ECMO and the 2013 Influenza A H1N1 Epidemic

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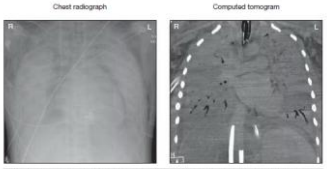
Why Is an Anesthesiologist Talking About the flu?

- In susceptible individuals, influenza leads to a severe ARDS
- In 2009/2010, there was a suggestion of a distinct survival benefit in patients with ARDS from the flu treated in centers that perform ECMO
- The ECMO program at St. Lukes is run out of the CVICU, which is staffed by Intensivists from the Department of Anesthesiology
- We are one of only hospitals that perform adult ECMO in Kansas City.
  - St. Luke's has up to nine ECMO beds
  - KU also offers adult ECMO
  - Children's Mercy provides pediatric ECMO

2009/2010 Influenza A and ECMO

- A small minority of patients with H1N1 developed a rapidly progressive ARDS associated with multi-organ Failure.
- In 2009 both the CESAR trial (Lancet, October 2009) and the ANZA trials (JAMA, November 2009) were published
- CESAR concluded that there was a significant reduction in mortality in patients with severe ARDS referred to an ECMO center.
- The ANZA trial was a case series demonstrating a 21% mortality with the use of ECMO with severe H1N1

Figure 3. Chest Radiograph and Computed Tomogram of 2 Patients Successfully Treated With ECMO for Confirmed 2009 Influenza A(H1N1)



ECMO indicates extracorporeal membrane oxygenation. The images demonstrate severe bilateral airspace disease with massive loss of normal aerated lung tissue.

From Davies et. al

Table 2. Severity of ARDS Before Commencement of ECMO

Characteristics	2009 Influenza A(H1N1) Confirmed Infection (n = 53)	2009 Influenza A(H1N1) Suspected Infection (n = 15)	All Infections (N = 68)
Ventilation parameters, median (IQR)			
Lowest $Pa_{O_2}/F_{I_{O_2}}$ ratio	55 (48-65)	57 (45-62)	56 (48-63)
Highest $F_{I_{O_2}}$	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Highest PEEP, cm H_2O	18 (15-20)	15 (14-18)	18 (15-20)
Highest peak airway pressure, cm H_2O	36 (34-40)	34 (29-36)	36 (33-38)
Lowest pH	7.2 (7.1-7.3)	7.2 (7.1-7.3)	7.2 (7.1-7.3)
Highest $Paco_2$, mm Hg	69 (54-86)	67 (61-73)	69 (54-83)
Highest tidal volume, mL/kg	6.6 (4.8-6.6)	6.7 (4.4-6.7)	6.6 (4.6-6.7)
Quadrants of radiograph infiltrate, No.	4 (4-4)	4 (4-4)	4 (4-4)
Acute lung injury score[a]	3.8 (3.3-4.0)	3.5 (3.3-3.8)	3.8 (3.5-4.0)
Pneumothorax pre-ECMO, No. (%)	9 (17)	1 (7)	10 (15)
Rescue ARDS therapies used, No. (%)			
Recruitment maneuver	30 (66)	8 (66)	38 (67)
Prone positioning	11 (22)	1 (8)	12 (20)
High-frequency oscillation	3 (6)	0	3 (5)
Nitric oxide	19 (38)	1 (8)	20 (32)
Prostacyclin	12 (23)	2 (15)	14 (22)

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; $F_{I_{O_2}}$, fraction of inspired oxygen; IQR, interquartile range; PEEP, positive-end-expiratory pressure.
[a]Data were missing in 4 cases for $Pa_{O_2}/F_{I_{O_2}}$ ratio, in 4 cases for PEEP, in 17 cases for lung compliance, and in 5 cases for quadrants of radiograph infiltrate.

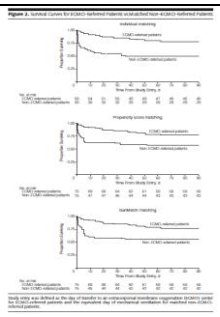
From Davies et. al

Noah Study

- Neither 2009 study compared H1N1 management with conventional ventilation vs. ECMO
- This question still existed: Did ECMO provide a survival benefit in severe ARDS over conventional ventilation during the 2009 H1N1 epidemic?
- Noah et. Al. *Referral to an Extracorporeal Membrane Oxygenation Center and Mortality Among Patients With Severe 2009 Influenza A(H1N1)* JAMA, October 2011
- Noah demonstrated a survival benefit in patients transferred to an ECMO center with H1N1 related severe respiratory failure

Inclusion Criteria by Noah

- UK study
- Used CESAR criteria
  - MURRAY Score > 3.0 or pH < 7.2
  - Age 18-65
  - Mechanical Ventilation for < 7 days at high settings
  - Lung injury determined to be reversible
  - No contra-indications to heparin, i.e. intracranial hemorrhage



From Noah et. al

Consequence:

- We saw a major uptick in ECMO referrals at Saint Luke's in 2014
  - Local
  - Joplin
  - Columbia
  - Eastern Kansas
- Most patients were fairly young
- Most patients were fairly obese

Counterpoint

- Pham et. Al published a study in the American Journal of Respiratory and Critical Care Medicine in February, 2013
- Cohort study
- French
- Did not find a significant survival benefit in matched cohorts, however in an umatched cohort of younger, healthier patients there was a benefit against all the matched patients.
- Cohort shows that younger age, lower lactate, and lower plateau pressures may be associated with survival
- Although not commented on in the study, it appears to me that corticosteroids may be associate with worse survival.

TABLE 2. BASELINE CHARACTERISTICS, ICU MANAGEMENT, AND OUTCOME OF 123 PATIENTS TREATED WITH ECMO, ACCORDING TO SURVIVAL

	Mean (SD), Median (IQR), or N (%)		
	Survivors ($n = 79$)	Nonsurvivors ($n = 44$)	*P* Value
Baseline characteristics			
Age, yr	40 (13)	45 (13)	0.06
Male sex	37 (47%)	24 (55%)	0.53
MacCabe 1*	71 (90%)	37 (84%)	0.51
Risk factor for influenza complication	62 (78%)	31 (70%)	0.44
Pregnancy or postpartum	14 (18%)	4 (9%)	0.30
BMI, kg/m²	31.5 (8.9)	28.6 (7.9)	0.09
On admission			
SAPS3 score	57 (11)	61 (17)	0.22
SOFA score	9.5 (3.9)	9.4 (4.6)	0.95
Bacterial coinfection	17 (22%)	11 (26%)	0.80
Before ECMO			
Shock	35 (44%)	25 (57%)	0.25
Steroids	21 (27%)	21 (48%)	0.03
Rescue therapy	57 (72%)	34 (77%)	0.68
Time from MV to ECMO, d	2 (1–5)	2 (1–4)	0.51
V-V ECMO	71 (90%)	36 (82%)	0.32

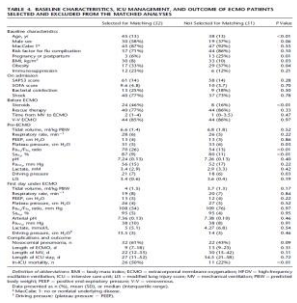
From Pham et. al

Pham Table 2 continued

Pre-ECMO			
Tidal volume, ml/kg PBW	6.4 (5.8–7.4)	6.7 (5.8–7.2)	0.96
Respiratory rate, min^{-1}	27 (5)	28 (7)	0.33
PEEP, cm H_2O	13 (4)	12 (4)	0.13
Plateau pressure, cm H_2O	32 (5)	32 (5)	0.86
Pa_{O_2}/F_{IO_2} ratio	62 (17)	65 (27)	0.38
Sa_{O_2}, %	94 (11)	94 (11)	0.80
Arterial pH	7.27 (0.12)	7.24 (0.14)	0.32
Pa_{CO_2}, mm Hg	60 (14)	58 (20)	0.75
Arterial lactate, mmol/L	2.4 (2)	4.1 (4.4)	0.06
Driving pressure†	19 (7)	20 (6)	0.33
LIS	3.3 (0.3)	3.3 (0.5)	0.27
First day on ECMO			
Tidal volume, ml/kg PBW	3.6 (2.7–4.5)	4.1 (3.5–5.4)	0.07
Respiratory rate, min^{-1}	19 (8)	20 (8)	0.51
PEEP, cm H_2O	13 (4)	12 (4)	0.93
Plateau pressure, cm H_2O	25 (3)	29 (5)	<0.01
Pa_{O_2}/F_{IO_2} ratio	105 (66)	116 (88)	0.53
Sa_{O_2}, %	95 (4)	94 (6)	0.36
Arterial pH	7.40 (0.08)	7.37 (0.16)	0.20
Pa_{CO_2}, mm Hg	37 (9)	39 (9)	0.26
Arterial lactate, mmol/L	2.7 (2.1)	7 (8.3)	<0.05
Driving pressure†	13 (4)	16 (7)	0.03
Delta plateau pressure	−7 (6)	−3 (5)	<0.05
Complications and outcome			
Nosocomial pneumonia	45 (64%)	24 (58%)	0.69
Length of ECMO, d	12 (5–23)	10 (4–21)	0.1
Length of MV, d	32 (23–53)	17.5 (9.3–32)	<0.01
Length of ICU stay, d	44 (29–67)	16.5 (9.5–34)	<0.01

Unmatched Cohort Characteristics

- A group of patients who received ECMO who were dropped from the analysis due to the inability to match with patients in the conventional group.
- Tended to be younger, sicker, have higher BMIs, and less likely to have received pre-ECMO corticosteroids.
- Had the highest survival rate (78%).



From Pham et. al

Meta-analysis?

- Zangrillo et. Al
- Trend for benefit in H1N1 patients treated with VV ECMO

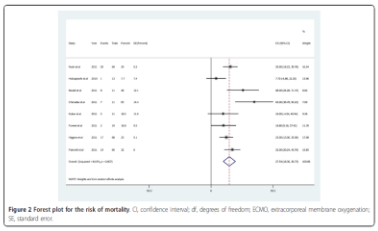


Figure 2 Forest plot for the risk of mortality. CI, confidence interval; df, degrees of freedom; ECMO, extracorporeal membrane oxygenation; SE, standard error.

My own take on ECMO

- We know cells need oxygen
- If cells don't get oxygen they die
- If cells die, organs die
- If organs die, people die
- ECMO provides oxygenation and CO2 removal in people who cannot be supported on mechanical ventilation.

BMJ 2003

Hazardous journeys

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

accepted intervention was a fabric device, secured by straps to a harness worn by the participant and released either automatically or manually during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.[1]

Meta-analysis

Our statistical approach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger's and Begg's tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

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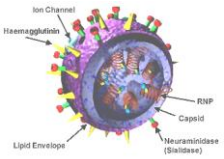
BMJ 2003;327:1459–61

BASIC SCIENCE



From Wikicommons

Hemagglutinin

- Binds to cell surface to initiate infection
- Got its name due to the fact that it agglutinates RBCs in the lab
- Target of neutralizing antibody
  - Will not infect cells, once hemagglutinin is neutralized

Neuraminidase

- Cleaves neuraminic acid which releases viruses from infected cells
  - Functions at the end of cellular infection
- Degrades mucous in the respiratory tract
- Antibody against neuraminidase does not neutralize infectivity, but does decrease the illness' severity by preventing the release of new viruses from host cells.

Life Cycle

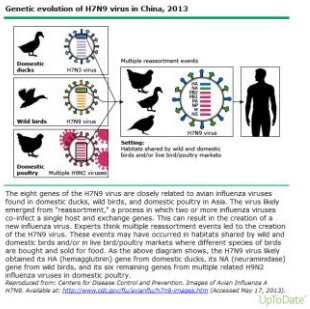
- The influenza virion enters a cell as the hemagglutinin attaches to sialic acid receptors on the cell surface.
- The virus' RNA polymerase transcribes the viral RNA to mRNA
- The mRNA is translated into viral proteins
- Progeny viral RNA genomes are synthesized in the nucleus
- The riboneucleoprotein is assembled in the cytoplasm
- The virion is released from the cell by budding

General Epidemiology

- Influenza A develops mutations in its neuraminidase and hemagluttinin proteins, which leads to resistance
- Influenza A is subject to genetic reassortment
  - Recombination of segments of the RNA genome
- Many animals can be infected by influenza A
- In areas in which humans live near animals, a person or animal can be infected with both an animal and a human flu virus
- Genetic reassortment may occur and the flu virus may be infectious towards humans with a novel hemagluttinin or neuramidase protein
- These new animal/human combinations are the source of the new antigenic types of flu that cause epidemics, i.e. bird flu (H5N1)

General Epidemiology

- Antigenic shifts
  - Genetic changes based on reassortment
  - Occur approximately every 10 yrs
- Antigenic drifts
  - Minor antigenic changes based on mutation



H7N9

- Novel influenza virus first detected in China in March 2013
- Derived from at least 4 avian influenza viruses
- Low virulence in poultry
  - Does not cause severe disease in birds, so epidemics may go undetected
- No sustained human to human infection. Most infections are in very close quarters or from direct exposure to poultry.
- Most affected patients are older with comorbidities
- Mortality is estimated at approximately 1/3rd of those hospitalized primarily from respiratory complications.

H5N1

- Highly pathogenic in chickens
  - Epidemics in poultry easily detected
- Endemic in certain Asian chicken populations
- First detected in humans in Hong Kong in 1997
  - All genes were avian in origin, i.e., the virus jumped species
- Transmission is primarily bird to human, but human to human spread is possible
- Since 2003, 640 cases have been reported to WHO with a case fatality rate of 60%
  - May be an overestimate
- Prediliction for younger and healthier people

Epidemics

- Epidemics occur when the antigenicity has changed to a point that pre-existing immunity is not effective
- Influenza A is responsible for most pandemics
  - Antigenic shifts occur approximately every 10 years
- Influenza B is responsible for some major outbreaks, but the antigenicity of influenza B does not vary as dramatically or as often
- Influenza C only causes minor disease

Infection

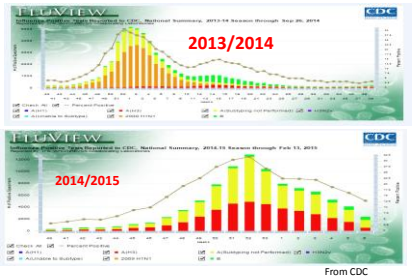
- Infection is generally limited to the respiratory tract
- Viremia is rare
- Cytokines cause most of the symptoms
- Influenza may cause a viral interstitial pneumonia with alveolar hemmorhage

Immunity

- Primarily from IgA in the respiratory tracty
- Lesser extent from IgG
- Cytotoxic T cells

CLINICAL EXPERIENCE WITH 2013/2014 INFLUENZA VS 2014/2015 SEASON

Circulating Influenza

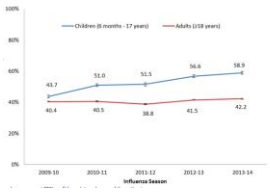


From CDC

The Flu Vaccine

- Types of vaccine
  - Live attenuated nasal mist (recommended for children 2-8)
  - Inactivated injection
- Effectiveness of the vaccine is dependent on both the match between the viruses in the vaccine and the circulating virus, and the characteristics of the person receiving the vaccine.
- Vaccine Effectiveness (VE) is the reduction in risk provided by the flu vaccine, i.e. a VE of 60% will reduce the risk a patient will present to the doctors office with flu like illness by 60%
- Even if the vaccine is not effective in preventing infection with influenza, it often makes the disease course significantly milder
  - Up to a 92% reduction in hospitalization for pregnant women
  - Up to a 70% reduction in hospitalization in the elderly

Figure 1. Seasonal Flu Vaccination Coverage, by Age Group and Season, United States, 2009-2014



From CDC

Table. Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2015

Influenza Season†	Reference	Study Site(s)	No. of Patients‡	Adjusted Overall VE (%)	95% CI
2004-05	Belongia 2009	WI	762	10	-36, 40
2005-06	Belongia 2009	WI	346	21	-52, 59
2006-07	Belongia 2009	WI	871	52	22, 70
2007-08	Belongia 2011	WI	1914	37	22, 49
2009-10	Griffin 2011	WI, MI, NY, TN	6757	56	23, 75
2010-11	Treanor 2011	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Unpublished	WI, MI, PA, TX, WA	5990	51	43, 58
2014-15	Flannery 2015	WI, MI, PA, TX, WA	2321	23	8, 36

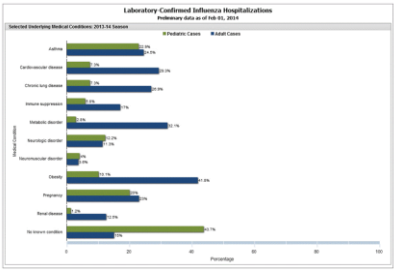
Antivirals

- CDC recommends treatment with antivirals as soon as possible in high-risk and severely ill patients
  - In outpatients, antiviral treatment is most effective if started within 48 hours of symptom onset, but the severely ill may still benefit from delayed treatment.
- High resistance to Adamantanes (amantadine and rimantadine)
- Low resistance to neuraminidase inhibitors
  - Ostelamavir
    - Available as an oral formulation
    - Recommended dose is 150 mg twice a day for seriously ill patients
    - Concern for ostelamavir resistant H1N1
      - Most resistant cases are in Texas
  - Zanamavir
    - Available for inhalation
    - Unable to use on patients on the ventilator
    - An IV formulation has been available in the past in a compassionate use basis from Glaxo-Smith-Klein. We were successful in obtaining some in January. (Thanks Tim)

Who were our patients?

- 2013/2014 H1N1 appears to have a predilection for healthy young and middle-aged adults.
- The 2009 H1N1 outbreak caused more illness in children and young adults
- The rapid flu test is poorly sensitive, so many of our patients initially tested negative
  - PCR is recommended due to high sensitivity and specificity
- In our ICU, we primarily saw influenza pneumonia as opposed to secondary bacterial infection
  - S. Aureus
  - Strep Pyogenes
  - Aspergillosis

As of Feb. 1, 2014



Who was on our team?

- CVICU nurses
- RTs
- Perfusionists
- Intensivists
- Surgeons
- Pharmacists
- Nutritionists
- PT
- OT

Single Caregiver Approach

- Our nurses managed both the critical care needs of the patient as well as the ECMO circuit
- Prior to managing these patients, our nurses took an introduction to ECMO course, given at our hospital
- Perfusionists, surgeons, and intensivists were on call 24/7, but not always in house

Conclusion

- H1N1 is unique in that it targets a normally healthy population
- In the worst cases, ECMO seems to provide benefit
- The rapid flu test is unreliable, so anyone admitted to our ICU with symptoms suggestive of the flu should be started on antivirals
- Get your flu shot