MHIF FEATURED STUDY:
KPL-301-C203

**CONDITION:**
Severe COVID-19 pneumonia and hyper-inflammation

**PI:**
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**SPONSOR:**
Kiniksa

**DESCRIPTION:**
Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of single IV dose of mavrilimumab in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation to reduce progression to respiratory failure or death. Mavrilimumab targets the GM-CSF receptor, neutralizing overexpression of GM-CSF associated with inflammation. This may address severe cytokine storm syndrome seen in subjects with COVID-19 and the immediate need to reduce rising mortality.

**CRITERIA LIST/QUALIFICATIONS:**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;18 years old</td>
<td>Onset of COVID-19 symptoms &gt;14 days</td>
</tr>
<tr>
<td>Positive SARS-CoV-2 within 14 days</td>
<td>Hospitalized for SARS-CoV-2 &gt;7 days</td>
</tr>
<tr>
<td>Bilateral pneumonia on chest x-ray or CT</td>
<td>Prior severe or concomitant illness (i.e., pulmonary alveolar proteinosis, severe and uncontrolled pulmonary disease other than COVID-19 pneumonia, pre-existing LVEF &lt;35%, MI/stroke/ hemodynamic instability/cardiogenic or septic shock &lt;30 days, concomitant uncontrolled systemic or bacterial infection)</td>
</tr>
<tr>
<td>Elevated ferritin, CRP, D-dimer, LDH, or history of fever &lt;7 days</td>
<td>Recent cell-depleting biological therapies or immunosuppressants (except corticosteroids)</td>
</tr>
<tr>
<td>Requiring non-invasive ventilation or oxygen supplementation to maintain SpO2 &gt;92% (i.e., nasal cannula, face mask, BiPAP, CPAP) or invasive ventilation &lt;48 hours</td>
<td>Received hydroxychloroquine within last 3 months</td>
</tr>
</tbody>
</table>

**OPEN AND ENROLLING:**
EPIC message: Research MHIF Patient Referral

**EPIC message:**
Research MHIF Patient Referral

Trouble in Thin Air: In-Flight Medical Emergencies

Jared M Routh, MD
Cardiology Fellow
Minneapolis Heart Institute
Outline/objectives

• Describe the physiologic changes of air travel.
• Identify the most common in-flight medical emergencies (IME).
• Understand why responding to an IME poses inherent challenges.
• Identify the contents of the emergency medical kit and other available resources.
• Understand the legal protections afforded to those who respond to IME and identify potential issues.
• Assess a patient’s cardiovascular fitness to fly.

Disclosures

• None
Air travel and the COVID-19 pandemic

COVID-19: Unprecedented Decline In Air Traffic

Number of flights tracked daily worldwide
(01 Feb-30 Mar, 2020)

Source: Flightradar24
Scope of the Topic

Scope of the topic: Air travel worldwide

- Nearly 4 billion annual commercial air passengers worldwide.
- In the US,
  - 16.4 million flights annually
  - 45,000 flights/day carrying 2.9 million passengers
  - 5,400 flights in the sky simultaneously at peak times
- Aging worldwide population

https://www.faa.gov/air_traffic/by_the_numbers
https://www.icao.int/annual_report_2018
Scope of the topic: In-flight medical emergencies

- 1 in 604 flights based on database review between 2008-2010
- 16 to 130 IME per 1 million passengers
- Estimate 44,000 IME occur worldwide per year

Epidemiology of IME
Epidemiology of IME

- Estimated IME
- Who responds?
- Most common IME
- Outcomes

By the numbers

- 7+ million flights and 744 million passengers
- 1 IME per 604 flights
- 16 IME per 1 million passengers

Who provides assistance?
- Physicians 48.1%
- Flight attendants 23.6%
- Nurses 20.1%
- EMS 4.4%
- Other 3.7%
Good news… Obstetric emergencies <1%

Common chief complaints
Diagnostic accuracy?

- 79% agreement between on-flight and hospital diagnosis
- Passenger’s condition improved in 60% prior to hospital arrival

Common in-flight conditions

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope or near-syncope</td>
<td>Vasovagal syncope, dehydration, hypoglycemia, toxic exposure, medication reaction, toxicity, acute coronary syndrome, arrhythmia, pulmonary thrombosis or air embolism, hypoxia</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Acute coronary syndrome, pulmonary thrombosis or air embolism, pneumonia, bronchospasm, aortic dissection, gastroesophageal reflux, musculoskeletal, anxiety</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Chronic obstructive pulmonary disease, asthma, pneumonia, pulmonary thrombosis or air embolism, toxic exposure</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>Cerebrovascular accident, transfemoral ischemic attack, hypoglycemia, seizure, syncope, intracerebral mass, complex migraine</td>
</tr>
<tr>
<td>Seizure</td>
<td>Seizure, syncope, hypoglycemia, eclampsia, cardiac arrest</td>
</tr>
<tr>
<td>Gastrointestinal illness</td>
<td>Motion sickness, foodborne illness, gastroenteritis, gastritis, gastroesophageal reflux, pancreatitis, medication/ substance withdrawal</td>
</tr>
<tr>
<td>Obstetric emergency</td>
<td>Preterm labor, miscarriage, ectopic pregnancy, eclampsia</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>Anaphylaxis, cellulitis, dermatitis</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>Cardiac arrest (ventricular fibrillation, ventricular tachycardia, asystole, pulseless electrical activity), syncope or other case of collapse (see above)</td>
</tr>
<tr>
<td>Substance abuse and misuse</td>
<td>Misuse of or withdrawal from opioids, alcohol, benzodiazepines, or stimulants</td>
</tr>
<tr>
<td>Psychiatric issue</td>
<td>Anxiety, depression, grief reaction, psychosis, posttraumatic stress disorder, personality disorders, somatization</td>
</tr>
</tbody>
</table>
The Cabin Environment
The cabin environment

- Pre-flight environment
- Pressurization/Oxygenation
- Air quality
- Limited space

The cabin environment: Pre-flight environment

- Anxiety
- Security measures
- Increased activity
The cabin environment: Physiology of air travel

- **Barometric pressure**
  - 760 mmHg -> 565 mmHg
- **Partial pressure of oxygen falls with increasing altitude**
  - Dalton’s Law

Cabin typically pressurized to 5,000 to 8,000 ft

- **PaO2**
  - Drops from ~95 mmHg to ~60 mmHg
- **Oxygen saturation**
  - Drops from 97% to 90-93%
- **At risk for hypobaric hypoxia**
The cabin environment: Physiology of air travel

- Boyle’s law \((P_1V_1 = P_2V_2)\)
- Cabin pressure drops
- Volume expansion up to 30%
- Air trapped in enclosed spaces expands
  - Sinus, middle ear, gastrointestinal
  - Recent surgery - wound dehiscence
  - Feeding tubes, catheters
  - Spontaneous pneumothorax

The cabin environment: Cabin air quality

- Pressurized and dehumidified
- Cycled through the engine compartment
- Humidity between 5-25%
  - Leading to dehydration
  - Exacerbation of reactive airway diseases

JAMA. 2018; 320:2580-2590.
The cabin environment: Space

- Tight, cramped space (and getting smaller)
  - Average seat width in 2000: 18.5” to 17” today
- Physically makes responding to IME more difficult
- Noise/vibration


Responding to an IME
The medical volunteer role

• Gather information
• Assess the ill passenger
• Aid in communication with ground-based support
• Provide an assessment and recommendation
• Administer medications and/or perform procedures

Available resources

• Flight attendants (FA)
  ○ Trained in CPR and the use of AEDs
  ○ Handle 25% of reported IME
• Ground-based medical consultation
• On-board medical kit
• Automatic external defibrillator (AED)
  ○ Mandated by the FAA in 2001
• Other passengers
On-board medical kit

- Calcium chloride
- Diazepam
- Digoxin
- Glucose gel
- Furosemide
- Lorazepam
- Ibuprofen
- Hydrocortisone
- Meclizine
- Methylprednisolone
- Metoprolol
- Morphine
- Nalbuphine
- Nitroglycerin
- Propofol
- Sodium bicarbonate

Ground-based medical consultation

MedAire
An International SOS Company

- AT THE GATE - IN THE AIR - AT DESTINATION
  - 24/7 ADVICE & ASSISTANCE
  - ARRANGEMENT OF LOCAL EMERGENCY SERVICES
  - REPORTING & ANALYSIS

Courtesy MedAire Medlink and STAT MD websites
Flight diversion

- 2-7% of IME result in diversion
- Decision solely the captain’s
- Ground-based medical support

**Factors**
- Weather
- Fuel load
- Physical ability of aircraft to land
- Medical resources at closest airport
- Time

**Cost:** $20,000 to $893,000
The medical volunteer role

- Decide if you are in proper condition to respond.
- Introduce yourself and state your medical qualifications.
- Ask the patient for consent to treat.
- Request the medical supply kit from the FA.
- Obtain vital signs, brief history and perform a physical examination.
- Identify high risk features.
- Inform the flight crew of your impression.
- Communicate and confer with airline provided ground-based medical resources.
  - Provide your recommendations for further care, diversion of the aircraft, and/or ground-based medical assistance.
- Administer available treatments within the scope of your expertise.
- Document the encounter and keep a personal copy.
- Patient privacy rights remain unchanged.

Adapted from Aviat Space Environ Med 1997;68:1134-8;
Legal Ramifications: Am I legally responsible when responding to an emergency in-flight?

(b) LIABILITY OF INDIVIDUALS.—An individual shall not be liable for damages in any action brought in a Federal or State court arising out of the acts or omissions of the individual in providing or attempting to provide assistance in the case of an in-flight medical emergency unless the individual, while rendering such assistance, is guilty of gross negligence or willful misconduct.

Legal ramifications

Table 2. Features of the Aviation Medical Assistance Act (AMAA) of 1998.*

The protections of the AMAA apply only to care rendered for “medical emergencies” and do not cover care rendered or medical advice given for nonemergencies.

Providers do not have to be asked to provide assistance in order to receive the protections of the AMAA.

The AMAA does not give providers any legal authority over the plane or its crew; thus, they cannot be held liable if a pilot does not follow their recommendations (e.g., to divert the plane).

The AMAA does not make providers responsible if a patient is harmed because of the failure of the airline to have appropriate medical equipment available.

Providers are not absolved of their legal duties (e.g., to avoid “gross negligence”) simply because they may use medical resources provided by the airlines.
Legal ramifications: Common questions

● Am I legally obligated to respond?
  ○ In the US, UK, Canada - No.
  ○ Countries in Europe, Australia and others - Yes.
  ○ Moral and professional obligations


Legal ramifications: Common questions

● Do I need to provide my credentials?
  ○ Technically unclear. Some laws provide for “in good faith” provisions.
  ○ Carry a digital copy on your cell phone.
Legal ramifications: Common questions

● What about protections on international flights?
  ○ It can get tricky.
  ○ Liability is determined by the law of the country in which the aircraft is registered.
  ○ International law governed by complex inter-country agreements.

Legal ramifications: Common questions

● What if I’ve had a few drinks? Should I decline to provide assistance?
  ○ Probably. Remember, gross negligence and willful misconduct.
  ○ Any type of impairment.
Legal ramifications: Common questions

- Does the AMAA provide full, unrestricted protection?
  - No, it protects the “good samaritan” from liability for actions taken by competent persons within the scope of his/her training (i.e. no heroics).

- Can I accept money, upgrades, or vouchers for my assistance?
  - AMAA protections
    - Volunteer, care rendered in good faith, no monetary compensation.
  - Any compensation in return for providing aid may jeopardize protection. Conflicting literature.
Legal ramifications: Common questions

● Has a physician ever been successfully sued for assisting in an IME?
  ○ Good samaritan laws do not stop a plaintiff from bringing a lawsuit (even if later dismissed).
  ○ Very little to no case law precedent to support this.


Legal ramifications: Common questions

● Can I bill for my services?
  ○ In 1997, a psychiatrist billed British Airways ~$750 for services rendered. He lost in court.
  ○ Negate protections under Good Samaritan laws.

Fitness to Fly: Pre-flight assessment of patients with cardiovascular disease

Fitness to fly: Contraindication to air travel

<table>
<thead>
<tr>
<th>TABLE IV. CARDIOVASCULAR CONTRAINDICTIONS TO COMMERCIAL AIRLINE FLIGHT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Uncomplicated myocardial infarction within 2-3 weeks</td>
</tr>
<tr>
<td>2. Complicated myocardial infarction within 6 weeks</td>
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<tr>
<td>3. Unstable angina</td>
</tr>
<tr>
<td>4. Congestive heart failure, severe, decompensated</td>
</tr>
<tr>
<td>5. Uncontrolled hypertension</td>
</tr>
<tr>
<td>6. CABG within 10-14 days</td>
</tr>
<tr>
<td>7. CVA within 2 weeks</td>
</tr>
<tr>
<td>8. Uncontrolled ventricular or supraventricular tachycardia</td>
</tr>
<tr>
<td>9. Eisenmenger syndrome</td>
</tr>
<tr>
<td>10. Severe symptomatic valvular heart disease</td>
</tr>
</tbody>
</table>
Fitness to fly: CAD/Recent ACS

**Influence of Altitude Exposure on Coronary Flow Reserve**

Christophe A. Wyss, MD*; Pascal Koeppfli, MD*; Gregory Fretz, MD; Magdalena Seebauer, PhD; Christian Schirilo, MD; Philipp A. Kaufmann, MD

**Background**—Although no data exist on the effect of altitude exposure on coronary flow reserve (CFR), patients with coronary artery disease (CAD) are advised not to exceed moderate altitudes of ~2500 m above sea level. We studied the influence of altitude on myocardial blood flow (MBF) in controls and CAD patients.

**Methods and Results**—In 10 healthy controls and 8 patients with CAD, MBF was measured by positron emission tomography and 13O-labeled water at rest, during adenosine stress, and after supine bicycle exercise. This protocol was repeated during inhalation of a hypoxic gas mixture corresponding to an altitude of 4500 m (controls) and 2500 m (CAD). Workload was targeted to comparable heart rate-blood pressure products at normoxia and hypoxia. Resting MBF increased significantly in controls at 4500 m (+24%, P<0.01) and in CAD patients at 2500 m (+24%, P<0.05). Altitude had no influence on adenosine-induced hyperemia and CFR. Exercise-induced hyperemia increased significantly in controls (+38%, P<0.01) at 4500 m (despite a reduction in workload, −28%, P<0.0001) but not in CAD patients at 2500 m (moderate decrease in workload, −11%, P<0.05). Exercise-induced reserve was preserved in controls (+10%, P=NS) but decreased in CAD patients (−18%, P<0.005).

**Conclusions**—At 2500 m altitude, there is a significant decrease in exercise-induced reserve in CAD patients, indicating that compensatory mechanisms might be exhausted even at moderate altitudes, whereas healthy controls have preserved reserve up to 4500 m. Thus, patients with CAD and impaired CFR should be cautious when performing physical exercise even at moderate altitude. *(Circulation. 2003;108:1202-1207.)*

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**Fitness to fly: CAD/Recent ACS**

- **Stable CAD, stable angina, and prior MI**
  - No contraindication to travel
  - Take medications normally
  - Bring copy of ECG

- **Recent, uncomplicated MI**
  - 2 weeks

- **Complicated MI**
  - 2 weeks after medically stable
  - Consider symptom limited GXT

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ACC/AHA Guidelines for the Management of Patients With STElevation Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction)

Developed in Collaboration With the Canadian Cardiovascular Society

**Administration regulation (1396).** Therefore, air travel within the first 2 weeks of STEMI should be undertaken only if there is no anemia or dyspnea at rest or fear of flying. The individual must have a companion, carry nitroglycerin, and request airport transportation to avoid rushing (personal communication, R.P. Gardner, PhD. November 2002). Air

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Fitness to fly: Recent ACS

2010 BMJ Heart *Fitness to Fly Report*

- Very low risk (<65 y/o, first event, successful reperfusion, EF>45%, uncomplicated)
  - 3 days
- Low risk (EF>40%, no symptoms of CHF, no ischemia or arrhythmia)
  - 10 days
- High risk (EF<40%, CHF symptoms, ischemia or arrhythmia)
  - Contraindicated

Heart. 2010; 96:ii1-ii16.
Fitness to fly: Heart failure

- Stable, chronic HF
  - No contraindication
- NYHA class III/IV symptoms*
  - O2 recommended with baseline SpO2<92%
  - Airport assistance
- Recent exacerbation
  - Some suggest waiting 6 weeks. Limited data.
- Severe, decompensated CHF
  - Absolutely contraindicated

Fitness to fly: Passengers with cardiac devices

- Airport metal detectors
  - Rarely set off, but carry information card
  - No evidence of device interaction
  - Can request hand search
- In-flight
  - EMI
  - Cosmic radiation
  - Vibration


Do Airport Metal Detectors Interfere With Implantable Pacemakers or Cardioverter-Defibrillators?
Christof Koth, MD, Sebastian Schmiechen, MD, Gunter Lehmann, MD, Berhard Zerenes, MD, Martin R. Kirsch, MD, Andreas Plewan, MD, Claus Schmidt, MD
Munich, Germany

The aim of this study was to determine whether airport metal detectors (AEDCs) influence with pacemakers (PMs) or implantable cardioverter-defibrillators (ICDs). It is currently unknown whether AEDCs influence with implanted PMs or ICDs. A total of 348 consecutive patients (209 PM and 139 ICD recipients) have been tested for the occurrence of electromagnetic interference (EMI) within the electromagnetic field of a worldwide-used airport metal detector. No interference, such as pacing or existing abnormalities, was observed in any of the 209 PM and 149 ICD patients also no programming occurred. In vivo testing of PM and ICD systems showed no EMI with a standard AMDC-Clinically significant results are reported in detail. - J Am Coll Cardiol.2005;41(2004-09) © 2005 by the American College of Cardiology Foundation.
Fitness to fly: DVT/PE

Recommendations: Long-Distance Travel
9.1. For travelers who are taking flights > 8 h, we recommend the following general measures: avoidance of constrictive clothing around the lower extremities or waist, maintenance of adequate hydration, and frequent calf muscle contraction (Grade 1C).
9.2. For long-distance travelers with additional risk factors for VTE, we recommend the general measures listed above. If active thromboprophylaxis is considered because of a perceived high risk of VTE, we suggest the use of properly fitted, below-knee GCS, providing 15 to 30 mm Hg of pressure at the ankle (Grade 2C), or a single prophylactic dose of LMWH, injected prior to departure (Grade 2C).
9.3. For long-distance travelers, we recommend against the use of aspirin for VTE prevention (Grade 1B).

Fitness to fly: Travel after cardiac procedures

- Elective coronary angiography without PCI
  - The next day
- Uncomplicated, elective PCI
  - ~2 days
- CABG
  - 10-14 days (time for intrathoracic air to reabsorb)
- PPM/ICD
  - 1-2 days*
  - *2 weeks if complicated by PTX
Comprehensive pre-flight evaluation

- Assess for signs/symptoms of decompensation
- Recent/upcoming procedures or surgeries
- Presence of cardiac devices
- Vital signs including resting SpO2
- Recommend in-flight oxygen if:
  - Needed at rest
  - $\text{PaO}_2 < 70 \text{ mmHg}$ or $\text{SpO}_2 < 92\%$
  - NYHA class III/IV symptoms
- Consider HAST or 50 m walk test
- Assess the need for DVT prophylaxis

Heart. 2010; 96:i1-i16. JAMA. 2018; 320:2580-2590

Fitness to fly: Hypoxia altitude simulation test

- Gas mixture 51.1% oxygen with nitrogen
  - Replicates in-flight $\text{PaO}_2$ at 8,000 ft
  - Oxygen recommended if
    - $\text{PaO}_2 < 50 \text{ mmHg}$
    - $\text{SpO}_2 < 85\%$
  - Can be paired with an exercise component

CHEST. 2008; 133:839-842.
Comprehensive pre-flight evaluation

- Recommendations
  - Sufficient medications in carry-on luggage with medication list
  - Bring copy of most recent ECG and device cards
  - Contact the airline for accommodations
    - Limit ambulation
  - In-flight oxygen
  - Consider medical evacuation insurance (international)

Heart. 2010; 96:i1-i16. JAMA. 2018; 320:2580-2590

Key Points

- The cabin environment may result in physiologic changes in patients with cardiopulmonary disorders
- Most IME are minor. Providers should be aware of common chief complaints.
- Medical providers should be familiar with the contents of the emergency medical kit.
- Airlines contract with ground based medical support.
- Medical providers who render aid are generally protected from liability.
AED use in-flight

- Peterson NEJM 2013 outcomes
  - 0.3% of IME, but accounts for 86% of in-flight deaths
  - AED applied in 24 cases, 5 shocks.
  - ROSC in 9 patients.
  - Flight not diverted in 42% of patients
- O’Rourke et al 1997
  - AED used 109 occasions (46 times for cardiac arrest)
  - 27 episodes of cardiac arrest (16 witnessed)
  - 2/127 unshockable rhythms
  - 6 with shockable rhythms, 5 with ROSC. 2 with long-term survival
- Brown et al 2010
  - AED used 169 occasions (40 cardiac arrests)
    - Sinus 114
    - Asystole/PEA 30
    - VT/VF 10 (9 defibrillations)
    - Atrial fibrillation/flutter 7
    - Complete heart block 4
    - SVT 4
- Overall survival, 14-55%
- Limited in space, interventions and resources
- Approach essentially limited to BLS (+ epinephrine)
- Diversion should be recommended if resuscitation is successful
Legal ramifications: Common questions

- Do any airlines themselves provide indemnity?
  - Some like British Airways and Virgin Atlantic.

The cabin environment: Physiology of air travel

- Coronary bed vasodilation
- Pulmonary vasoconstriction
- Increased HR and BP
- Increased myocardial contractility
- Increased PA pressure