For a variety of surgical emergencies, a patient must currently receive definitive surgical intervention after medical evacuation to Earth. Until the establishment of robust surgical and medical facilities on future space stations, complex surgical procedures are not practical in LEO due to limitations in mass, crew training, and potentially deleterious outcomes. On-orbit surgical interventions should focus only on short-term stabilization to facilitate re-entry and return to a DMCF.[110] Procedures integral to trauma resuscitation, such as laceration repair, chest tube insertion, and cricothyroidotomy, have been performed in simulated microgravity on animal models.[8,18] In order to confirm that procedures could be performed with the supplies available on the ISS, nonstandard techniques were used in one study, such as using an endotracheal tube in place of a standard chest tube.[18] Researchers found these procedures to be more difficult to perform in simulated microgravity. All simulated procedures except peritoneal lavage were found to be safe and effective. Peritoneal lavage, which has been largely removed from terrestrial standards of care, was considered dangerous given increased abdominal pressure and a high-risk of bowel damage.[18] Future investigations are required to design surgical equipment optimized for each procedure, to integrate equipment into spacecraft systems, to assess the impacts of re-entry on surgical equipment, and to assess the clinical outcomes of procedures performed on-orbit.

Intravenous Fluid Considerations

A mainstay of terrestrial trauma and medical resuscitation is the transfusion of crystalloid fluids and blood products. Due to physiologic changes of spaceflight, astronauts have an estimated 15% decrease in circulating red blood cells and plasma on-orbit, which is equivalent to a terrestrial patient with Class I hemorrhage.[103] In the setting of this relative deficiency, astronauts suffering from acute blood loss may be more susceptible to shock during re-entry. Animal models with varying levels of hemorrhage induced by phlebotomy showed significant changes in cardiac output and blood pressure when subjected to +Gx centrifugation.[25,86] This experiment did not control for on-going hemorrhage or additional gastric fluid loss due to motion sickness. Such losses are likely to worsen overall hypovolemia during medical evacuation. As it is unlikely blood products will be available in LEO in the near future due to storage restrictions and short shelf lives, fluid resuscitation capability prior to medical evacuation is limited to crystalloid products such as normal saline and lactated Ringer's solution.

The microgravity environment complicates intravenous fluid delivery. As gravity no longer pulls fluids out of fluid bags and into the body, an external force is required. While intravenous pumps can deliver set rates of fluid, studies in simulated microgravity show that some intravenous pumps struggle due to bubble formation.[21] Current protocol in microgravity involves using a pressure bag to provide an external force against the intravenous fluid bag. Unfortunately, it is difficult to control the rate of fluid administration using such techniques.[21] Care also must be taken to remove gas from intravenous bags prior to administration to prevent air emboli, which does not occur on Earth due to the effects of gravity. Techniques have been developed to remove gas bubbles in bags, such as rapidly spinning the bag to push out bubbles using centrifugal force. There are no objective data, however, describing the effectiveness of these techniques or impact on fluid sterility. There is limited discussion in the medical literature regarding the risk of air emboli in microgravity, the acceptable bubble burden a patient can tolerate prior to clinically significant effects, or the impact of the re-entry environment on the formation or dissolution of bubbles in fluids. There are engineering solutions to prevent air embolism using gas-liquid separators, but it is unclear if these solutions will impact the rate of fluid administration or type of fluids which can be administered.[31]

Limited amounts of commercial, off-the-shelf intravenous crystalloid fluids are currently available on the ISS but have high mass and volume and can be consumed rapidly in the event of an emergency.[107] Previous experimentation suggests that medical grade crystalloid fluids can be generated on-orbit using recycled water.[31,82,100] One notable experiment, known as IVGEN, produced normal saline using recycled water on the ISS. The produced saline met eight of nine US Pharmacopeia standards for terrestrially-produced, normal saline. While this experiment was technically complex and faced challenges such as air bubbles clogging medical tubing and difficulty reconstituting salts, the product would likely be clinically acceptable in the event of an emergency.[31] This suggests that resuscitation fluids may be able to be generated on-orbit and stocked before use. Research is required to develop these technologies given challenges in production, storage, cost, and safety.

In terrestrial critical care resuscitation, it is common to perform procedures to obtain central intravenous access for fluid and medication delivery and invasive physiologic monitoring. These interventions are currently unavailable in LEO.[107] While there is early development of alternative, non-invasive physiologic monitoring, there is limited mention of these interventions and their applications during spaceflight in the medical literature, and it is improbable these interventions will be available in the near future. This may become a liability when rapid expansion of human travel to and beyond LEO becomes a reality.[124] Discovering the limitations and challenges associated with these interventions, such as the reliability of arterial line blood pressure readings during re-entry or the maximum rate of fluid delivery through a central line in microgravity, will lay the foundation for future critical care interventions during spaceflight.

Even with the most advanced medical resources, terrestrial critical care and emergent resuscitation may have sub-optimal clinical outcomes. As human spaceflight becomes more common, ongoing discussions about the role of medical interventions will be required to balance medical resources with public and crew expectations. Difficult ethical questions remain largely unanswered in the medical literature, such as when withdrawal of care is appropriate to conserve limited medical resources, the management of patient remains, and the cost-effectiveness of resuscitation and medical evacuation. These challenges will require honest and open conversation between astronauts, leaders in government and commercial spaceflight, and space medicine physicians.

Limitations

This systematic review has potential limitations. The subject matter covered a wide variety of topics from diverse sources. There are no large-scale, Level I studies regarding emergency medical evacuation from LEO. Publication bias is a concern in systematic reviews, and it is possible adverse events or negative outcomes may not have been reported in those articles involving subjects. The search strategy incorporated a low inclusion threshold of all published and unpublished reports but may have missed relevant articles regardless. There is an additional possibility sensitive, protected, or classified government documents may not have been accessible for the purposes of this review.

Conclusion

In the next decade, the United States will have spacecraft capable of carrying astronauts into and beyond LEO. Along with the growth of commercial space partners, there is potential for rapid expansion of personnel operating in space, and with this development comes inherent risk of medical and traumatic emergencies. The challenges of providing critical care medical evacuation from these environments are immense, but as human spaceflight expands, the expectation and need for advanced medical care in increasingly austere environments becomes paramount. These challenges can be overcome with investment and research in medical evacuation spacecraft and development of medical technology optimized for re-entry.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1049023X19004734

References

1. Barratt MR, Pool SL, (eds). *Principles of Clinical Medicine for Space Flight*. New York, USA: Springer; 2008
2. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;1(4):1.
3. Oxford Centre for Evidence-Based Medicine. 2011 Levels of Evidence. http://www.cebm.net/index.aspx?o=5653. Published 2011. Accessed July 25, 2019.
4. Braunecker S, Douglas B, Hinkelbein J. Comparison of different techniques for in microgravity-a simple mathematic estimation of cardiopulmonary resuscitation quality for space environment. *Am J Emerg Med*. 2015;33(7):920–924.
5. Komorowski M, Fleming S, Mawkin M, Hinkelbein J. Anesthesia in austere environments: literature review and considerations for future space exploration missions. *NPJ Microgravity*. 2018;4:5.
6. Billica R, Gosbee J, Krupa D. Evaluation of cardiopulmonary resuscitation techniques in microgravity. https://ntrs.nasa.gov/search.jsp?R=19910023475. Published 1991. Accessed July 25, 2019.
7. Billica R, Young J, Rushing D, Kizzee V. Fluid handling 2: surgical applications. http://hdl.handle.net/2060/19910023476. Published 1991. Accessed July 25, 2019.
8. Gosbee J, Kupra D, Pepper L, Orsak D. ATLS: Catheter and tube placement. https://ntrs.nasa.gov/search.jsp?R=19910023468. Published 1991. Accessed July 25, 2019.
9. Maidlow K, Schulz J, Lloyd C, Breeding T. Shuttle Orbiter medical system equipment/supplies evaluation. https://ntrs.nasa.gov/search.jsp?R=19910023479. Published 1991. Accessed July 25, 2019.
10. McCuaig KE, Houtchens BA. Management of trauma and emergency surgery in space. *J Trauma*. 1992;33(4):610–625.
11. Campbell MR, Billica RD, Johnston SL. Surgical bleeding in microgravity. *Surg Gynecol Obstet*. 1993;177(2):121–125.
12. Guy HJ, Prisk GK, Elliott AR, Deutschman RA, West JB. Inhomogeneity of pulmonary ventilation during sustained microgravity as determined by single-breath washouts. *J Appl Physiol*. 1994;76(4):1719–1729.

13. Prisk GK, Guy HJ, Elliott AR, West JB. Inhomogeneity of pulmonary perfusion during sustained microgravity on SLS-1. *J Appl Physiol*. 1994;76(4):1730–1738.
14. Leach CS, Alfrey CP, Suki WN, et al. Regulation of body fluid compartments during short-term spaceflight. *J Appl Physiol*. 1996;81(1):105–116.
15. Harris BA, Billica RD, Bishop SL, et al. Physical examination during space flight. *Mayo Clin Proc*. 1997;72(4):301–308.
16. Cuttino CM. Martian emergency medical crisis management. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.664.3137&rep=rep1&type=pdf. Published 1999. Accessed July 25, 2019.
17. Keller C, Brimacombe J, A FR, et al. Airway management during spaceflight: a comparison of four airway devices in simulated microgravity. *Anesthesiol*. 2000;92(5):1237–1241.
18. Campbell MR, Billica RD, Johnston SL, Muller MS. Performance of advanced trauma life support procedures in microgravity. *Aviat Space Environ Med*. 2002;73(9):907–912.
19. Jay GD, Lee P, Goldsmith H, Battat J, Maurer J, Suner S. CPR effectiveness in microgravity: comparison of three positions and a mechanical device. *Aviat Space Environ Med*. 2003;74(11):1183–1189.
20. Johnston SL, Campbell MR, Billica RD, Gilmore SM. Cardiopulmonary resuscitation in microgravity: efficacy in the swine during parabolic flight. *Aviat Space Environ Med*. 2004;75(6):546–550.
21. Spaulding J, Gaukler E, Syracuse E, Brodsky L, Shean D. Assessment of intravenous fluid delivery systems for a microgravity environment. http://arc.aiaa.org/doi/10.2514/6.IAC-04-G.2.11. Published 2004. Accessed July 25, 2019.
22. Evetts SN, Evetts LM, Russomano T, Castro JC, Ernsting J. Basic life support in microgravity: evaluation of a novel method during parabolic flight. *Aviat Space Environ Med*. 2005;76(5):506–510.
23. Groemer GE, Brimacombe J, Haas T, et al. The feasibility of laryngoscope-guided tracheal intubation in microgravity during parabolic flight: a comparison of two techniques. *Anesth Analg*. 2005;101(5):1533–1535.
24. Rabitsch W, Moser D, Inzunza MR, et al. Airway management with endotracheal tube versus Combitube during parabolic flights. *Anesthesiol*. 2006;105(4):696–702.
25. Stepaniak PC, Hamilton GC, Olson JE, Gilmore SM, Stizza DM, Beck B. Physiologic effects of simulated + Gx orbital reentry in primate models of hemorrhagic shock. *Aviat Space Environ Med*. 2007;78(4 Suppl):A14–25.
26. Barnes SL, Branson R, Gallo LA, Beck G, Johannigman JA. En-route care in the air: snapshot of mechanical ventilation at 37,000 feet. *J Trauma*. 2008;64 (2 Suppl):S129–135.
27. Mathers CH. Measurement of accelerations experienced by rough stock riders: a model for examining acceleration-induced head injuries in astronauts. https://utmb-ir.tdl.org/utmb-ir/handle/2152.3/146. Published 2009. Accessed July 25, 2019.
28. Hurst VW, Whittam SW, Austin PN, Branson RD, Beck G. Cardiopulmonary resuscitation during spaceflight: examining the role of timing devices. *Aviat Space Environ Med*. 2011;82(8):810–813.
29. Kordi M, Cardoso RB, Russomano T. A preliminary comparison between methods of performing external chest compressions during microgravity simulation. *Aviat Space Environ Med*. 2011;82(12):1161–1163.
30. Rehnberg L, Ashcroft A, Baers JH, et al. Three methods of manual external chest compressions during microgravity simulation. *Aviat Space Environ Med*. 2014;85(7):687–693.
31. McQuillen J, McKay T, Griffin D, Brown D, Zoldak J. Final report for intravenous fluid generation (IVGEN) spaceflight experiment. https://ntrs.nasa.gov/search.jsp?R=20110014585. Published 2011. Accessed July 25, 2019.
32. Blue RS, Riccitello JM, Tizard J, Hamilton RJ, Vanderploeg JM. Commercial spaceflight participant G-force tolerance during centrifuge-simulated suborbital flight. *Aviat Space Environ Med*. 2012;83(10):929–934.
33. Russomano T, Baers JH, Velho R, et al. A comparison between the 2010 and 2005 basic life support guidelines during simulated hypo-gravity and microgravity. *Extrem Physiol Med*. 2013;2:11.
34. Blue RS, Pattarini JM, Reyes DP, et al. Tolerance of centrifuge-simulated suborbital spaceflight by medical condition. *Aviat Space Environ Med*. 2014;85(7):721–729.
35. Rehnberg L, Russomano T, Falcão F, Campos F, Everts SN. Evaluation of a novel basic life support method in simulated microgravity. *Aviat Space Environ Med*. 2011;82(2):104–110.
36. Komorowski M, Fleming S. Intubation after rapid sequence induction performed by non-medical personnel during space exploration missions: a simulation pilot study in a Mars analogue environment. *Extreme Physiol Med*. 2015;4:19.
37. Reschke MF, Good EF, Clément GR. Neurovestibular symptoms in astronauts immediately after Space Shuttle and International Space Station missions. *OTO Open*. 2017;1(4):2473974X1773876.
38. Suresh R, Blue RS, Mathers CH, Castleberry TL, Vanderploeg JM. Dysrhythmias in laypersons during centrifuge-simulated suborbital spaceflight. *Aerosp Med Hum Perform*. 2017;88(11):1008–1015.
39. Bacal K, Billica R, Bishop S. Neurovestibular symptoms following space flight. *J Vestib Res*. 2003;13(2–3):93–102.
40. Gontcharov IB, Kovachevich IV, Pool SL, et al. In-flight medical incidents in the NASA-Mir program. *Aviat Space Environ Med*. 2005;76(7):692–696.
41. Johannigman J, Gerlach T, Cox D, et al. Hypoxemia during aeromedical evacuation of the walking wounded. *J Trauma Acute Care Surg*. 2015;79 (4 Suppl 2):S216–220.
42. Keenan A, Young M, Saile L, et al. The Integrated Medical Model: a probabilistic simulation model predicting in-flight medical risks. https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20150018879.pdf. Published 2015. Accessed July 25, 2019.
43. Menon AS, Jourdan D, Nusbaum DM, et al. Crew recovery and contingency planning for a manned stratospheric balloon flight – the StratEx program. *Prehosp Disaster Med*. 2016;31(5):524–531.
44. Maddry JK, Mora AG, Savell SC, et al. Impact of Critical Care Air Transport Team (CCATT) ventilator management on combat mortality. *J Trauma Acute Care Surg*. 2018;84(1):157–164.
45. Myers J, Garcia Y, Griffin D, et al. The Integrated Medical Model: outcomes from independent review. https://ntrs.nasa.gov/search.jsp?R=20170004392. Published 2017. Accessed July 25, 2019.
46. Blue RS, Reyes DP, Castleberry TL, Vanderploeg JM. Centrifuge-simulated suborbital spaceflight in subjects with cardiac implanted devices. *Aerosp Med Hum Perform*. 2015;86(4):410–413.
47. Levin DR, Blue RS, Castleberry TL, Vanderploeg JM. Tolerance of centrifuge-simulated suborbital spaceflight in subjects with implanted insulin pumps. *Aerosp Med Hum Perform*. 2015;86(4):407–409.
48. Blue RS, Blacher E, Castleberry TL, Vanderploeg JM. Centrifuge-simulated suborbital spaceflight in a subject with cardiac malformation. *Aerosp Med Hum Perform*. 2015;86(11):999–1003.
49. Suresh R, Blue RS, Mathers C, Castleberry TL, Vanderploeg JM. Sustained accelerated idioventricular rhythm in a centrifuge-simulated suborbital spaceflight. *Aerosp Med Hum Perform*. 2017;88(8):789–793.
50. Seeler H. Complete emergency life sustaining system for spacecraft. *Aerospace Med*. 1964;35:37–40.
51. Hinton MG. Space rescue operations. http://hdl.handle.net/2060/19710025596. Published 1971. Accessed July 25, 2019.
52. Perchonok E. Advanced missions' safety. Volume 2: Technical discussion. Part 1: Space Shuttle rescue capability. https://ntrs.nasa.gov/search.jsp?R=19730003145. Published 1972. Accessed July 25, 2019.
53. LeJeune FE. Laryngoscopy in space travel. *Ann Otol Rhinol Laryngol*. 1979; 88(Pt 1):813–817.
54. Frey R, Dürner P, Von Baumgarten R, Vogel H. Emergency medical care on space stations. *Acta Astronaut*. 1980;7(12):1483–1484.
55. Griswold HR, Trusch RB. Emergency and rescue considerations for manned space missions. *Acta Astronaut*. 1981;8(9–10):1123–1133.
56. Stazhadze LL, Goncharov IB, Neumyvakin IP, Bogomolov VV, Vladimirov IV. Anesthesia, surgical aid and resuscitation in manned space missions. *Acta Astronaut*. 1981;8(9–10):1109–1113.
57. Houtchens B. System for the management of trauma and emergency surgery in space. https://ntrs.nasa.gov/search.jsp?R=19840012977. Published 1984. Accessed July 25, 2019.
58. Kelly BK. A systems analysis of emergency escape and recovery systems for the US Space Station. http://www.dtic.mil/docs/citations/ADA179233. Published 1986. Accessed July 25, 2019.
59. Halsell JD, Widhalm JW, Whitsett CE. Design of an interim space rescue ferry vehicle. *J Spacecraft Rocket*. 1988;25:180–186.
60. Naftel J, Powell R, Talay T. Ascent, abort, and entry capability assessment of a Space Station rescue and personnel/logistics vehicle. http://arc.aiaa.org/doi/10.2514/6.1989-635. Published 1989. Accessed July 25, 2019.
61. National Aeronautics and Space Administration (NASA). Preliminary subsystem designs for the Assured Crew Return Vehicle (ACRV). http://hdl.handle.net/2060/19900016723. Published 1990. Accessed July 25, 2019.
62. Cerimele CJ. Assured Crew Return Vehicle. https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/19900014139.pdf. Published 1991. Accessed July 25, 2019.
63. Nicogossian AE, Rummel JD, Leveton L, Teeter R. Development of countermeasures for medical problems encountered in space flight. *Adv Space Res*. 1992;12(1):329–337.
64. Campbell MR, Billica RD. A review of microgravity surgical investigations. *Aviat Space Environ Med*. 1992;63(6):524–528.
65. Chandler MR. Space Station Freedom Assured Crew Return Vehicle medical issues. http://papers.sae.org/921143. Published 1992. Accessed July 25, 2019.
66. Dons RF, Fohlmeister U. Combined injury syndrome in space-related radiation environments. *Adv Space Res*. 1992;12(2–3):157–163.

67. Siegel JH. Medical and surgical evaluation and care of illness in space. https://ntrs.nasa.gov/search.jsp?R=19950004524. Published 1994. Accessed July 25, 2019.
68. McCuaig K. Surgical problems in space: an overview. *J Clin Pharmacol.* 1994;34(5):513–517.
69. Mazanek DD, Garn M, Troutman P, Wang Y, Kumar R, Heck M. International Space Station (ISS) accommodation of a single US Assured Crew Return Vehicle (ACRV). https://ntrs.nasa.gov/search.jsp?R=19980007312. Published 1997. Accessed July 25, 2019.
70. Smith SM, Krauhs JM, Leach CS. Regulation of body fluid volume and electrolyte concentrations in spaceflight. *Adv Space Biol Med.* 1997;6:123–165.
71. Wilson JR. CRV investment offers safe return. *Aerosp Am.* 1997;35(6):28–32;38.
72. National Aeronautics and Space Administration (NASA). The Space Shuttle Extravehicular Mobility Unit (EMU). https://www.nasa.gov/pdf/188963main_Extravehicular_Mobility_Unit.pdf. Published 1998. Accessed July 25, 2019.
73. Norfleet WT. Anesthetic concerns of spaceflight. *Anesthesiol.* 2000;92(5):1219–1222.
74. Stepaniak P, Hamilton GC, Stizza D, Garrison R, Gerstner D. Considerations for medical transport from the Space Station via an Assured Crew Return Vehicle (ACRV). =https://ntrs.nasa.gov/search.jsp?R=20010073453. Published 2001. Accessed July 25, 2019.
75. Agnew JW, Fibuch EE, Hubbard JD. Anesthesia during and after exposure to microgravity. *Aviat Space Environ Med.* 2004;75(7):571–580.
76. Bacal K, Beck G, McSwain NE. A concept of operations for contingency medical care on the International Space Station. *Mil Med.* 2004;169(8):631–641.
77. Beck G. Emergency airway management in orbit: an evidence-based review of possibilities. *Respiratory Care Clinics.* 2004;10(3):401–421.
78. Kaczka D, Beck G. Mechanical ventilation in orbit: emphasis on closed-loop ventilation. *Resp Care Clin.* 2004;10(3):369–400.
79. Cooke WH, Convertino VA. Cardiovascular consequences of weightlessness promote advances in clinical and trauma care. *Curr Pharm Biotechnol.* 2005;6(4):285–297.
80. Summers RL, Johnston SL, Marshburn TH, Williams DR. Emergencies in space. *Ann Emerg Med.* 2005;46(2):177–184.
81. Convertino VA, Ryan KL. Identifying physiological measurements for medical monitoring: implications for autonomous health care in austere environments. *J Gravit Physiol.* 2007;14(1):P39–42.
82. Miller F, Niederhaus C, Barlow K, Griffin D. Intravenous solutions for exploration missions. http://arc.aiaa.org/doi/10.2514/6.2007-544. Published 2007. Accessed July 25, 2019.
83. Muratore JF. Space rescue. https://ntrs.nasa.gov/search.jsp?R=20070025530. Published 2007; Accessed July 25, 2019.
84. Roan RM, Boyd GL. Prediction of a low success rate of astronauts in space in performing endotracheal intubation. *Anesthesiol.* 2007;106(6):1247–1248.
85. Stewart LH, Trunkey D, Rebagliati GS. Emergency medicine in space. *J Emerg Med.* 2007;32(1):45–54.
86. Hamilton D, Smart K, Melton S, Polk JD, Johnson-Throop K. Autonomous medical care for exploration class space missions. *J Trauma.* 2008;64(4 Suppl):S354–363.
87. Hatfield T. Lightweight trauma module – LTM. https://ntrs.nasa.gov/search.jsp?R=20080012521. Published 2008. Accessed July 25, 2019.
88. Smith LJ, Arenare BA, Smart KT. Medical evacuation and vehicles for transport. In: Barratt MR, Pool SL (eds). *Principles of Clinical Medicine for Space Flight.* New York USA: Springer; 2008:139–162.
89. Kirkpatrick AW, Ball CG, Campbell M, et al. Severe traumatic injury during long duration spaceflight: light years beyond ATLS. *J Trauma Manag Outcomes.* 2009;3:4.
90. Minard CG, Freire de Carvalho M, Iyengar MS. Optimizing medical kits for space flight. https://ntrs.nasa.gov/search.jsp?R=20100031230. Published 2010. Accessed July 25, 2019.
91. Haidegger T, Sándor J, Benyó Z. Surgery in space: the future of robotic telesurgery. *Surg Endosc.* 2011;25(3):681–690.
92. National Aeronautics and Space Administration (NASA). CHeCS (Crew Health Care Systems): International Space Station (ISS) medical hardware catalog. Version 10.0. https://ntrs.nasa.gov/search.jsp?R=20110022379. Published 2011. Accessed July 25, 2019.
93. Stewart GE, Drudi L. Medical education for exploration class missions: NASA aerospace medicine elective at the Kennedy Space Centre. *Mcgill J Med.* 2011;13(2):55.
94. Drudi L, Ball CG, Kirkpatrick AW, Saary J, Grenon SM. Surgery in space: where are we at now? *Acta Astronaut.* 2012;79:61–66.
95. Hinkelbein J, Schwalbe M, Dambier M, Spelten O, Wetsch W, Neuhaus C. Current concepts for anesthesia and emergency medicine in space. *Resuscitation.* 2012;83(3):e79–80.
96. Law J, Vanderploeg J. An emergency medical planning guide for commercial spaceflight events. *Aviat Space Environ Med.* 2012;83(9):890–895.
97. National Aeronautics and Space Administration (NASA). Ventilator technologies sustain critically injured patients. http://hdl.handle.net/2060/20120001890. Published 2011. Accessed July 25, 2019.
98. Komorowski M, Watkins SD, Lebuffe G, Clark JB. Potential anesthesia protocols for space exploration missions. *Aviat Space Environ Med.* 2013;84(3):226–233.
99. Kuypers MI. Emergency and wilderness medicine training for physician astronauts on exploration class missions. *Wilderness Environ Med.* 2013;24(4):445–449.
100. McQuillen J. Design constraints regarding the use of fluids in emergency medical systems for space flight. https://ntrs.nasa.gov/search.jsp?R=20140003970. Published 2013. Accessed July 25, 2019.
101. Keenan A, Foy M, Myers J. Mass and volume optimization of space flight medical kits. https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20140008662.pdf. Published 2014. Accessed July 25, 2019.
102. Kirkpatrick A, LaPorta A, Brien S, et al. Technical innovations that may facilitate real-time tele-mentoring of damage control surgery in austere environments: a proof of concept comparative evaluation of the importance of surgical experience, telepresence, gravity and mentoring in the conduct of damage control laparotomies. *Can J Surgery.* 2015;58(3 Suppl 3):S88–90.
103. Alexander D. Trauma and surgical capabilities for space exploration. In: Gillman LM, Widder, S, Blaivas M, Karakitsos D (eds). *Trauma Team Dynamics.* Berlin, Germany: Springer; 2016:253–266.
104. Garbino A, Nusbaum DM, Buckland DM, Menon AS, Clark JB, Antonsen EL. Emergency medical considerations in a space-suited patient. *Aerosp Med Hum Perform.* 2016;87(11):958–962.
105. Komorowski M, Fleming S, Hinkelbein J. Anesthesia in outer space: the ultimate ambulatory setting? *Curr Opin Anaesthesiol.* 2016;29(6):649–654.
106. Komorowski M, Fleming S, Kirkpatrick AW. Fundamentals of anesthesiology for spaceflight. *J Cardiothorac Vasc Anesth.* 2016;30(3):781–790.
107. National Aeronautics and Space Administration (NASA). Emergency medical procedures manual for the International Space Station (ISS). http://www.governmentattic.org/19docs/NASA-ISSmedicalEmergManual_2016.pdf. Published 2016. Accessed July 25, 2019.
108. Halberg EE, Robinson S, Onishi R, Blaesser N. An ISS space ambulance based on X-37B technology. http://arc.aiaa.org/doi/10.2514/6.2016-5476. Published 2016. Accessed July 25, 2019.
109. Hodkinson PD, Anderton RA, Posselt BN, Fong KJ. An overview of space medicine. *Br J Anaesth.* 2017;119(Suppl 1):i143–i153.
110. Kirkpatrick AW, McKee JL, Tien H, et al. Damage control surgery in weightlessness: a comparative study of simulated torso hemorrhage control comparing terrestrial and weightless conditions. *J Trauma Acute Care Surg.* 2017;82(2):392–399.
111. Cheatham ML. Advanced Trauma Life Support for the injured astronaut. http://www.surgicalcriticalcare.net/Resources/ATLS_astronaut.pdf. Accessed July 25, 2019.
112. Hinkelbein J, Russomano T, Hinkelbein F, Komorowski M. Cardiac arrest during space missions: specificities and challenges. *Trend Anaesth Crit Care.* 2018;19(4):6–12.
113. Hailey M, Urbina M, Hughlett J, et al. Evaluating the medical kit system for the International Space Station (ISS) – a paradigm revisited. https://ntrs.nasa.gov/search.jsp?=20100036577. Published 2010. Accessed July 25, 2019.
114. United States US Pharmacopeia. Pharmaceutical compounding—nonsterile preparations. http://www.usp.org/sites/default/files/usp/document/our-work/compounding/usp-gc-795-proposed-revision.pdf. Accessed July 25, 2019.
115. Davis JR. Fundamentals of aerospace medicine. https://nls.ldls.org.uk/welcome.html?ark:/81055/vdc_100031348710.0x000001. Published 2011. Accessed July 25, 2019.
116. Gibbs Y. NASA Armstrong Fact Sheet: X-38 Prototype Crew Return Vehicle. NASA. http://www.nasa.gov/centers/armstrong/news/FactSheets/FS-038-DFRC.html. Published 2014. Accessed July 25, 2019.
117. Wright J. Russian Soyuz TMA Spacecraft Details. NASA. http://www.nasa.gov/mission_pages/station/structure/elements/soyuz/spacecraft_detail.html. Published 2015. July 25, 2019.
118. Britton T, Blakeman TC, Eggert J, Rodriquez D, Ortiz H, Branson RD. Managing endotracheal tube cuff pressure at altitude: a comparison of four methods. *J Trauma Acute Care Surg.* 2014;77(3 Suppl 2):S240–244.
119. Pomprapa A, Muanghong D, Köny M, et al. Artificial intelligence for closed-loop ventilation therapy with hemodynamic control using the open lung concept. *Int J Intelligent Comput Cybernetics.* 2015;8(1):50–68.
120. Gates S, Quinn T, Deakin CD, Blair L, Couper K, Perkins GD. Mechanical chest compression for out of hospital cardiac arrest: systematic review and meta-analysis. *Resuscitation.* 2015;94:91–97.
121. Electronic Medicines Compendium. Ketamine summary of product characteristics. https://www.medicines.org.uk/emc/product/2420/smpc#SHELF_LIFE. Published 2016. Accessed July 25, 2019.

122. Guldner GT, Petinaux B, Clemens P, Foster S, Antoine S. Ketamine for procedural sedation and analgesia by non-anesthesiologists in the field: a review for military health care providers. *Mil Med*. 2006;171(6):484–490.
123. Kurdi M, Theerth K, Deva R. Ketamine: current applications in anesthesia, pain, and critical care. *Anesth Essays Res*. 2014;8(3):283.
124. NASA Johnson Space Center. Non-invasive and unobtrusive blood pressure measurement: 2018 Wearable Technologies Workshop Challenge Request. https://techcollaboration.center/wp-content/uploads/Workshops/WearableTechnologies/Challenges/TCC_WT_Challenge-NASAJSC-Non-Invasive-and-Unobtrusive-Blood-Pressure-Measurement.pdf. Published 2018. Accessed July 25, 2019.