Advancing therapeutics for ARDS

Cecilia O'Kane
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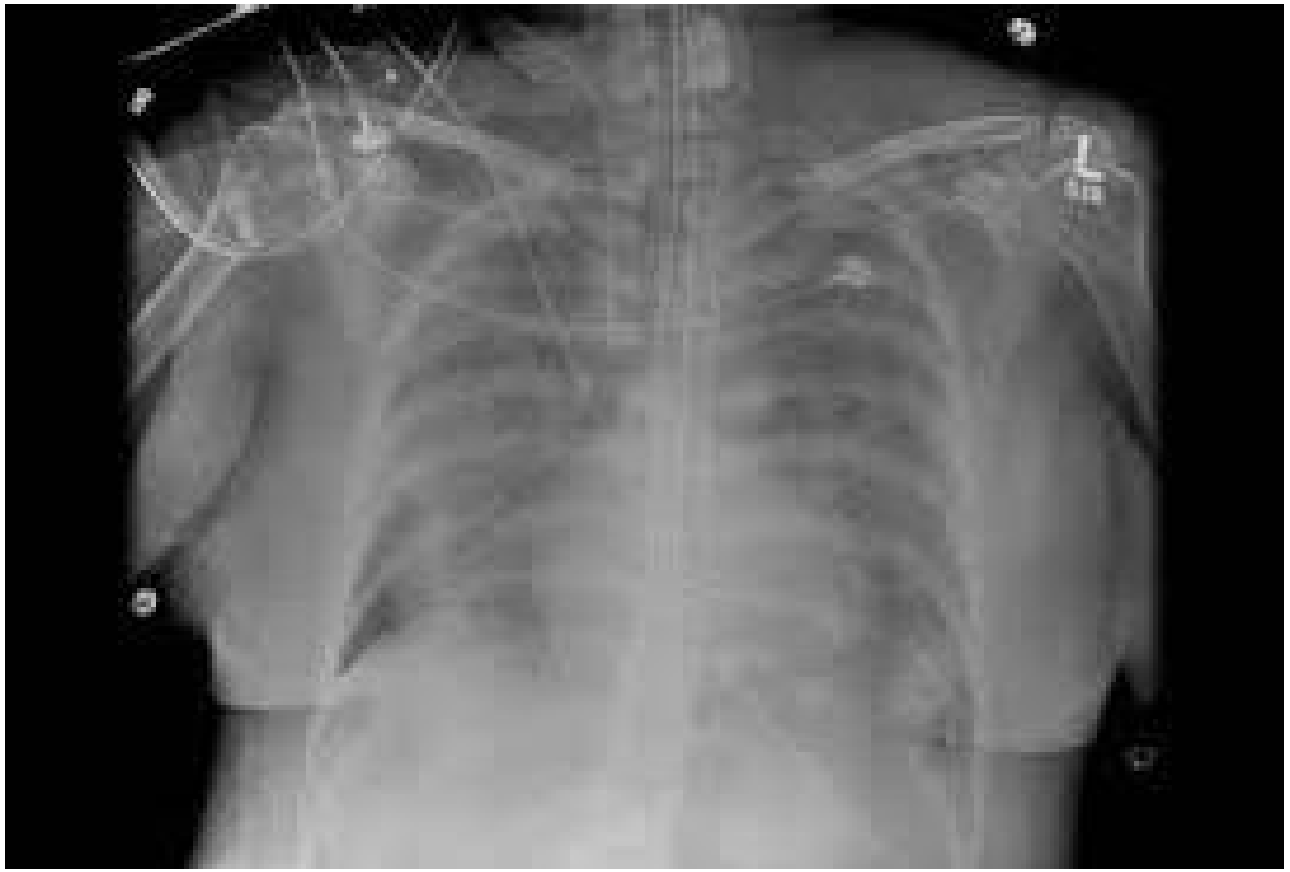
Incidence of ARDS

- 7% ICU admissions and 20% patients requiring mechanical ventilation
- Mortality ranges 25 – 65%
  - Greater than asthma, breast cancer and HIV
- 15,000 cases of ALI and 4,000-5,000 deaths per year in UK and Ireland

Presentation of ARDS



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ARDS clinical definition

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg $<$ Pao_2/Fio_2 $\leq$ 300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O[c]
Moderate	100 mm Hg $<$ Pao_2/Fio_2 $\leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O
Severe	Pao_2/Fio_2 $\leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

ARDS Taskforce, JAMA. 2012;307(23):2526-2533

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Aetiology of ARDS

- Direct lung injury
  - Pneumonia (also ‘flu)
  - Aspiration
  - Inhalation
  - Contusion
  - Fat/amniotic fluid embolism
  - Near drowning
  - Reperfusion/re-expansion injury
  - Transfusion related injury
  - *Ventilator associated injury*
- Indirect lung injury
  - Systemic sepsis
  - Trauma
  - Shock
  - Pancreatitis
  - Cardiopulmonary bypass
  - Reperfusion
  - Drug overdose
  - Blood products
  - DIC

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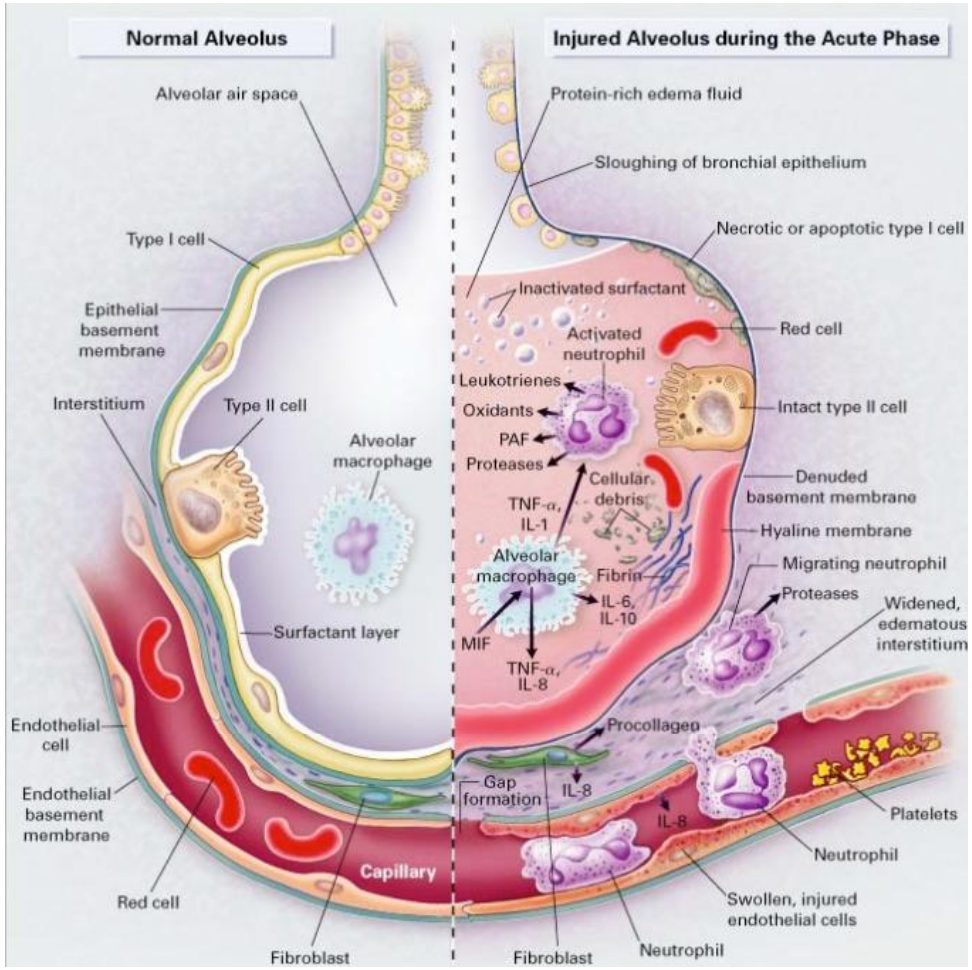
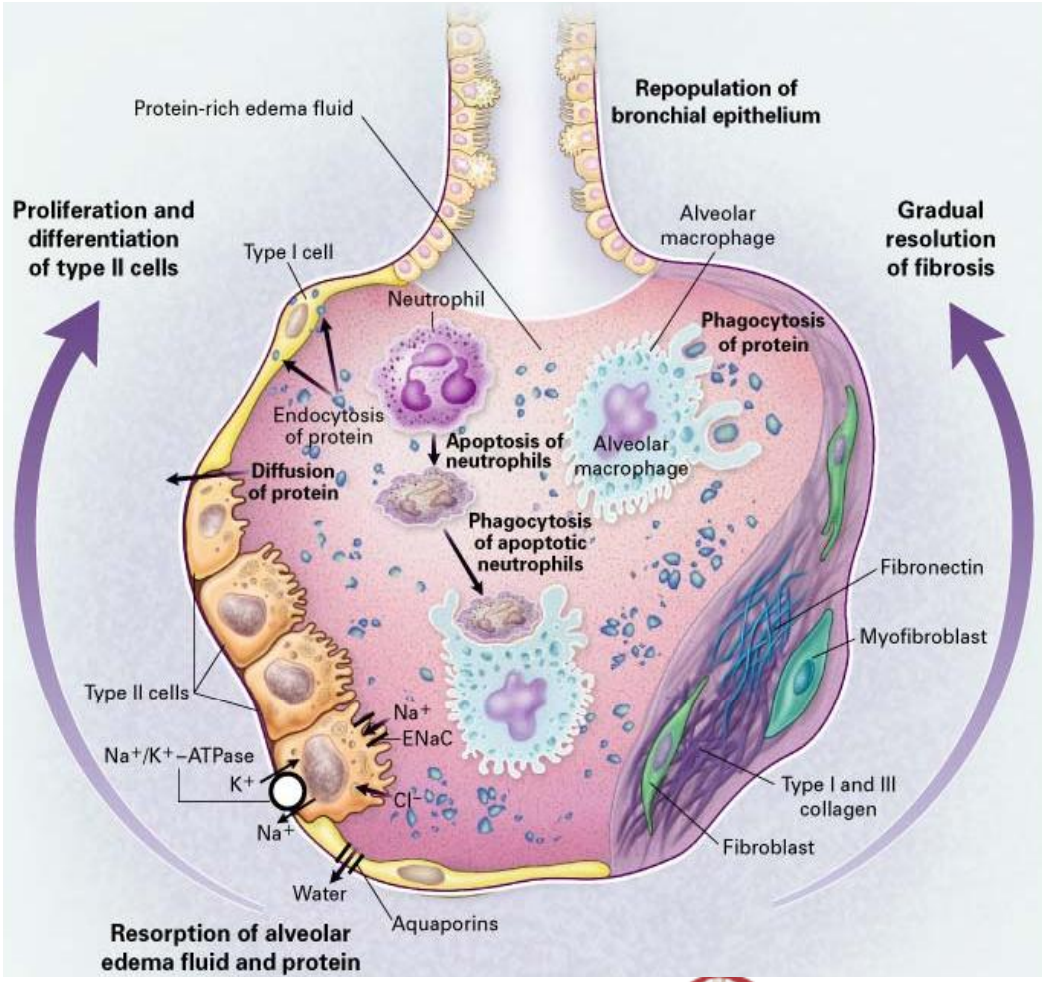
ARDS Taskforce, JAMA. 2012;307(23):2526-2533

Pathophysiology of ARDS





NEJM 2000;342:1334

Lancet 2016; 388: 2416–30

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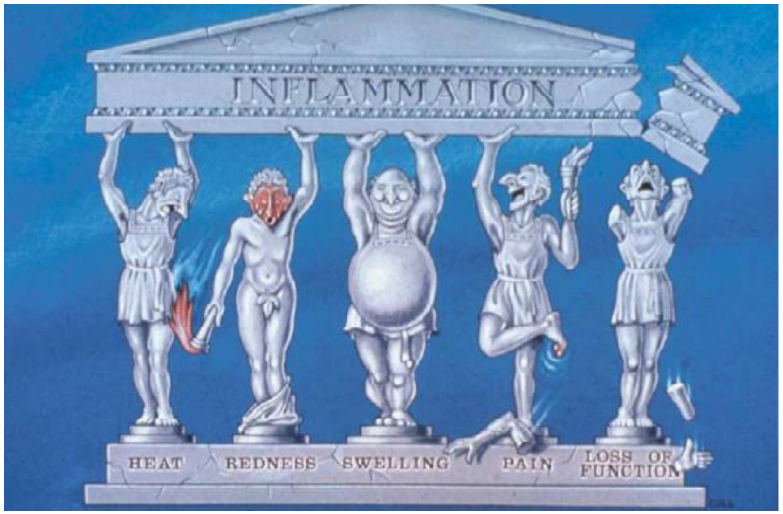
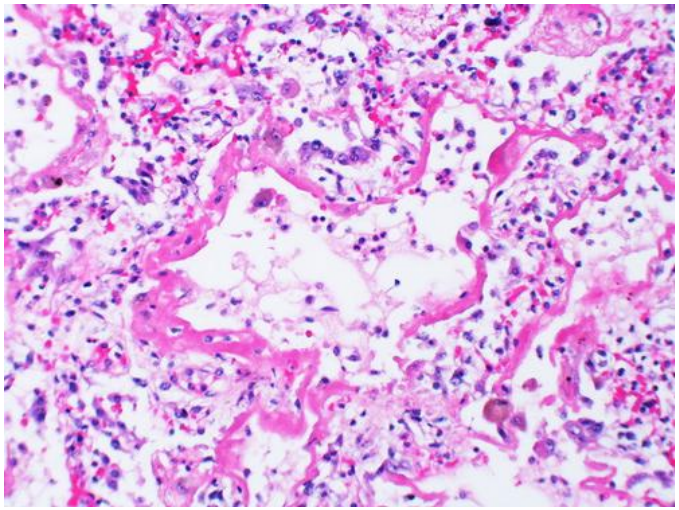
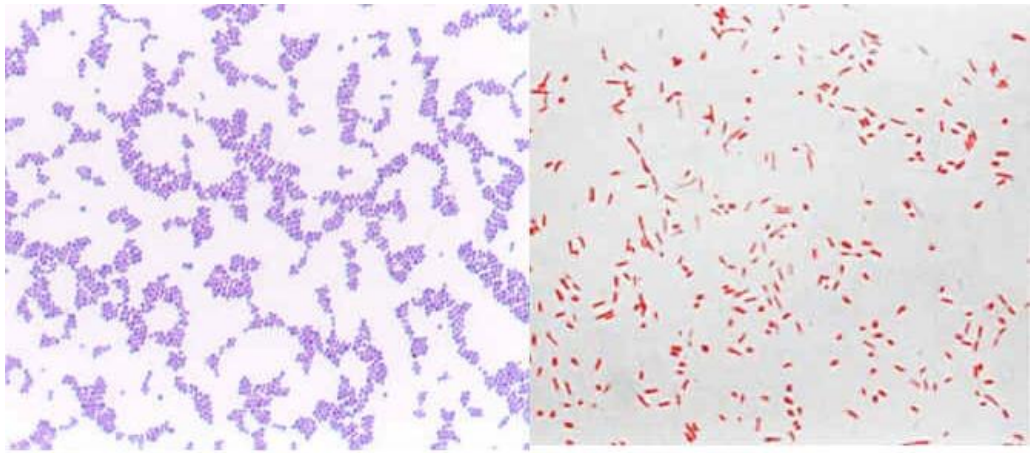
Pathophysiology summary





Epithelial denudation/ endothelial disruption

+/-



Gram +ve Bacteria

Gram -ve Bacteria

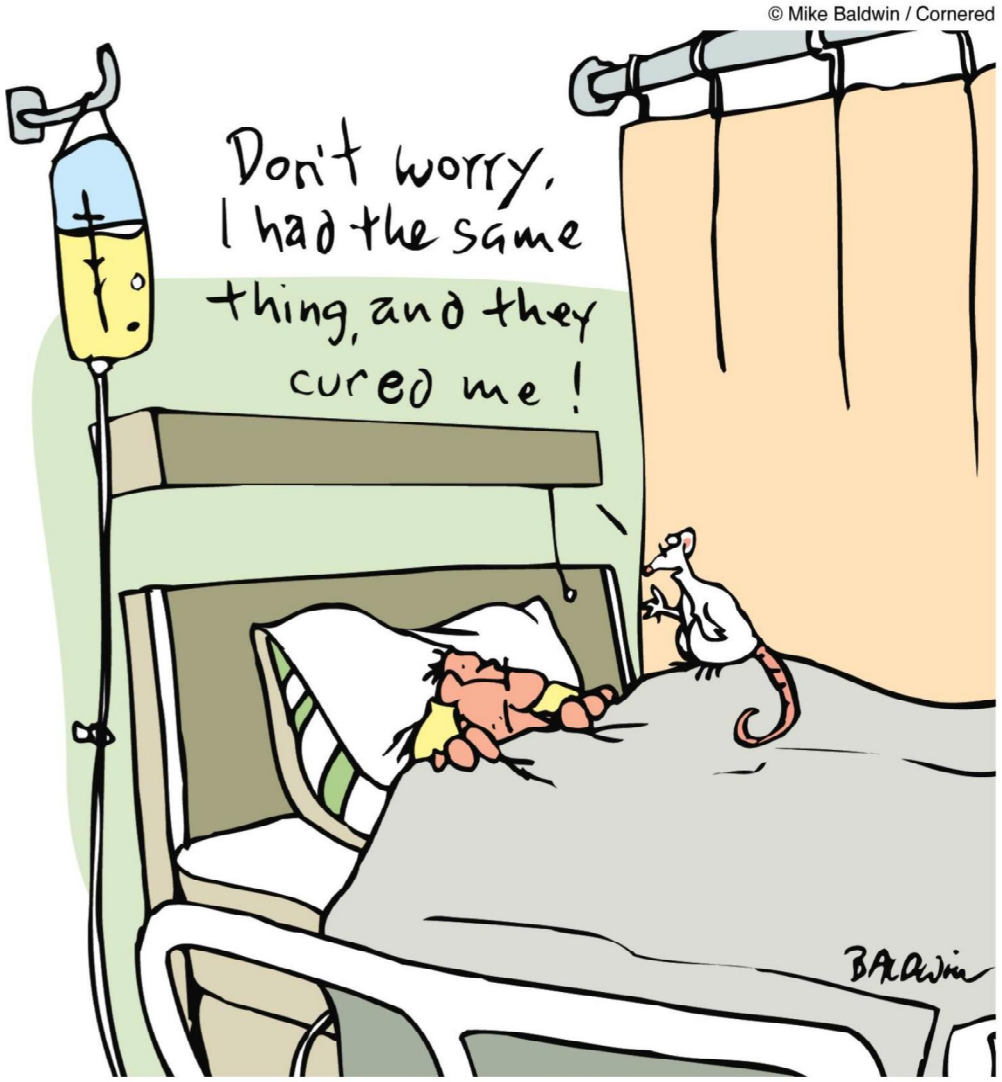
50+ years of ARDS research

No pharmacological therapy

- Protective ventilation
- Neuromuscular blockade?
- Prone positioning
- Conservative fluid management

In vivo vs clinical studies in ARDS

Translating animal data to man



First clue that the latest medical breakthrough isn't quite there yet.

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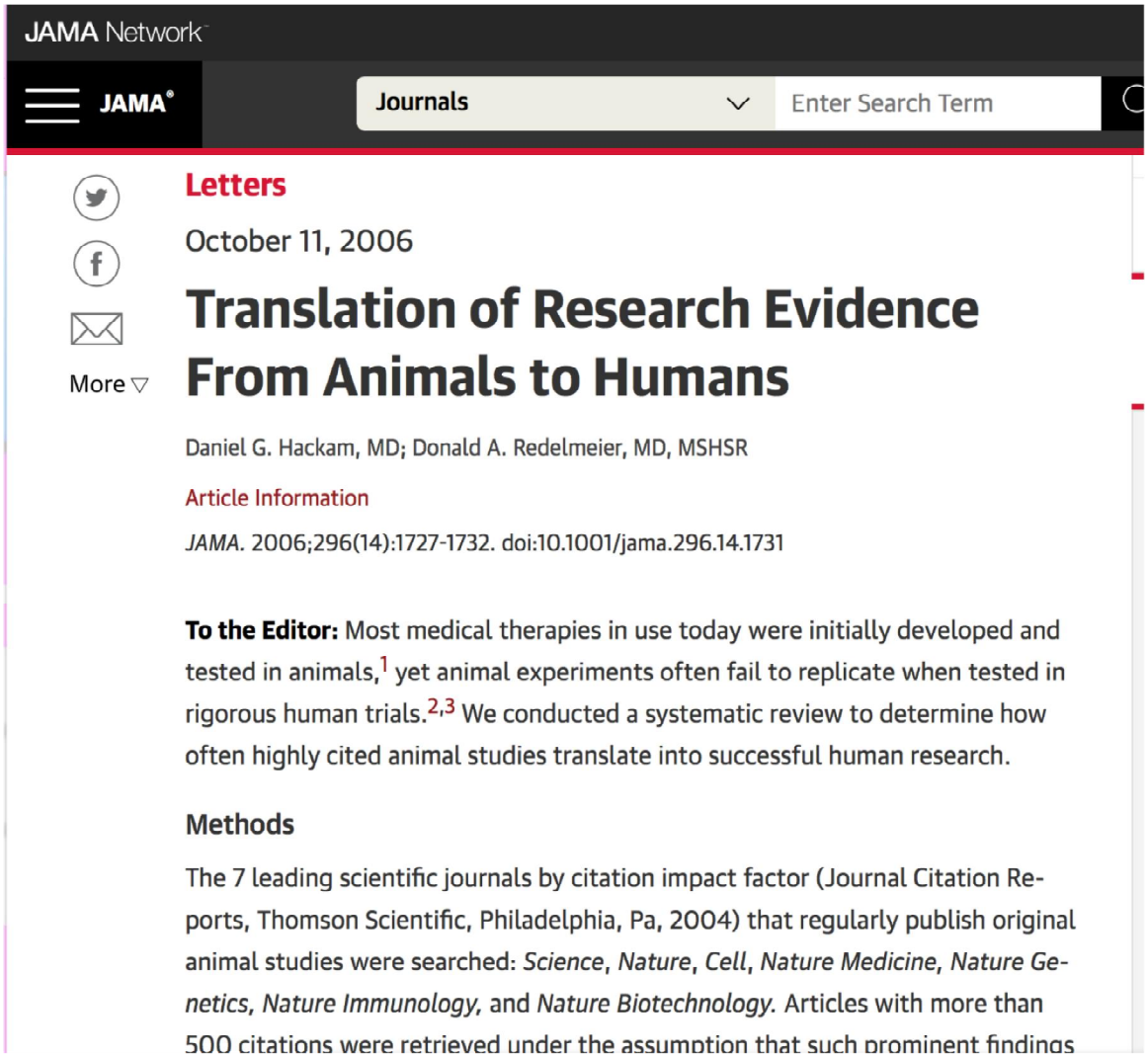
In vivo research



JAMA Network

JAMA

Journals

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Letters

October 11, 2006

Translation of Research Evidence From Animals to Humans

More

Daniel G. Hackam, MD; Donald A. Redelmeier, MD, MSHSR

Article Information

JAMA. 2006;296(14):1727-1732. doi:10.1001/jama.296.14.1731

To the Editor: Most medical therapies in use today were initially developed and tested in animals,[1] yet animal experiments often fail to replicate when tested in rigorous human trials.[2,3] We conducted a systematic review to determine how often highly cited animal studies translate into successful human research.

Methods

The 7 leading scientific journals by citation impact factor (Journal Citation Reports, Thomson Scientific, Philadelphia, Pa, 2004) that regularly publish original animal studies were searched: *Science*, *Nature*, *Cell*, *Nature Medicine*, *Nature Genetics*, *Nature Immunology*, and *Nature Biotechnology*. Articles with more than 500 citations were retrieved under the assumption that such prominent findings

Highly cited animal studies of a therapeutic intervention

37% replicated effect in clinical trial

18% opposite findings in clinical trial

Remainder ?untested

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Why mice are easy to study/cure

- Genetically very similar
- Animals same age
- Often same gender
- Bred in pathogen-free environment
- Same diet
- Identical insult (nature/magnitude & timing)
- Usually no co-morbidity
- Infrequently multiple medications

Limitations

- Not human….

Examples from ARDS and sepsis

- Different molecules regulate fundamental innate immune responses e.g. IL-8 is absent in mice
- Profound species variation in response to simple insult (LPS)

Response to LPS in mice and humans

PNAS

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[t,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

PNAS 2013 110(9) pp 3507-12

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Response to LPS in mice and humans

matory diseases are nonexistent. Here, we show that, although acute inflammatory stresses from different etiologies result in highly similar genomic responses in humans, the responses in corresponding mouse models correlate poorly with the human conditions and also, one another. Among genes changed significantly in humans, the murine orthologs are close to random in matching their human counterparts (e.g., R^2 between 0.0 and 0.1). In addition to improve-

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Can we improve pre-clinical models?

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In vivo human basic research

- Human challenge models e.g. LPS inhalation or administration i.v.
- Blood, urine and bronchoalveolar lavage (BAL) sampling
- Study cellular, inflammatory and immunological responses to injury

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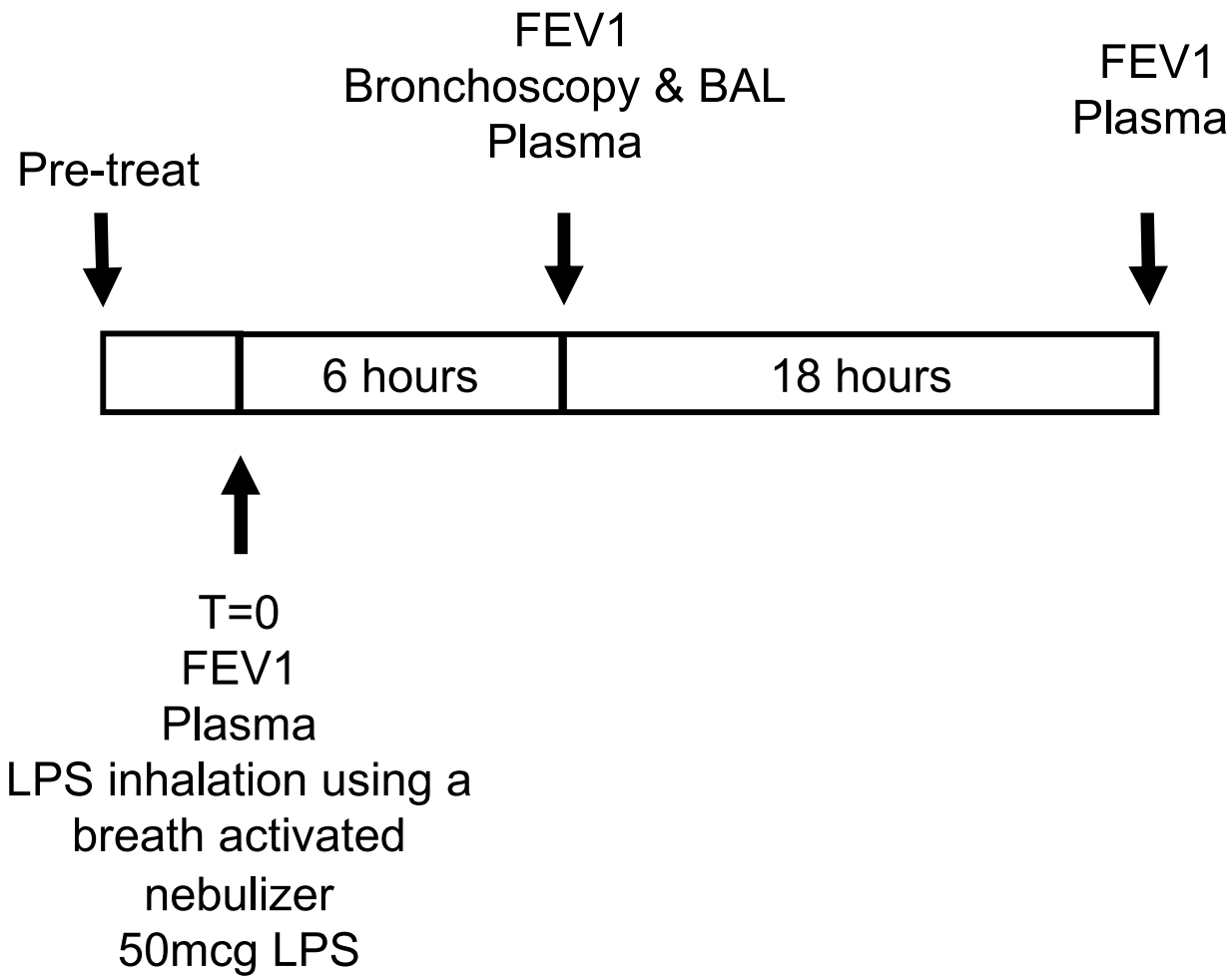
Healthy volunteer inhaled LPS model

Healthy volunteer inhaled LPS model



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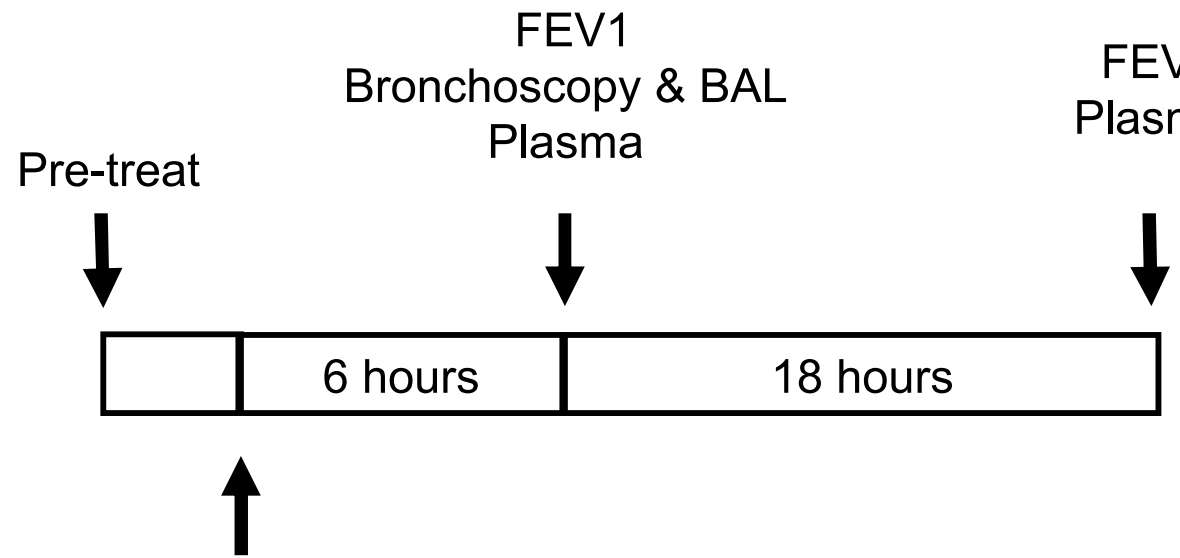
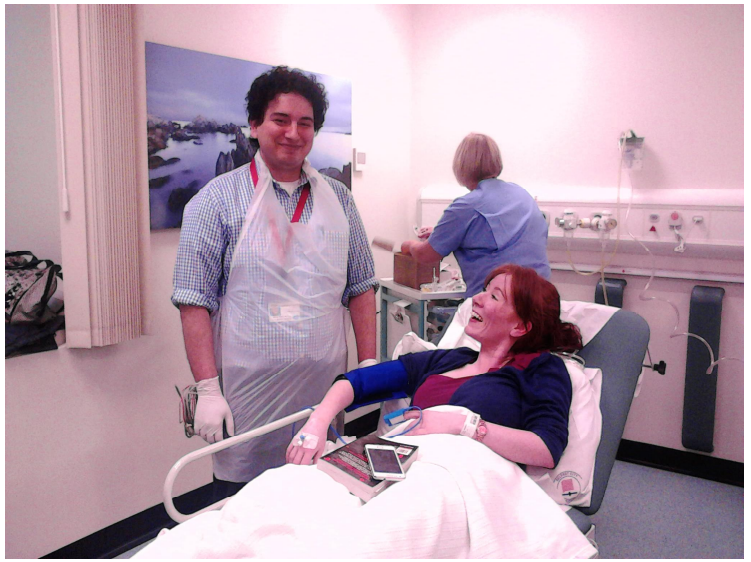
Healthy volunteer inhaled LPS model





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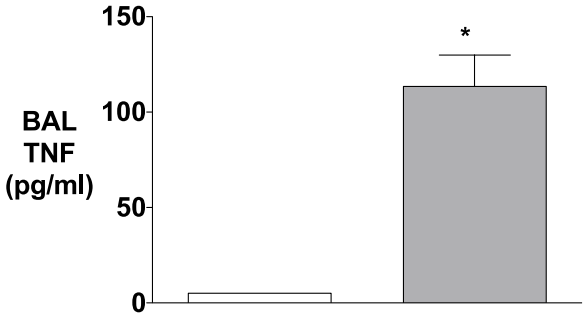
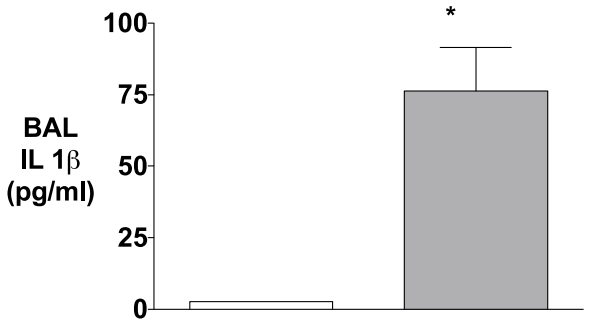
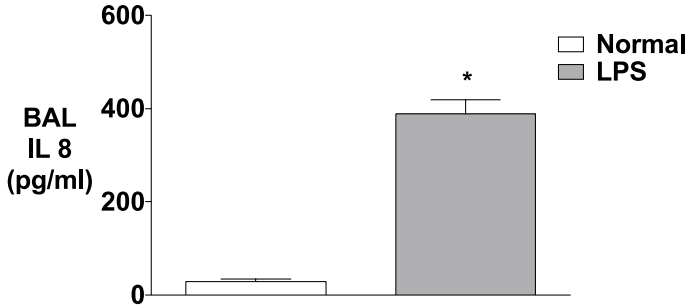
Inhaled LPS induces inflammatory cytokines in pulmonary compartment



p = 0.0006, unpaired t test



p = 0.0056, unpaired t test



p <0.0001, unpaired t test

Also drives

- neutrophil recruitment to alveolar space
- protease activity
- alveolar epithelial and endothelial injury

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Basic human *in vivo* research

- Proof of concept that an intervention may work in whole human
- Predict effect size in human study
- May give PK/PD data
- Mechanistic data from biological samples

- Limited severity of insult
- Often biological rather than physiological response
- Limited sampling (blood, urine, airway)
- Repeat injury/ sampling limited

Ex vivo human research

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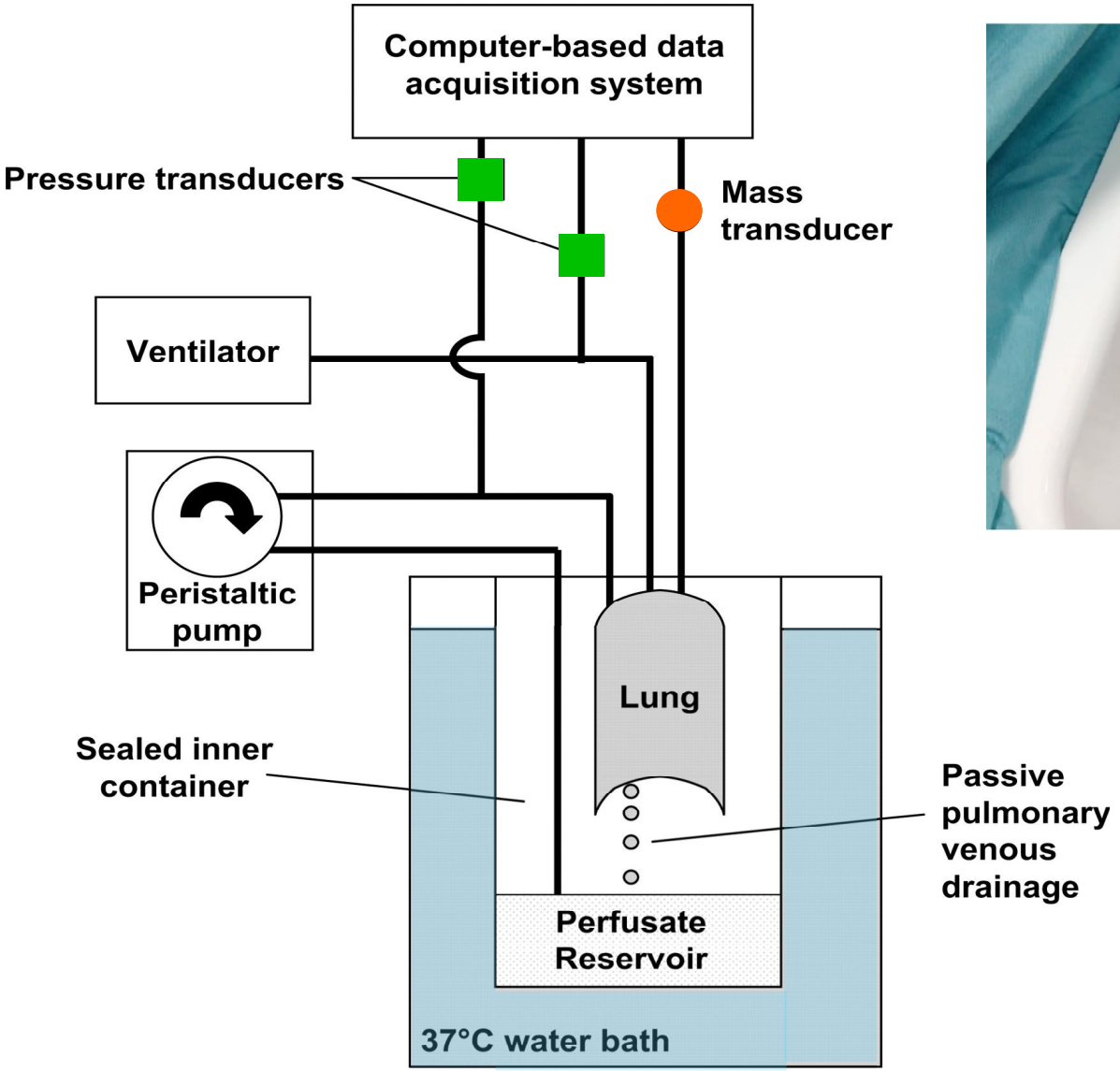
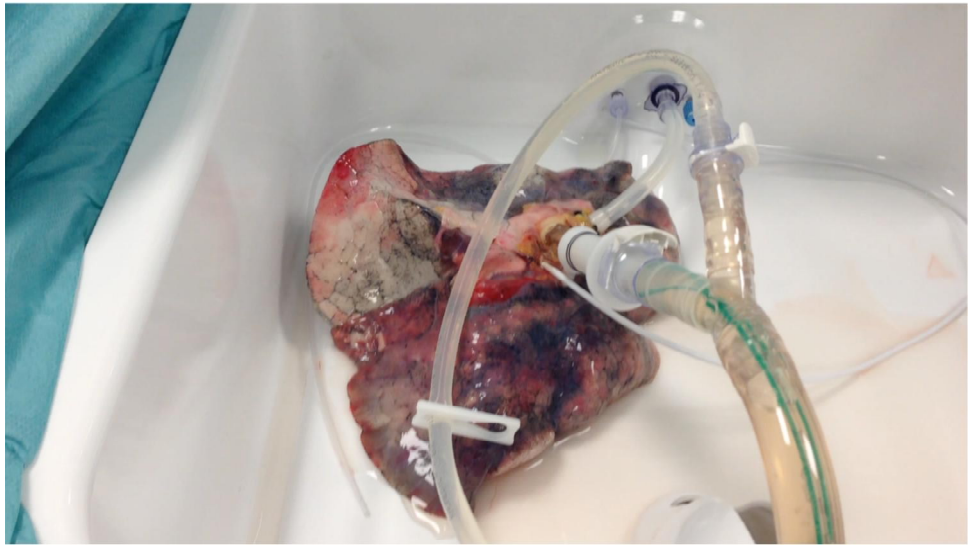
Human *ex vivo* lung perfusion





Proudfoot AG et al. Disease Models & Mechanisms 2011 4: 145-153

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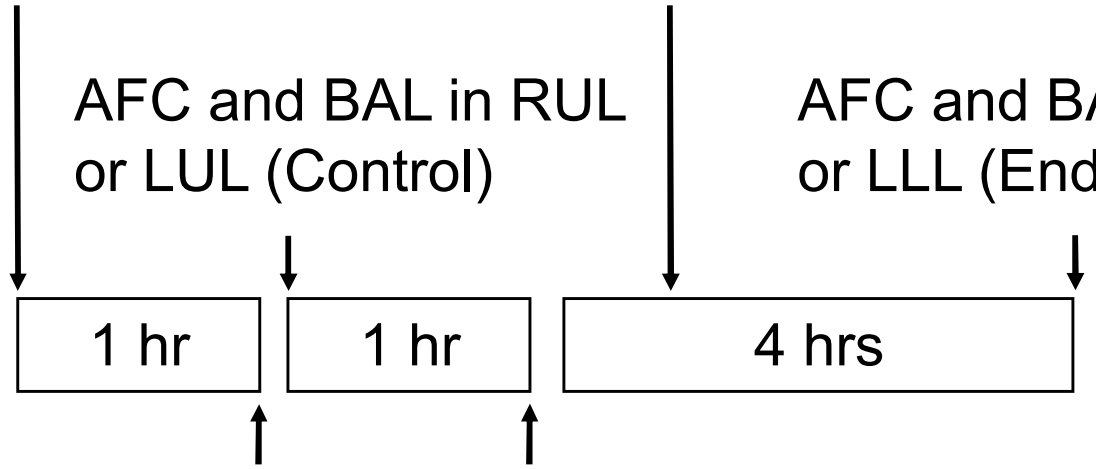
Human *ex vivo* lung perfusion

Surgical preparation of lung
Begin perfusion without blood

Intervention



- Lung temp 36° C
- Apply CPAP

Add 100 ml fresh whole blood to perfusate

Instill 0.1 mg/kg of endotoxin into the airspaces of the RML or LLL

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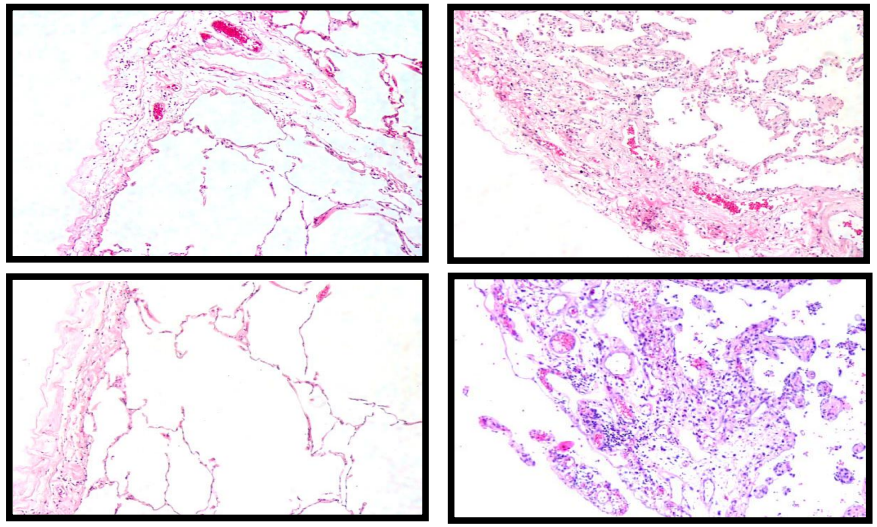
Histological evidence of ARDS



Control Lung Lobe **LPS Lung Lobe**

Absolute Neutrophil Counts

$9 \pm 6 \times 10^6$ cells $25 \pm 25 \times 10^6$ cells

*

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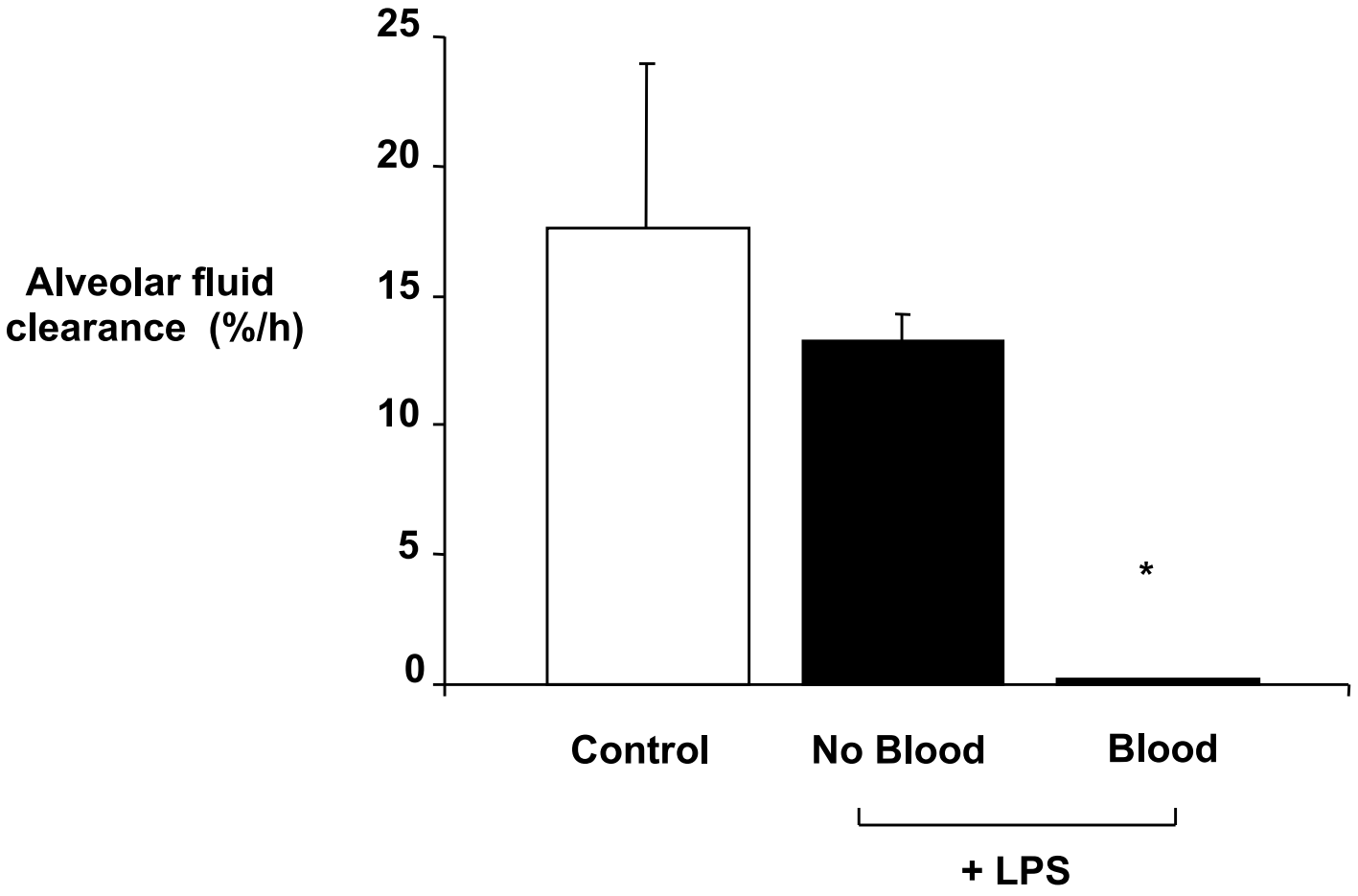
Impaired alveolar fluid clearance



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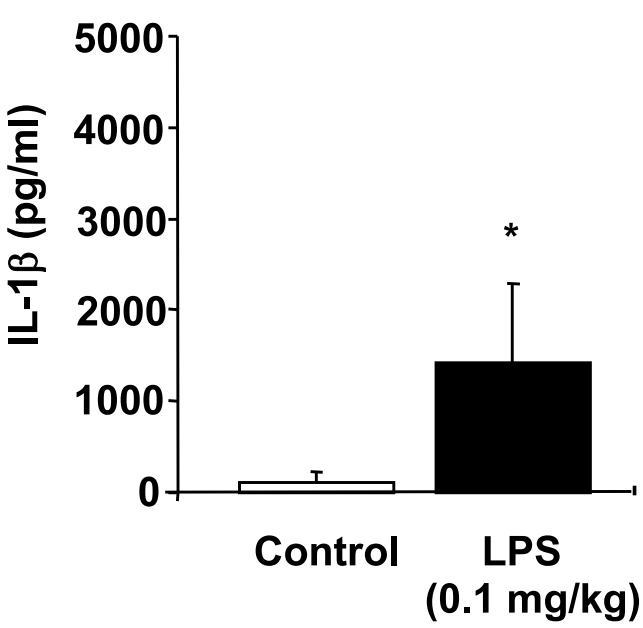
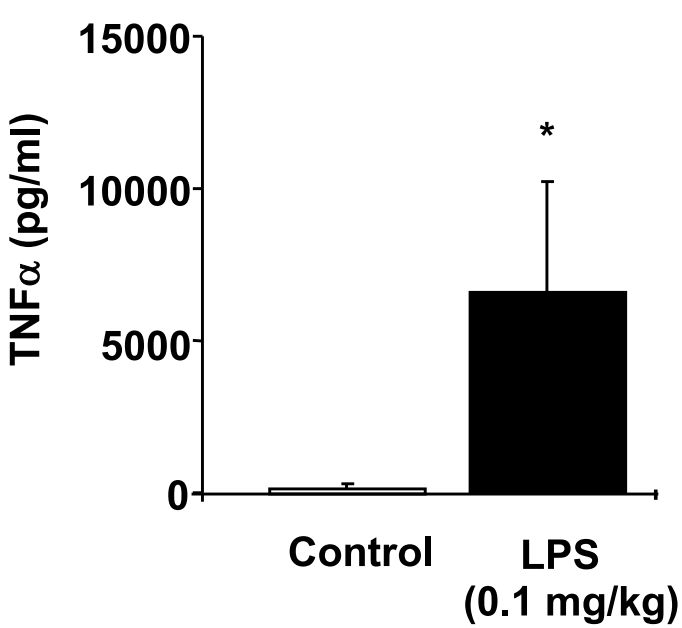
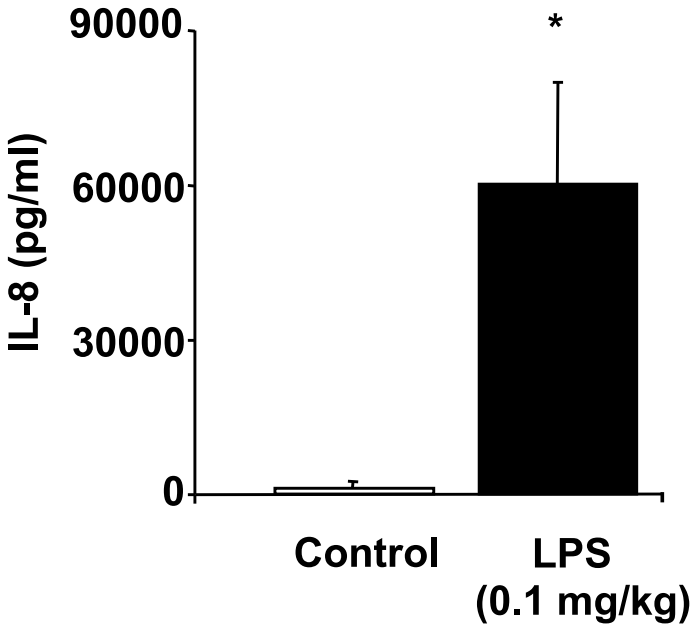
Cytokine response in *ex vivo* lung consistent with ALI







Similar to LPS inhalation
- Neutrophil recruitment
- Protease activity

But also
- Pulmonary edema
- Permeability markers

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Other advantages of *ex vivo* lung injury model

- Can use live bacterial infection/ other injuries
- Physiological parameters
- Whole lung tissue environment

- Proof of concept an intervention can have an effect in human tissue

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Limitations of *ex vivo* lung injury model

- Isolated perfused lung – no haematopoietic/ reticuloendothelial system, no liver or kidney
- Short-lived
- Organs usually impaired at baseline – variability
- Noisy system – age, smoking, gender, race, co-morbidity, medication
- Variable cold-ischaemic time

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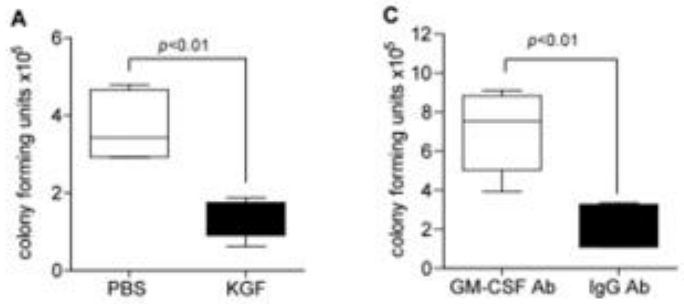
Using the models for pre-clinical testing of therapeutics

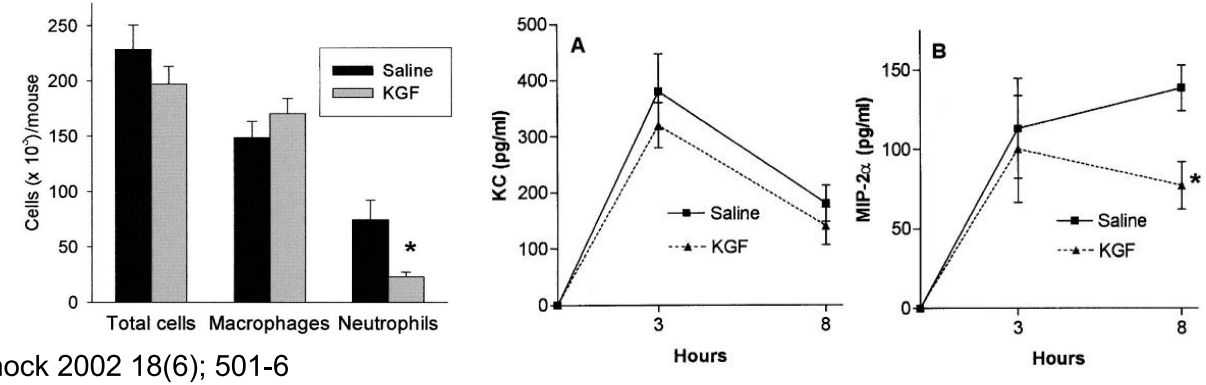
KGF

KGF *in vivo*



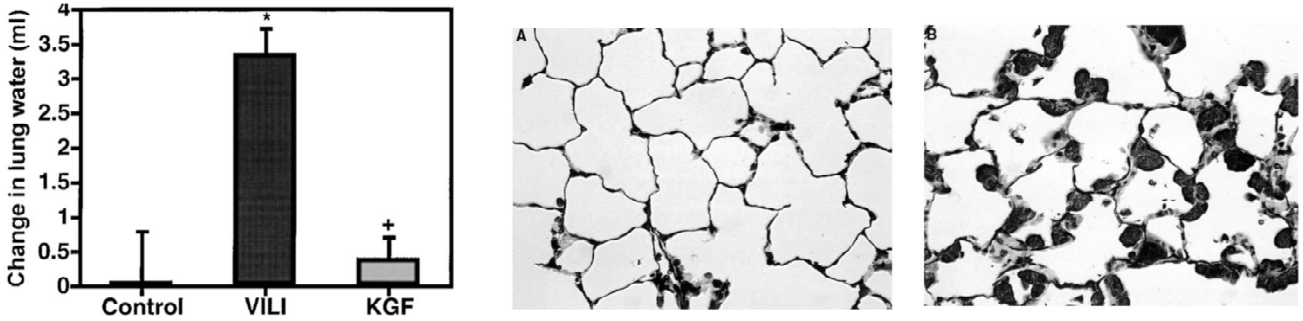
Bacterial infection model - enhanced bacterial clearance via GM-CSF production

J Biol Chem 2011;286:14932–14940.



CLP followed by acid aspiration – reduced neutrophil influx to lungs mediated by reduced MIP-2α

Shock 2002 18(6); 501-6



Rat – KGF reduced ventilator induced injury. KGF instillation drives ATII hyperplasia

AJRCCM 2000:162(3) 1081-86

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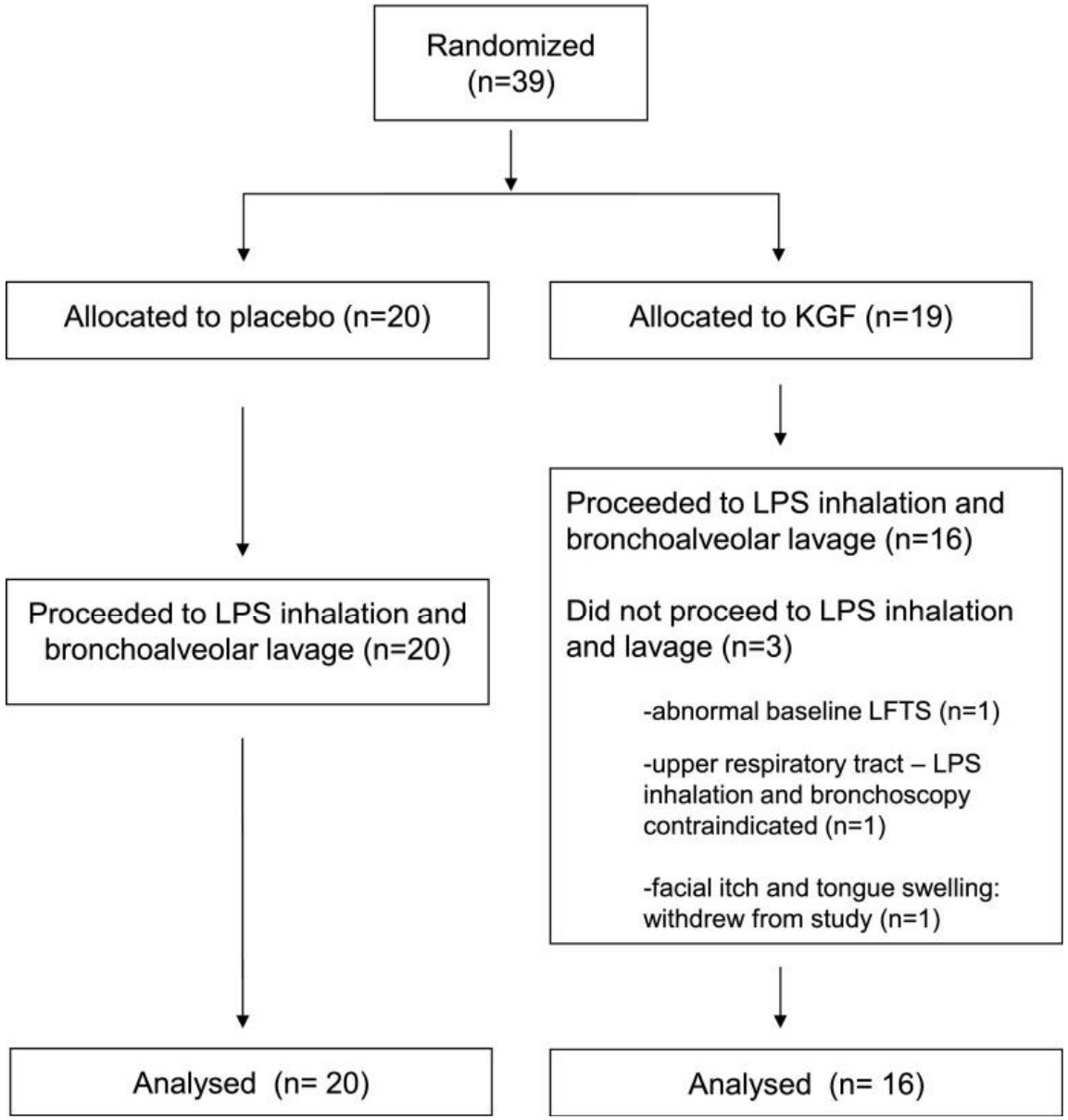
KGF in healthy volunteer model of ARDS



AJRCCM 2014; 189(12) pp 1520-29

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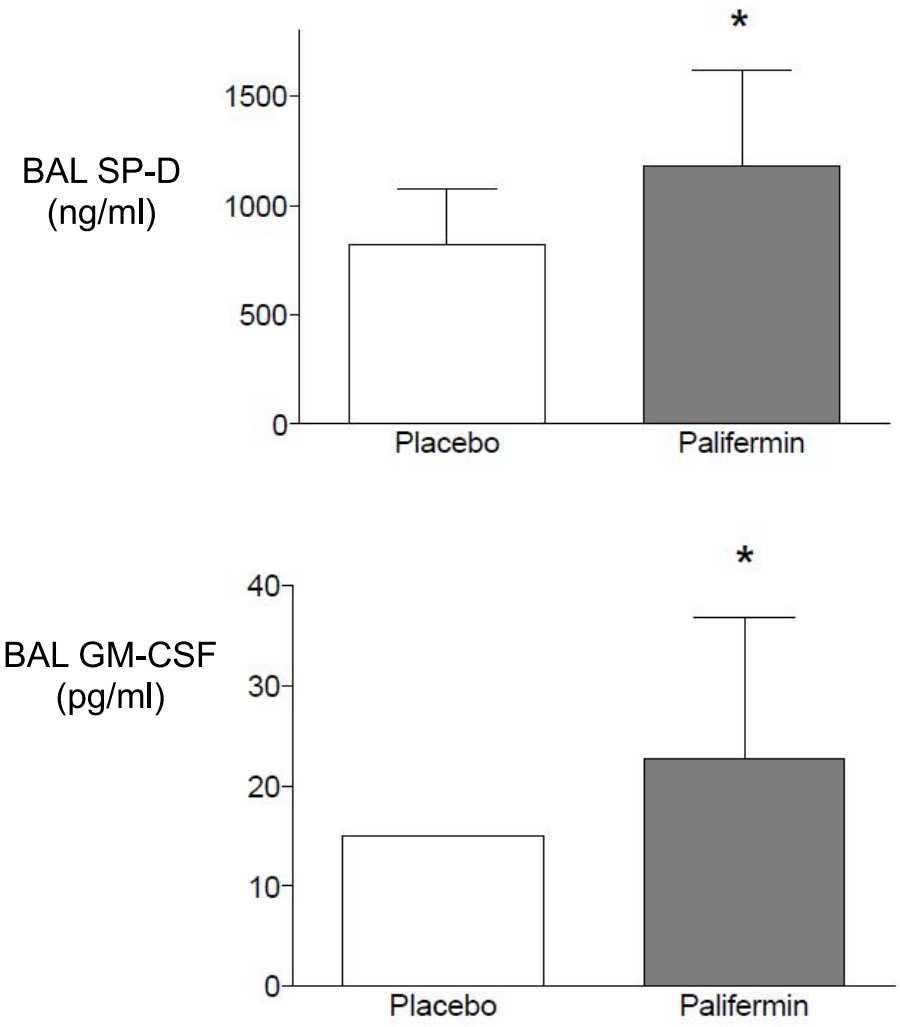

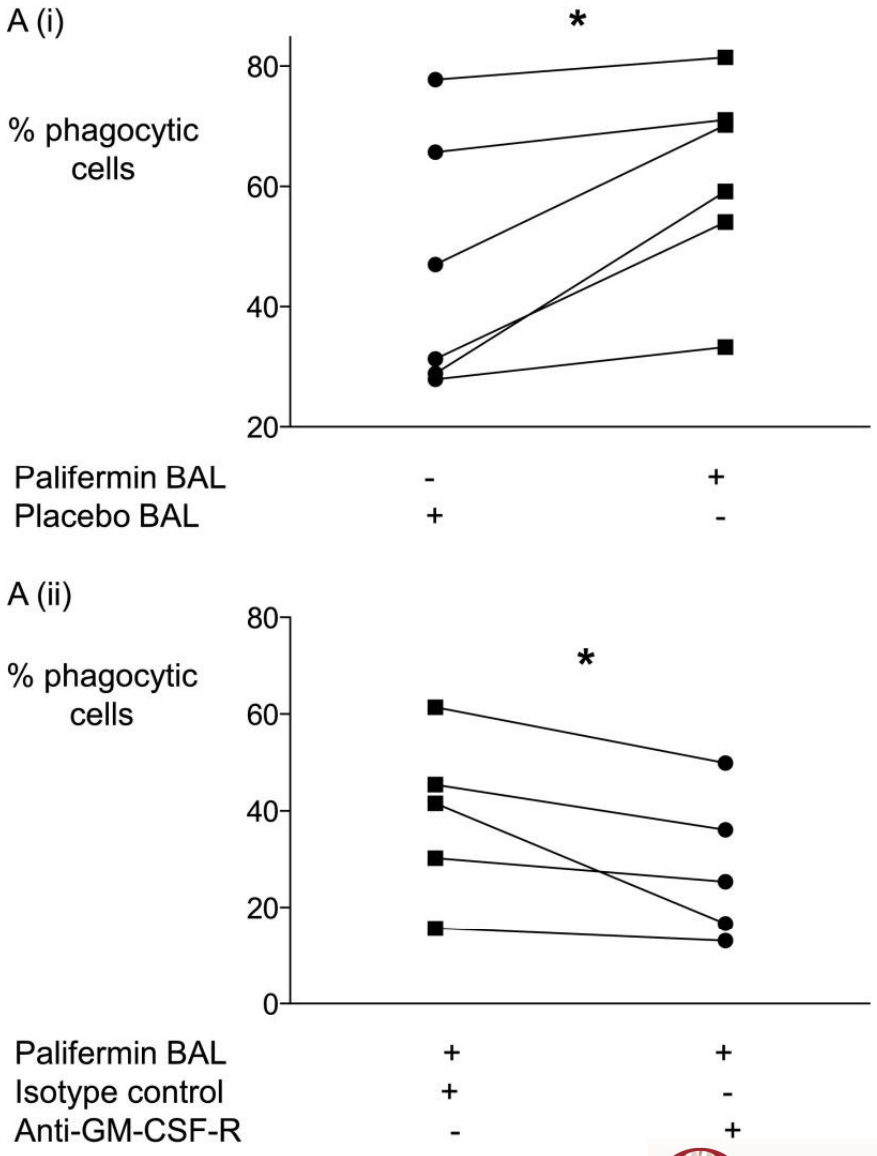

AJRCCM 2014; 189(12) pp 1520-29

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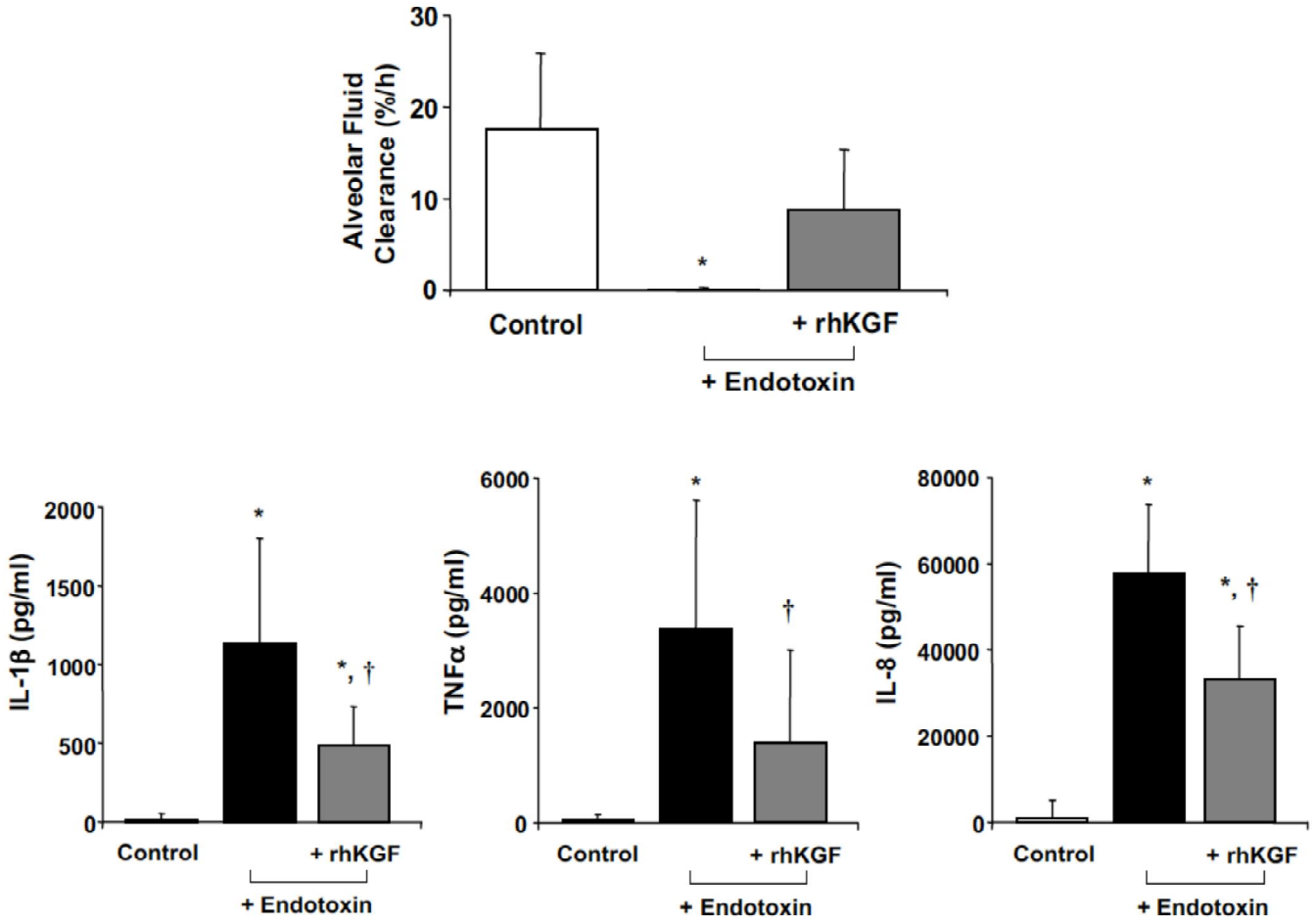
KGF in the *ex vivo* perfused lung model of ARDS



PNAS 2009 22;106(38):16357–16362.

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KGF

Keratinocyte growth factor for the treatment of the acute respiratory distress syndrome (KARE): a randomised, double-blind, placebo-controlled phase 2 trial

Daniel F McAuley, LJ Mark Cross, Umar Hamid, Evie Gardner, J Stuart Elborn, Kathy M Cullen, Ahilanandan Dushianthan, Michael PW Grocott, Michael A Matthay, Cecilia M O'Kane

Summary

Lancet Respiratory Medicine 2017; 5(6) pp 484-91

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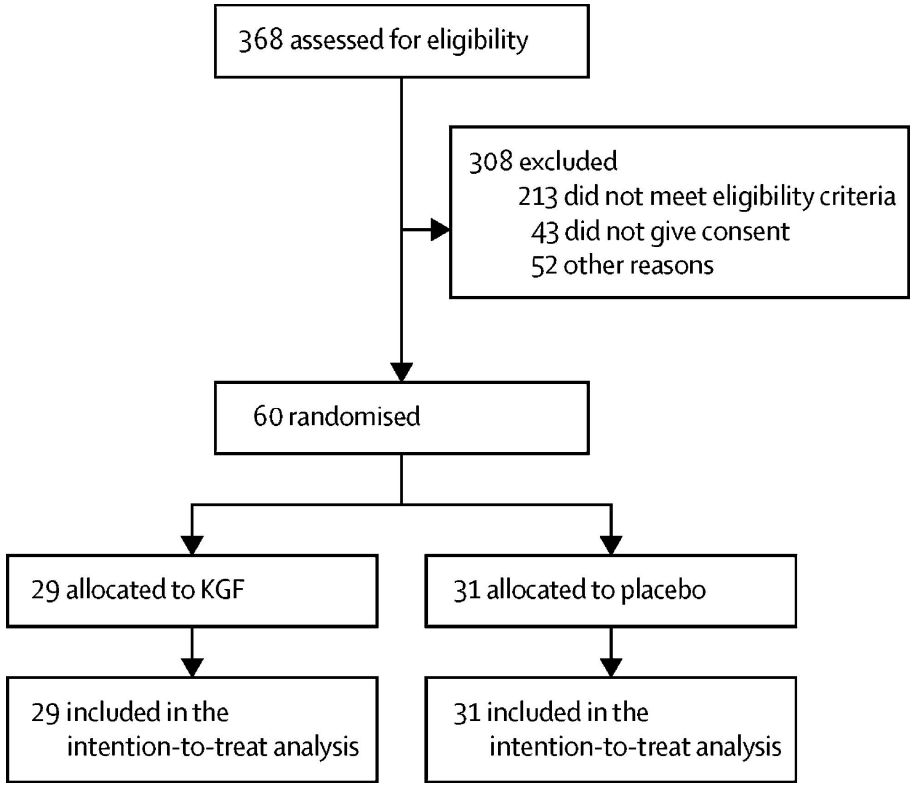

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Summary

	KGF group	Placebo group	Mean difference (95% CI)	p value
Oxygenation index				
Last available OI*	..	..	..	..
Day 3	66·9 (55·0; n=29)	60·1 (45·4; n=31)	6·8 (−19·2 to 32·8)	0·60
Day 7 (primary outcome)	62·3 (57·8; n=29)	43·1 (33·5; n=31)	19·2 (−5·6 to 44·0)	0·13
Day 14	59·4 (58·4; n=29)	30·1 (24·2; n=31)	29·3 (5·6 to 53·0)	0·02
Measured OI†				
Day 3	62·8 (50·1; n=26)	60·9 (45·9; n=30)	1·8 (−23·9 to 27·6)	0·89
Day 7	45·4 (32·1; n=23)	48·6 (38·6; n=21)	−3·2 (−24·8 to 18·3)	0·76
Day 14	52·9 (35·2; n=11)	43·3 (37·2; n=5)	9·6 (−31·8 to 51·0)	0·63
Respiratory compliance				
Day 3	48·6 (16·4; n=16)	53·5 (28·8; n=20)	−4·8 (−21·3 to 11·6)	0·55
Day 7	51·1 (25·2; n=14)	65·1 (15·4; n=7)	−14·0 (−35·9 to 7·9)	0·20
Day 14	45·0 (10·4; n=6)	77·5‡ (n=1)	..	..
PaO_2/FIO_2 ratio†				
Day 3	23·1 (9·1; n=26)	20·3 (6·0; n=31)	2·8 (−1·4 to 7·1)	0·18
Day 7	27·6 (10·4; n=23)	24·6 (7·6; n=21)	3·0 (−2·6 to 8·6)	0·29
Day 14	27·2 (12·0; n=11)	21·3 (9·0; n=7)	5·9 (−5·3 to 17·2)	0·28

Lancet Respiratory Medicine 2017; 5(6) pp 484-91

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Day 7	45·4 (32·1; n=23)	48·6 (38·6; n=21)	–3·2 (–24·8 to 18·3)	0·76
Day 14	52·9 (35·2; n=11)	43·3 (37·2; n=5)	9·6 (–31·8 to 51·0)	0·63
Respiratory compliance				
Day 3	48·6 (16·4; n=16)	53·5 (28·8; n=20)	–4·8 (–21·3 to 11·6)	0·55
Day 7	51·1 (25·2; n=14)	65·1 (15·4; n=7)	–14·0 (–35·9 to 7·9)	0·20
Day 14	45·0 (10·4; n=6)	77·5‡ (n=1)	..	..
PaO_2/FIO_2 ratio†				
Day 3	23·1 (9·1; n=26)	20·3 (6·0; n=31)	2·8 (–1·4 to 7·1)	0·18
Day 7	27·6 (10·4; n=23)	24·6 (7·6; n=21)	3·0 (–2·6 to 8·6)	0·29
Day 14	27·2 (12·0; n=11)	21·3 (9·0; n=7)	5·9 (–5·3 to 17·2)	0·28

	KGF group (n=29)	Placebo group (n=31)	Median difference or risk ratio (95% CI)
Ventilator-free days to day 28	1 (0–17)	20 (13–22)	–8 (–17 to –2)
Duration of ventilation, days*	16 (13–30)	11 (8–16)	6 (2 to 14)
ICU stay (days)*	22 (14–32)	12 (10–19)	9 (3 to 17)
Hospital length of stay (days)*	39 (30–67)	23 (18–33)	17 (7 to 33)
28-day mortality	9 (31%)	3 (10%)	3·2 (1·0 to 10·7)
90-day mortality	13 (45%)	5 (16%)	2·8 (1·1 to 6·8)
ICU mortality	12 (41%)	2 (7%)	6·4 (1·6 to 26·2)
Hospital mortality	14 (48%)	4 (13%)	3·7 (1·4 to 10·1)
1-year mortality	15 (52%)	8 (26%)	2·0 (1·0 to 4·0)

Lancet Respiratory Medicine 2017; 5(6) pp 484-91

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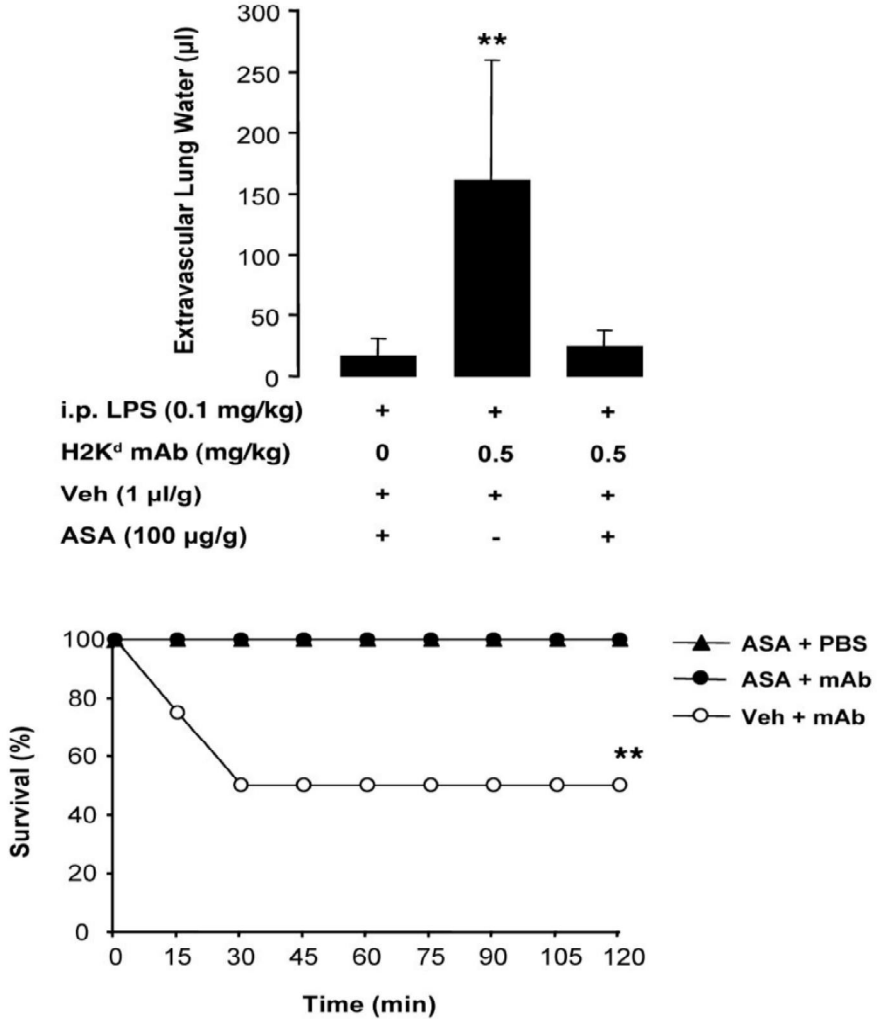
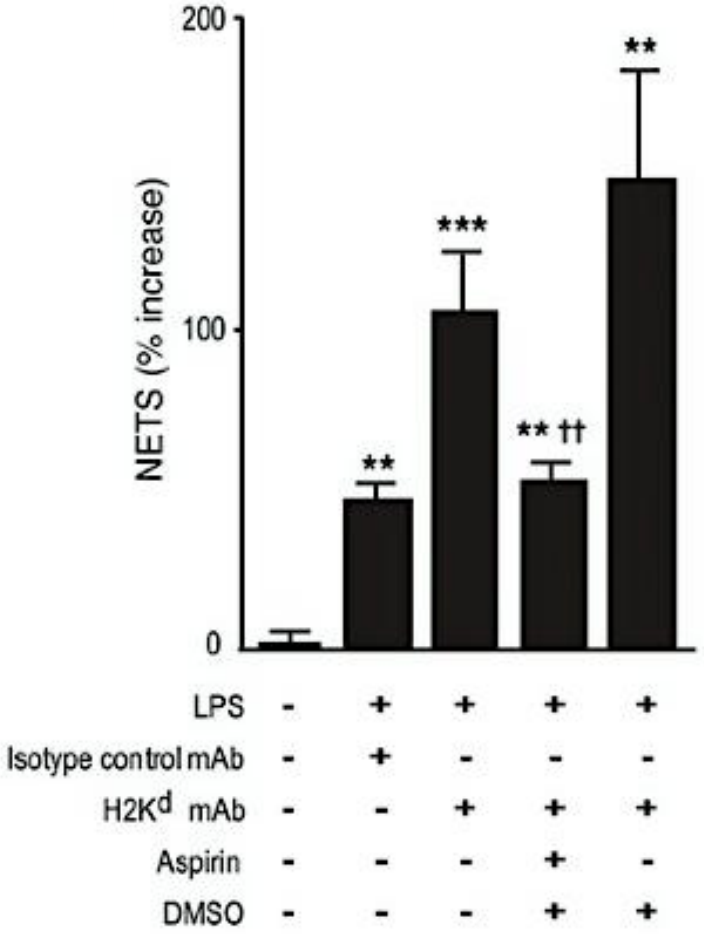
Aspirin

Aspirin improves outcome in a murine model of ARDS

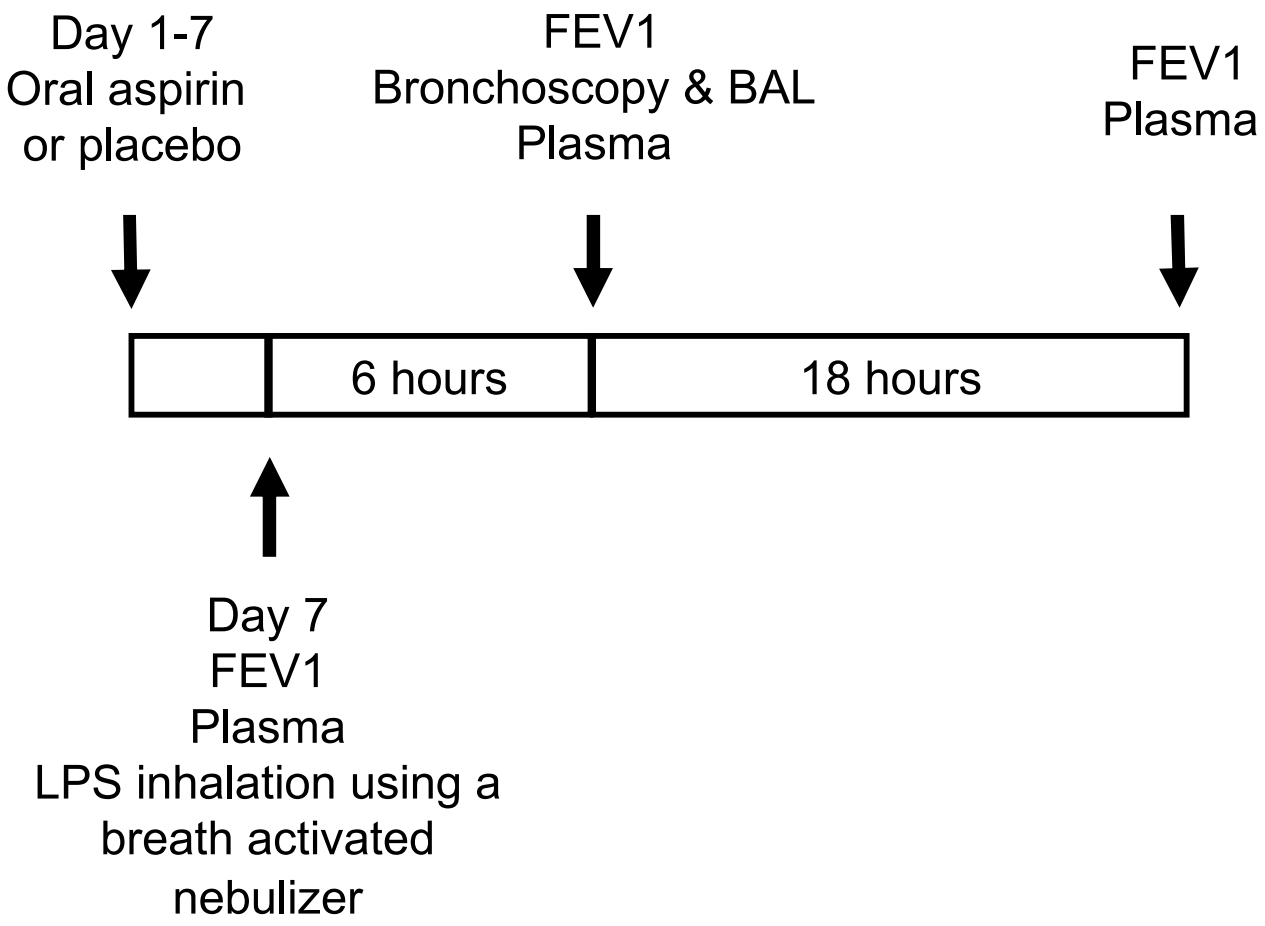


Looney et al. J Clin Invest. 2009



Looney et al. J Clin Invest. 2012

Effect of **A**spirin on **RE**ducing i**N**flammation in an in vivo model of Acute lung injury - ARENA



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ARENA

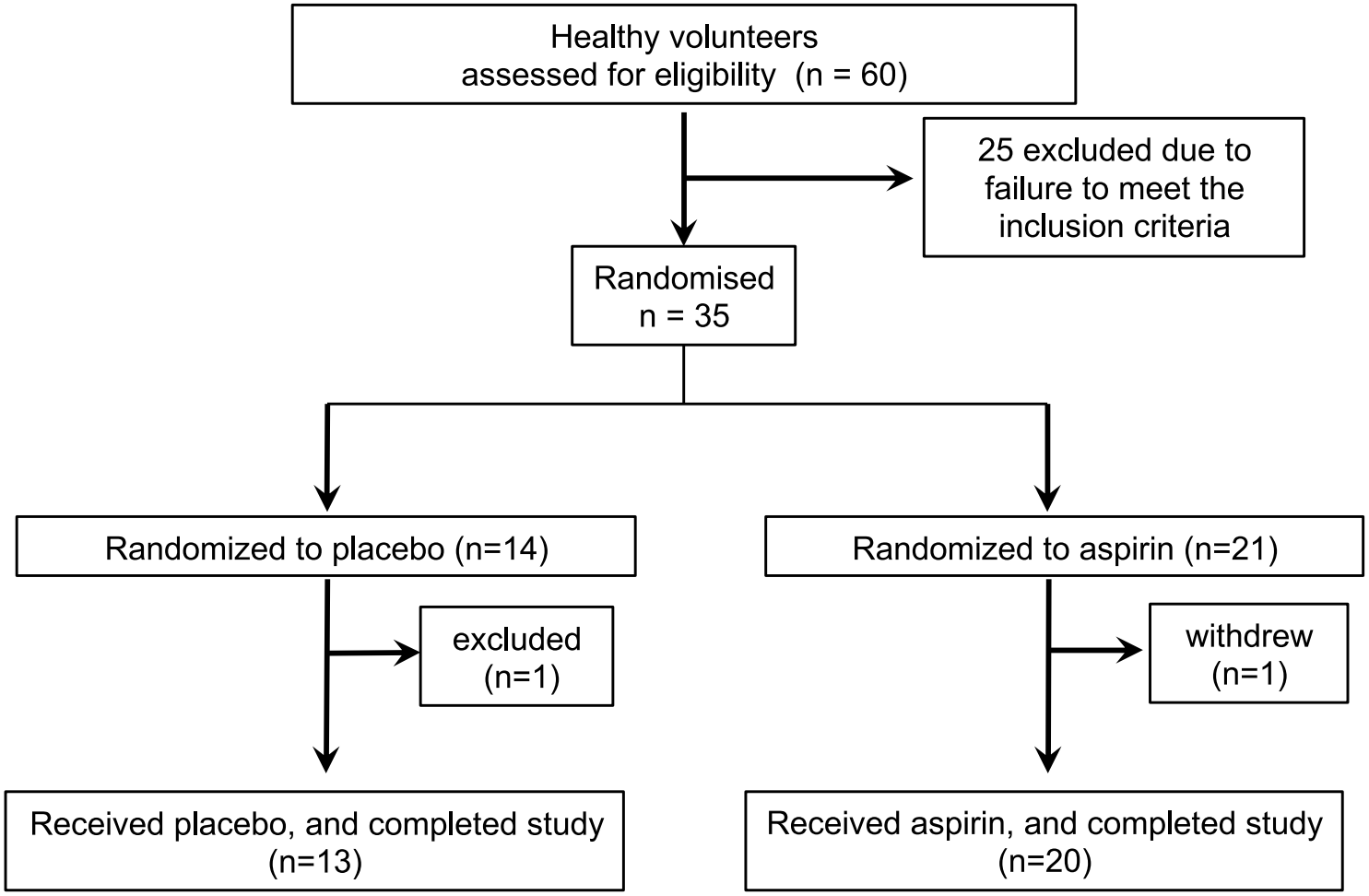
Inclusion

- 18yrs or over
- Healthy volunteers
- No regular medication

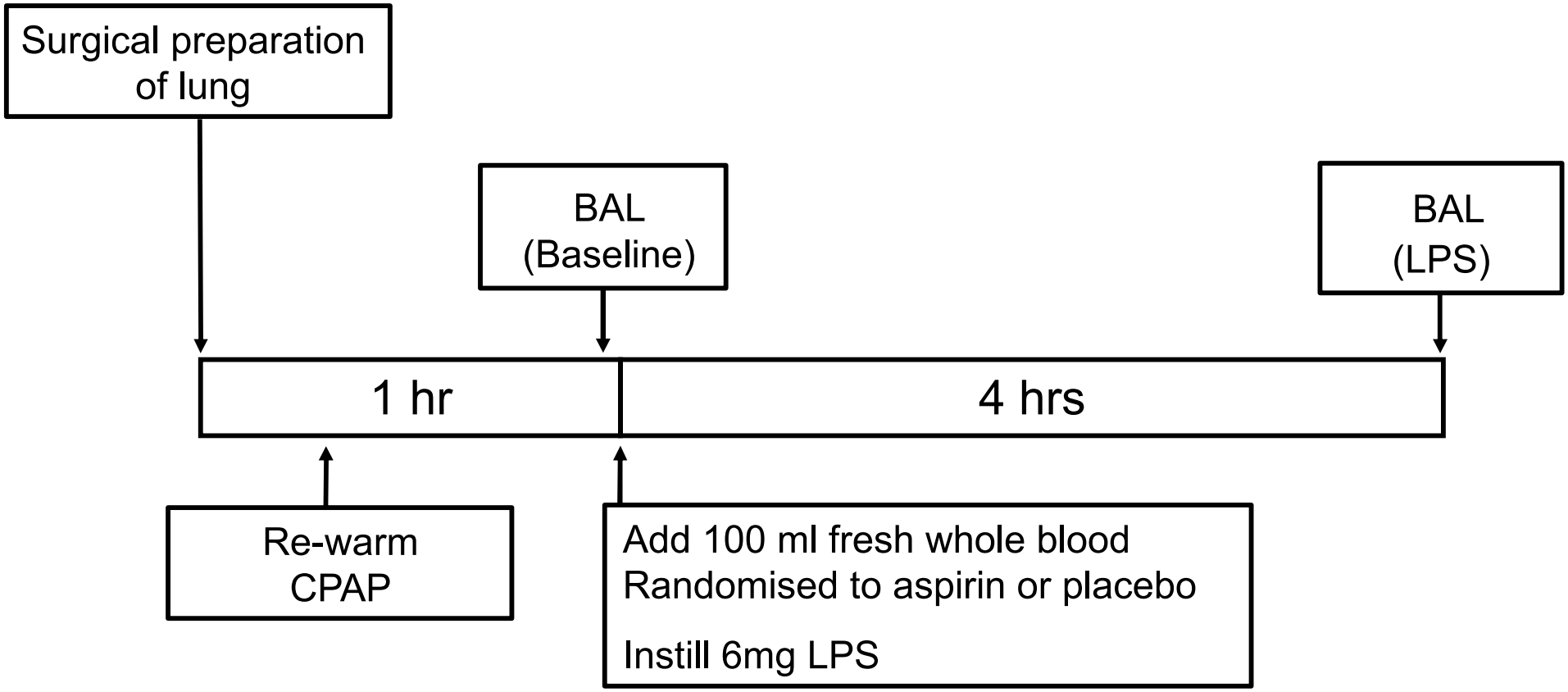
Exclusion

- Pregnancy/breastfeeding
- h/o asthma
- h/o aspirin/NSAID sensitivity
- Aspirin/NSAID use in past 4/52
- h/o peptic ulcer
- Platelets $<150x10^6$/ml

Healthy volunteer (ARENA) study

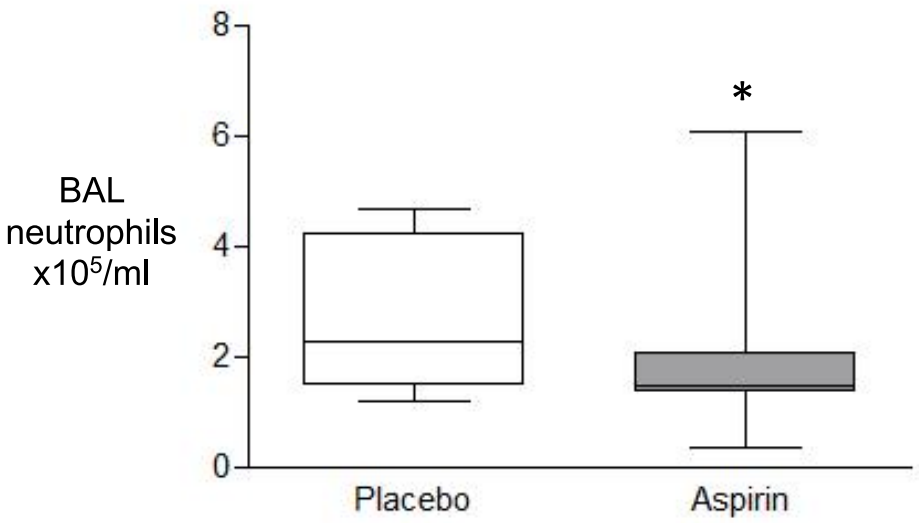


Aspirin in human EVLP model



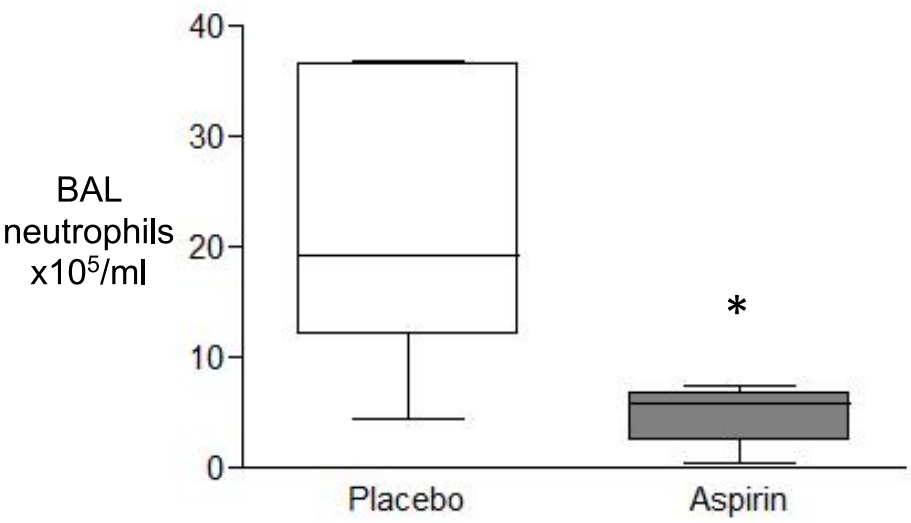
Aspirin reduces BAL neutrophilia

LPS inhalation in HVs



p=0.03

EVLP model



p=0.02

Thorax 2017, 72 (11):971-80

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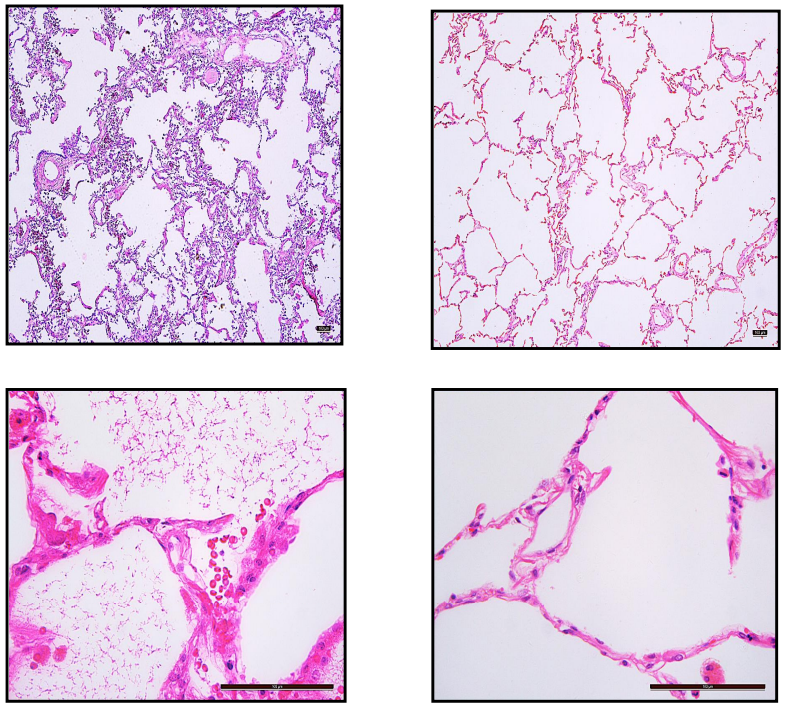
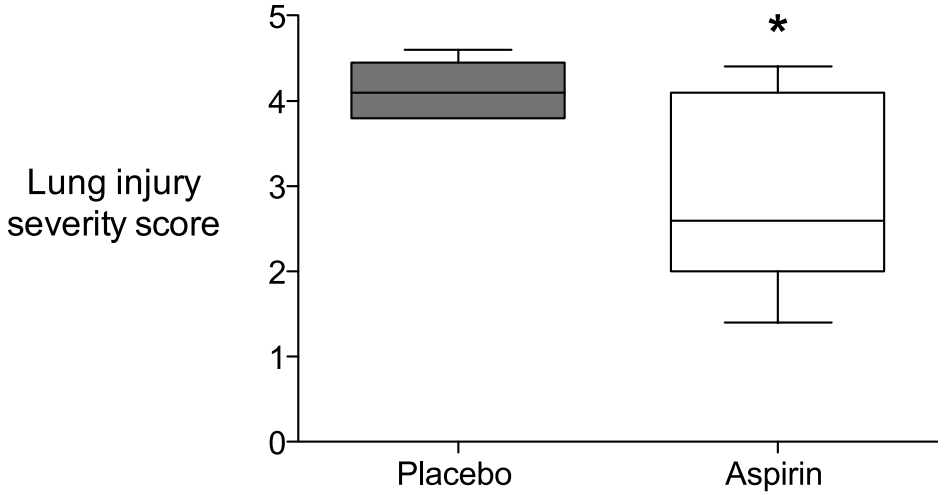
Aspirin reduces histological injury

Placebo

Aspirin



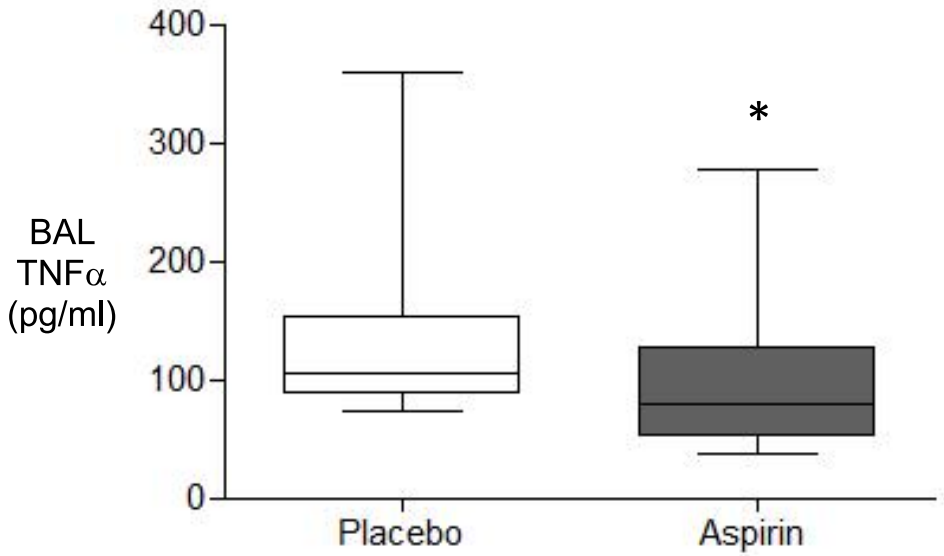
Scale bar 100μ



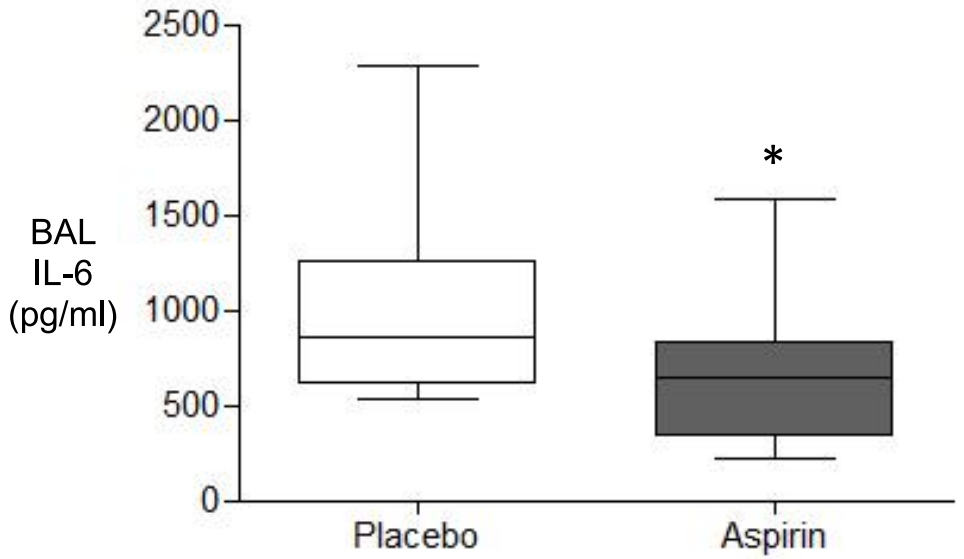
*p<0.05

Thorax 2017, 72 (11):971-80

Aspirin reduces BAL inflammatory cytokines



p=0.04



p=0.03

Trend towards reduction in IL-1β (p=0.07), IL-8 (p=0.15), but underpowered

Thorax 2017, 72 (11):971-80

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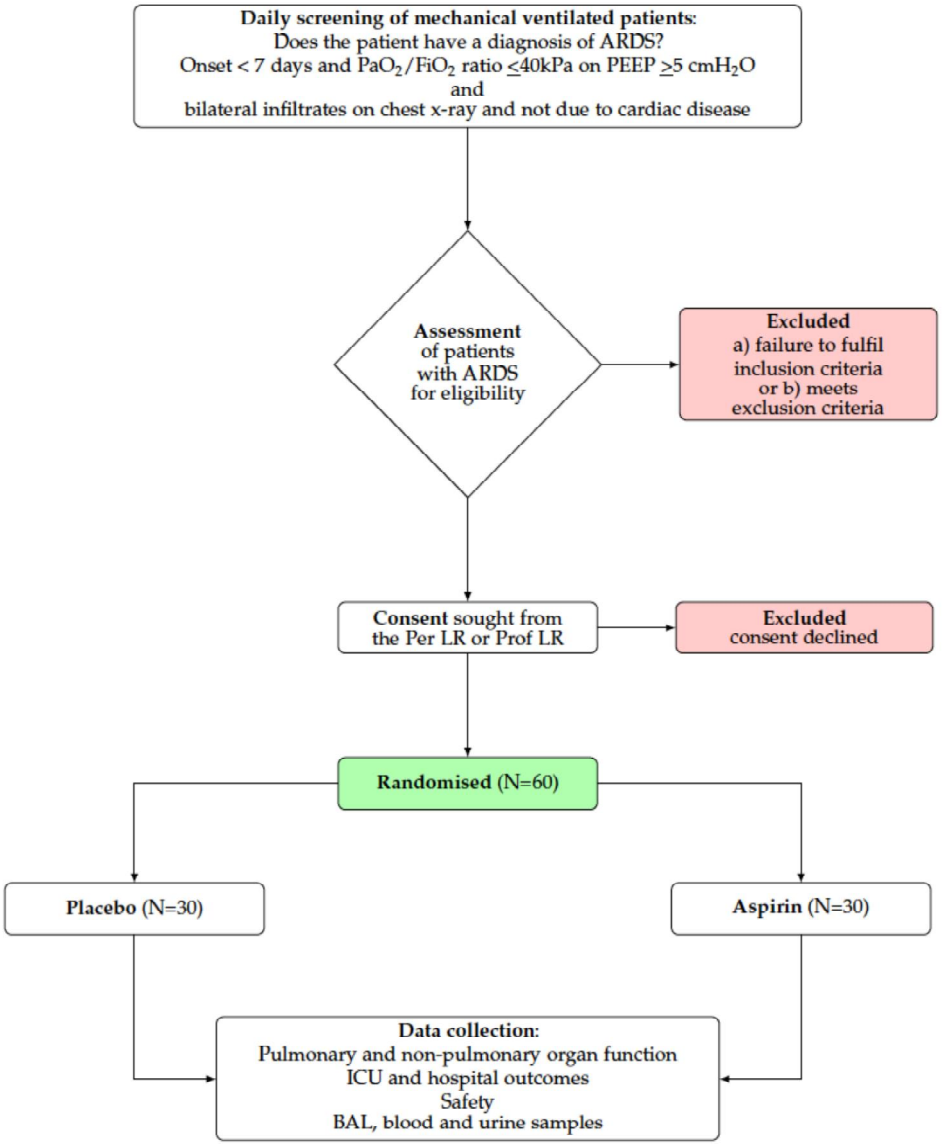
STAR (aSpirin as a Treatment for ARDS)



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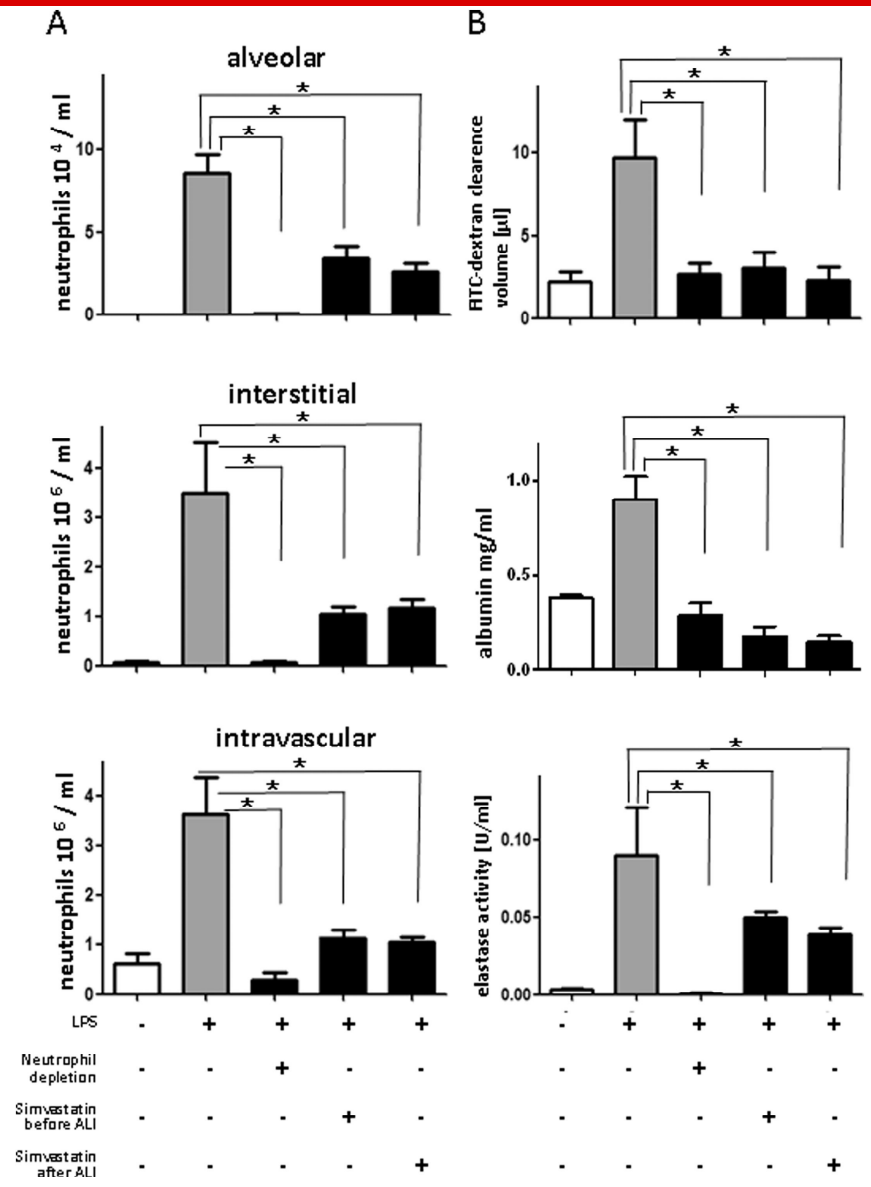
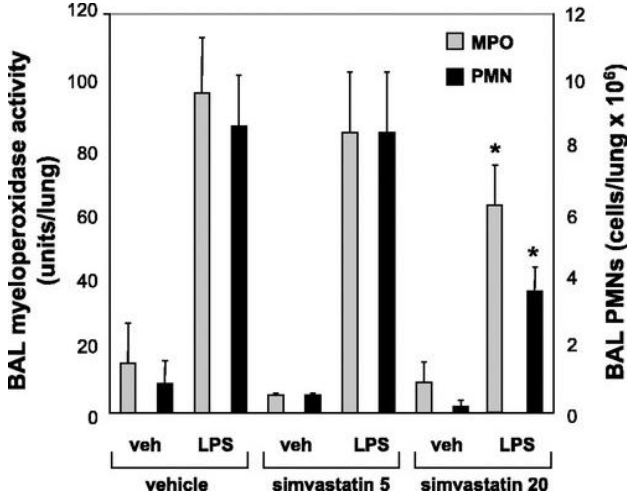
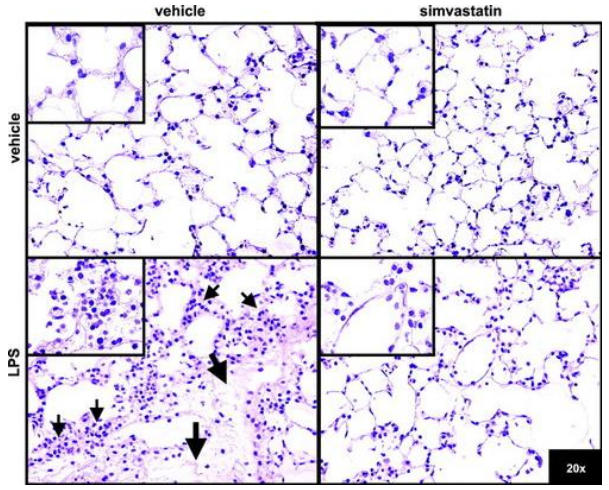
Simvastatin

*

Simvastatin *in vivo*







PLoS One. 2012;7(6):e38917

AJP Lung 2005; 288(6)L1026-L1032

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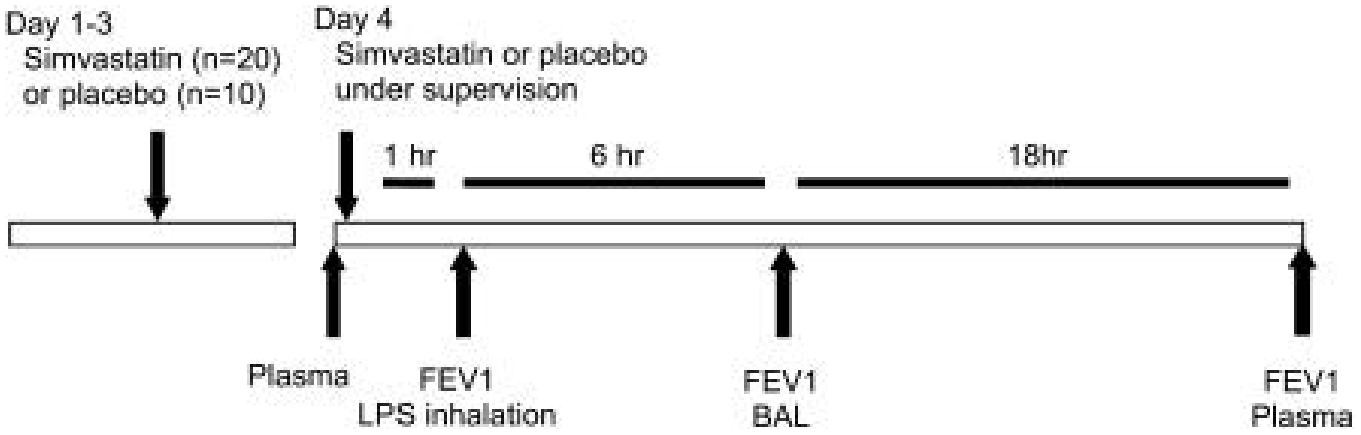
Simvastatin in healthy volunteer model



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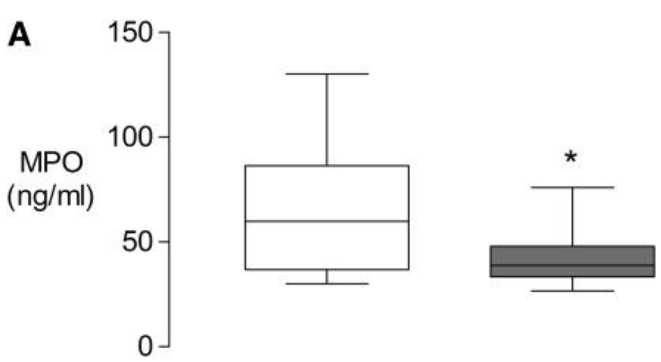
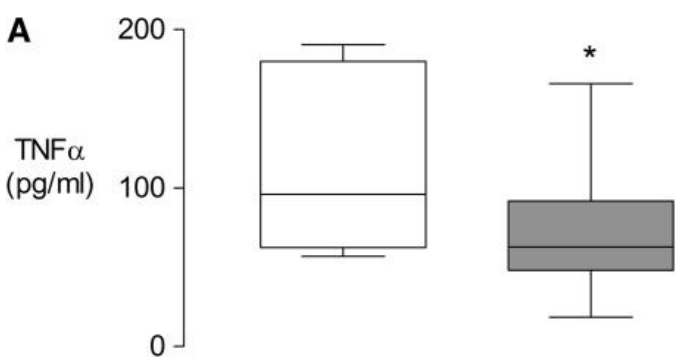
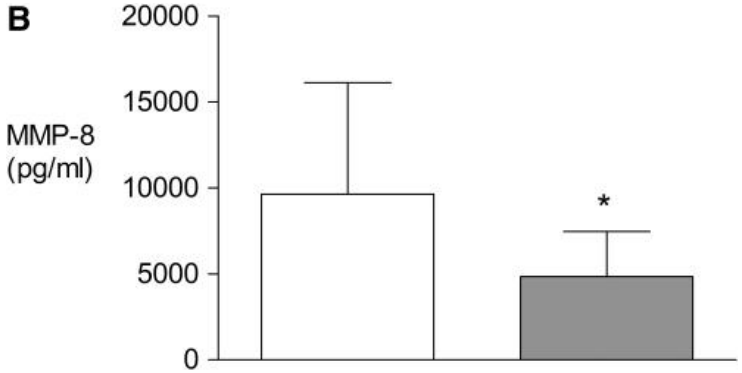
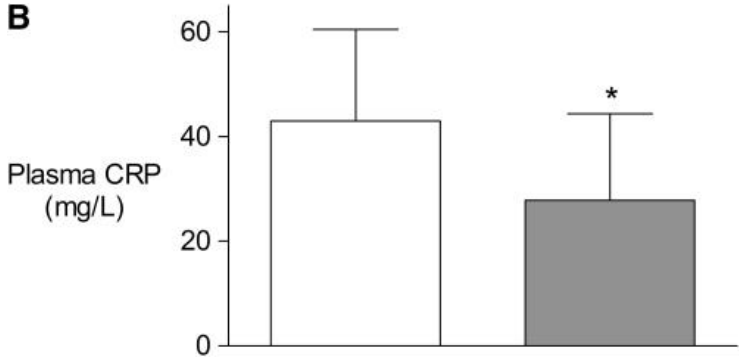
Simvastatin in healthy volunteer model









AJRCCM 2009 179(12) 1107-1114

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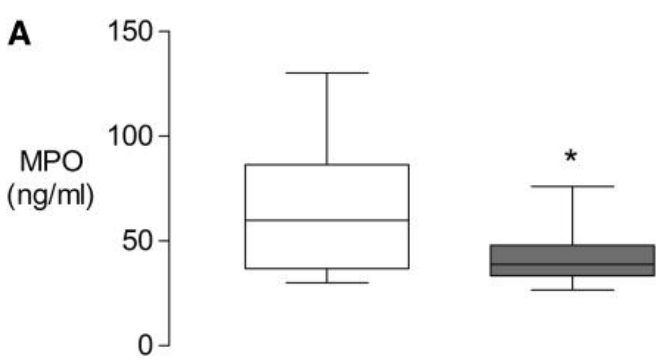
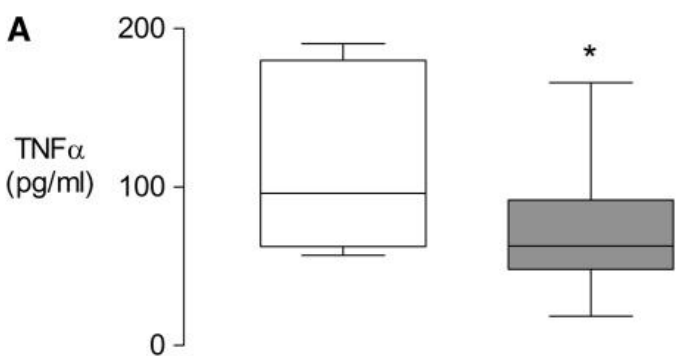
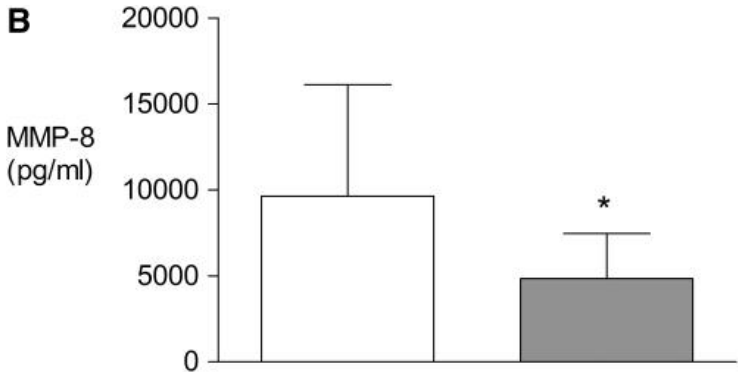
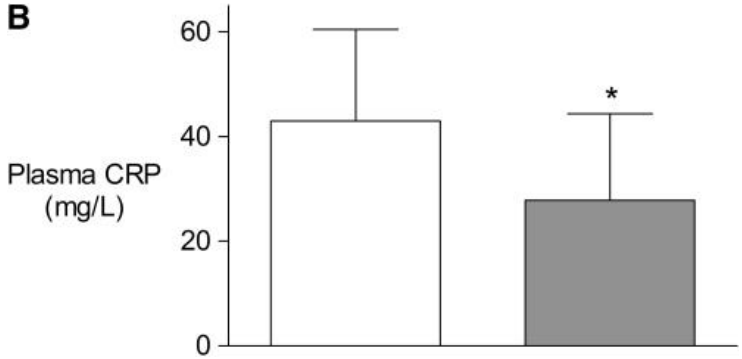
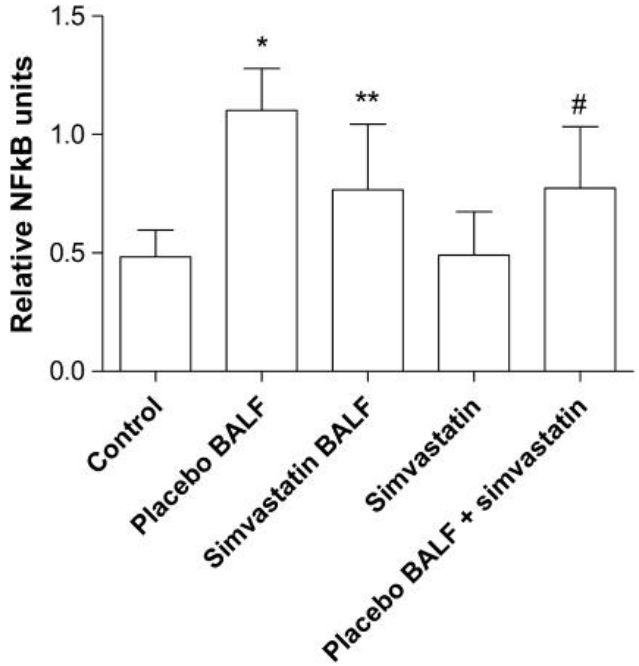
Simvastatin in healthy volunteer model











AJRCCM 2009 179(12) 1107-1114

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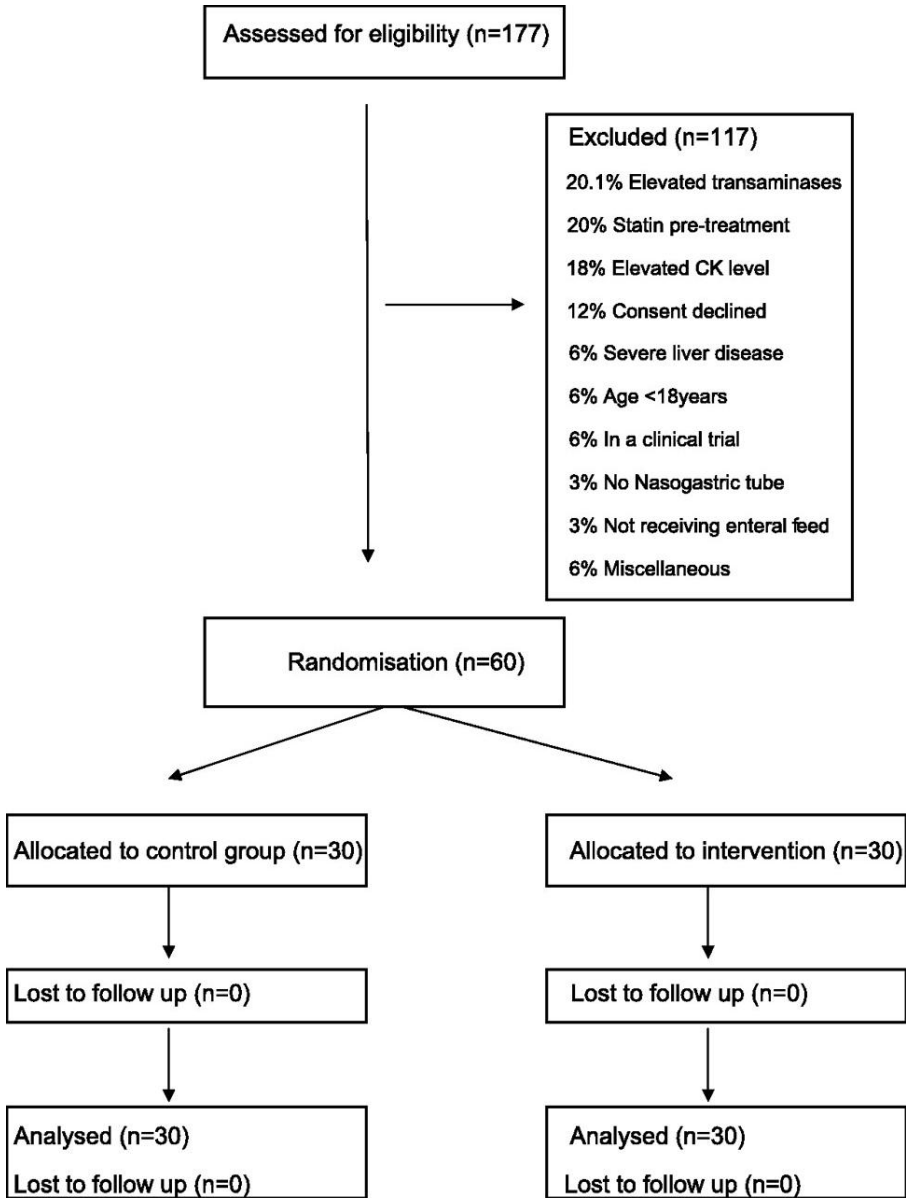
HARP (HMGCo-A Reductase inhibition to Prevent ALI)



AJRCCM 2011 183(5)

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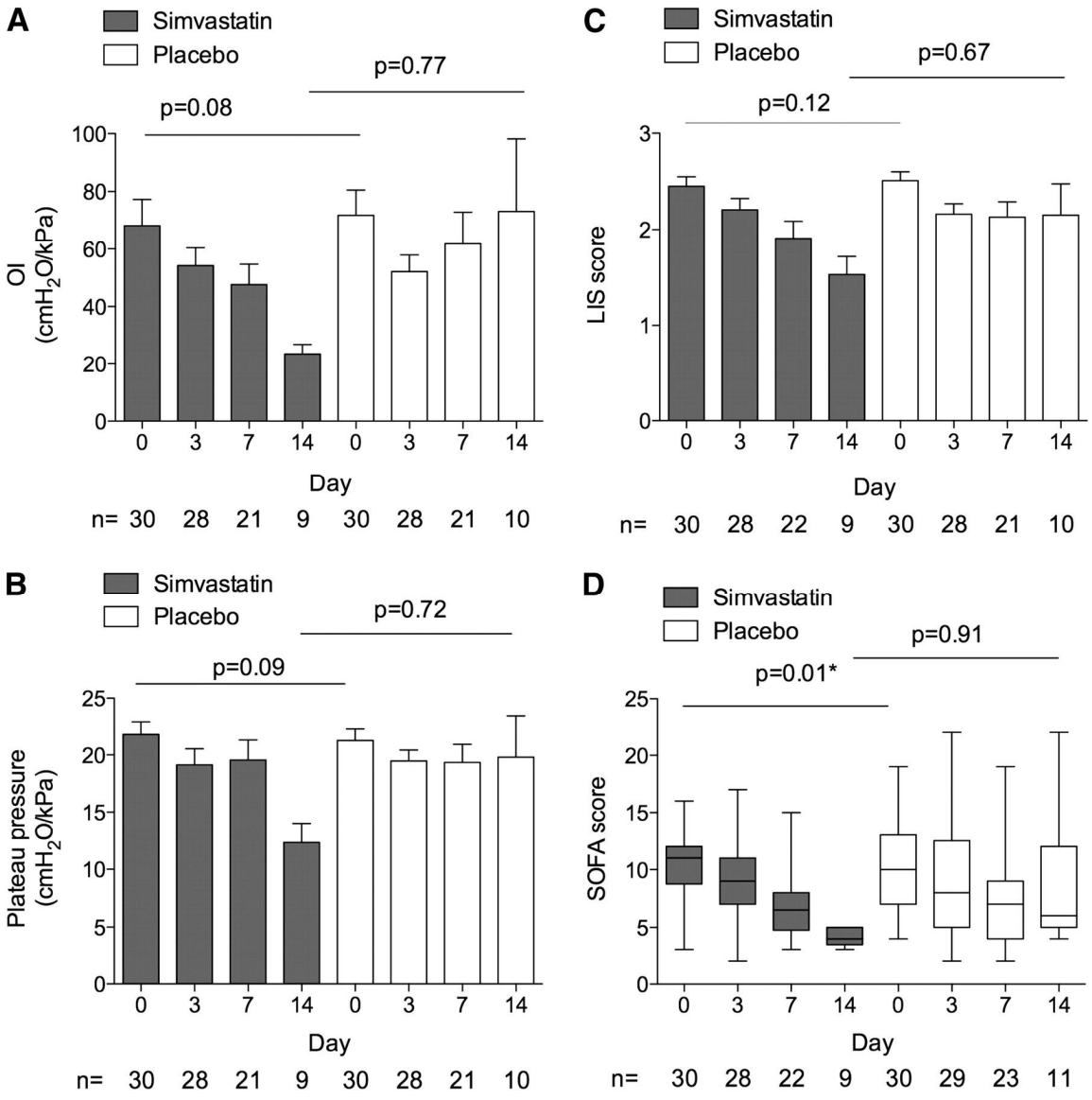
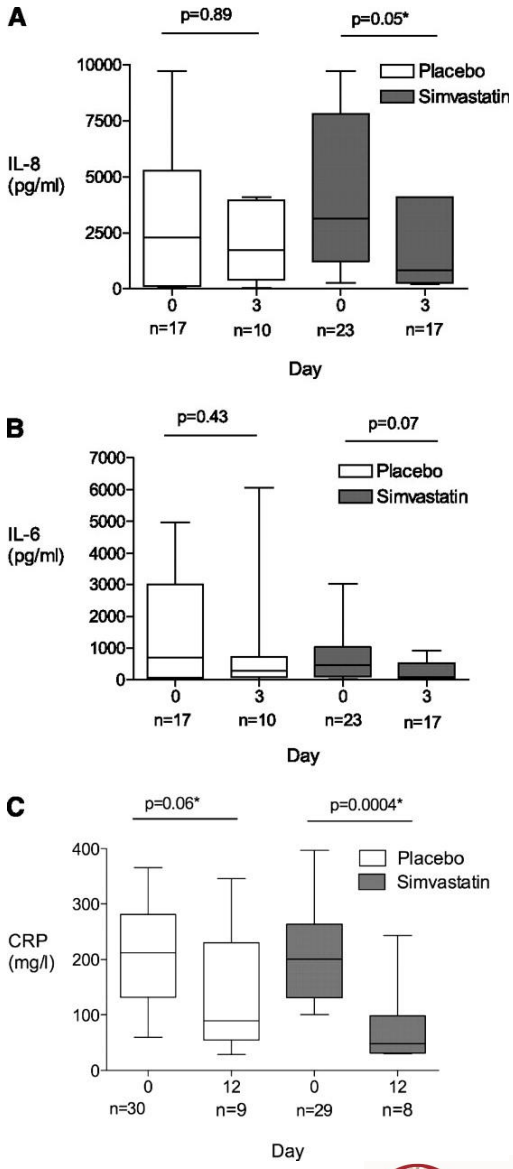
HARP (HMGCo-A Reductase inhibition to Prevent ALI)





AJRCCM 2011 183(5)

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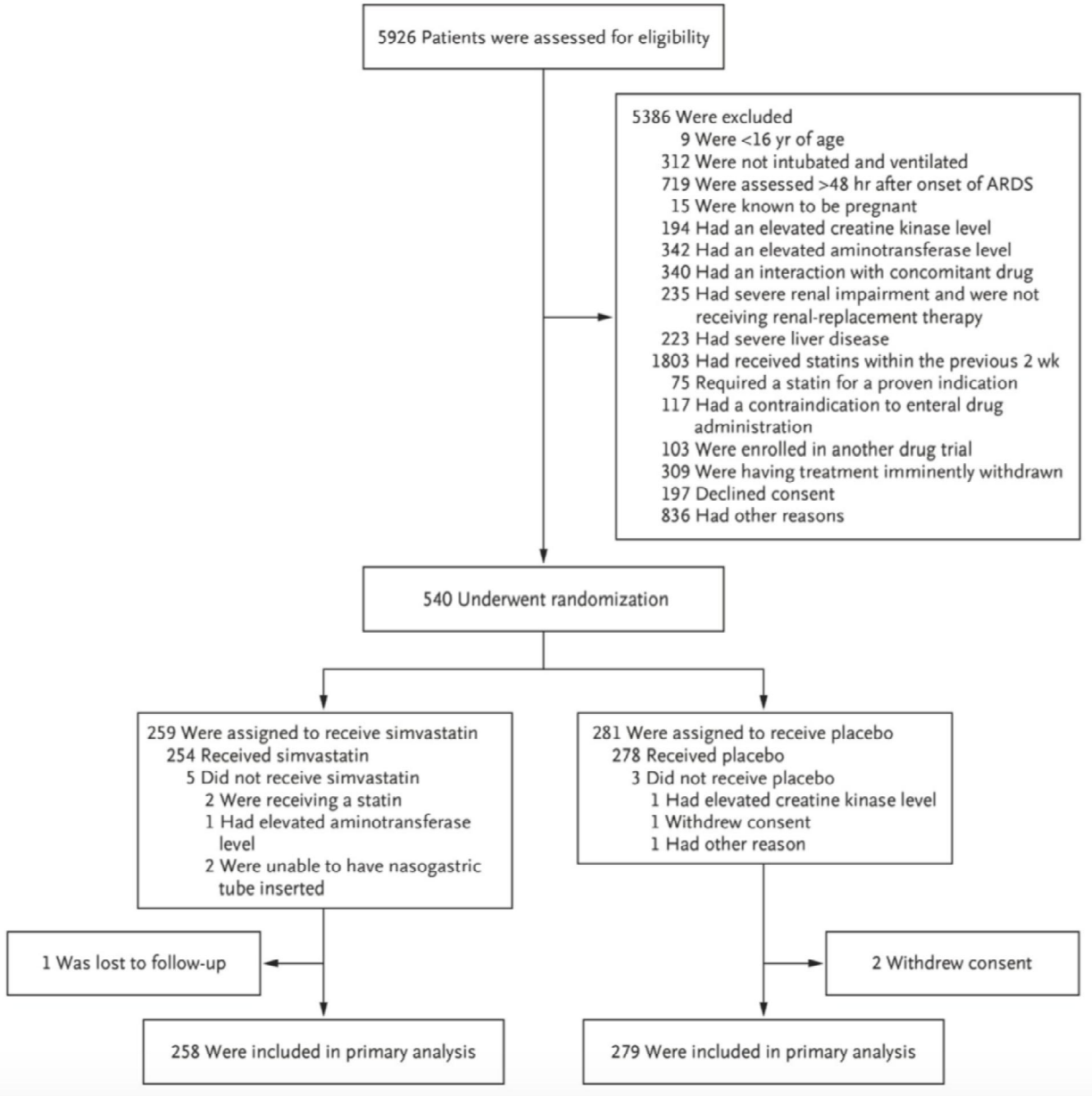
HARP-2



NEJM 2014 371:1695-1703

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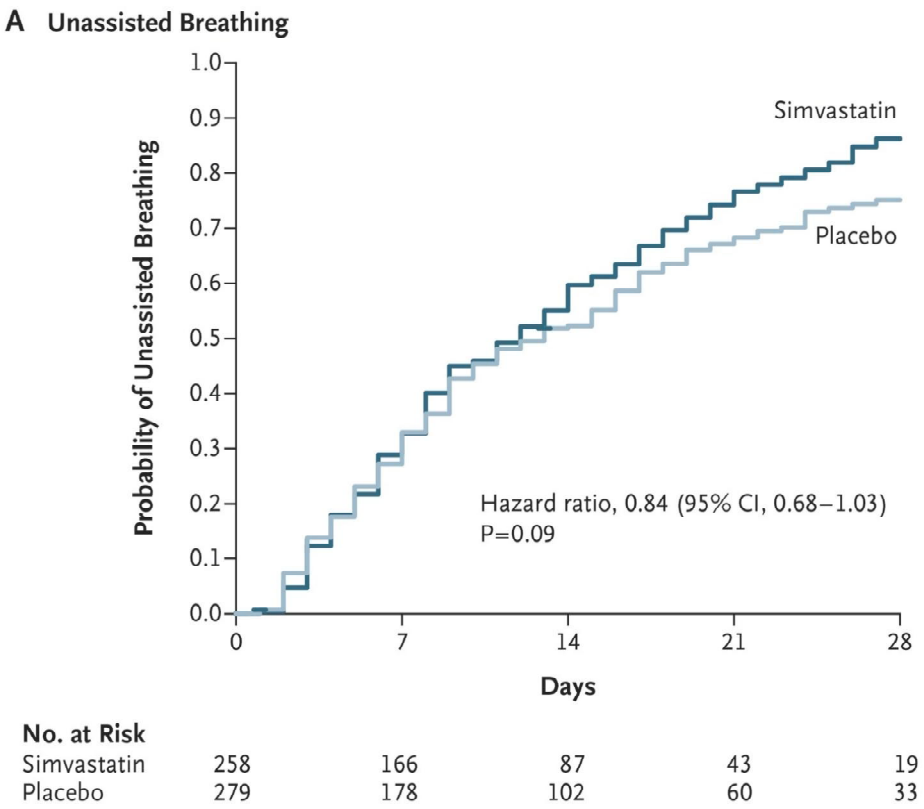
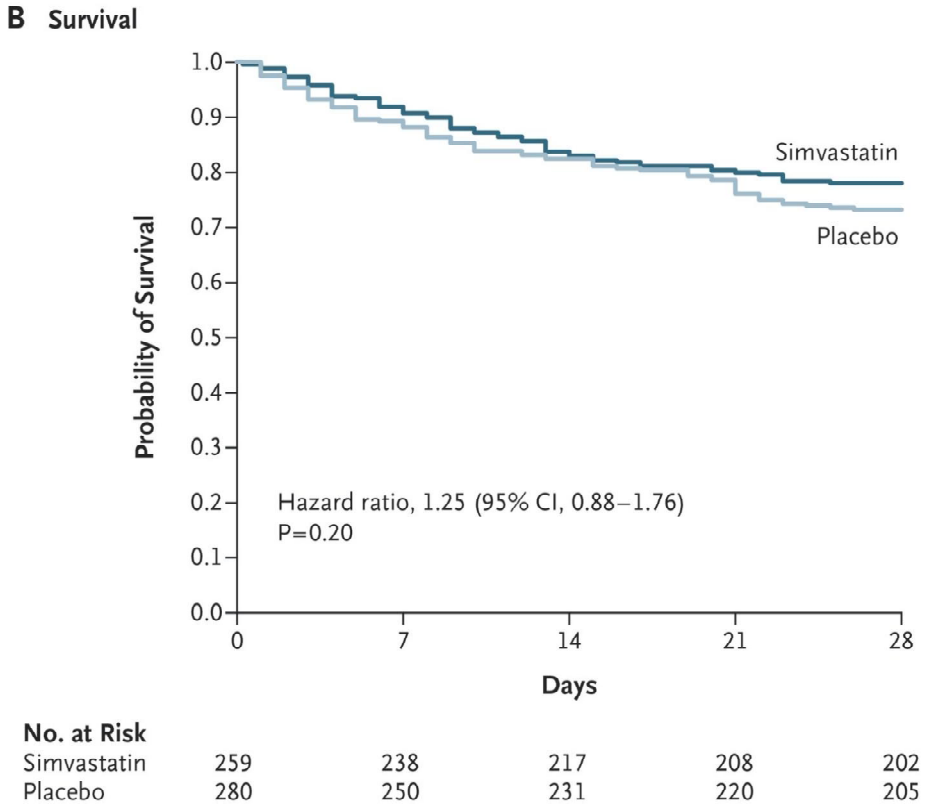
HARP-2





NEJM 2014 371:1695-1703

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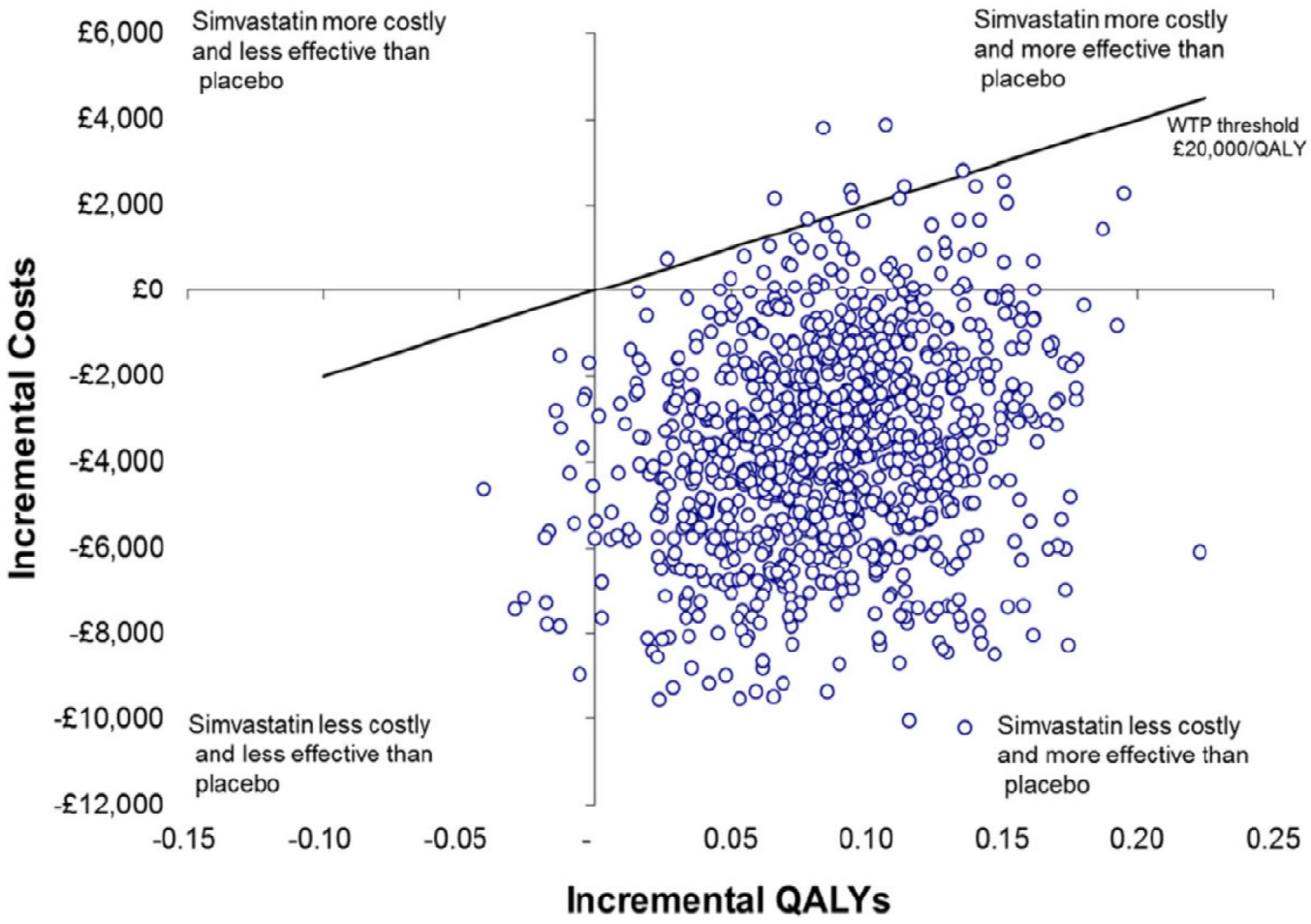
HARP-2 – health economic analysis



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Crit Care 2017 21(1):108

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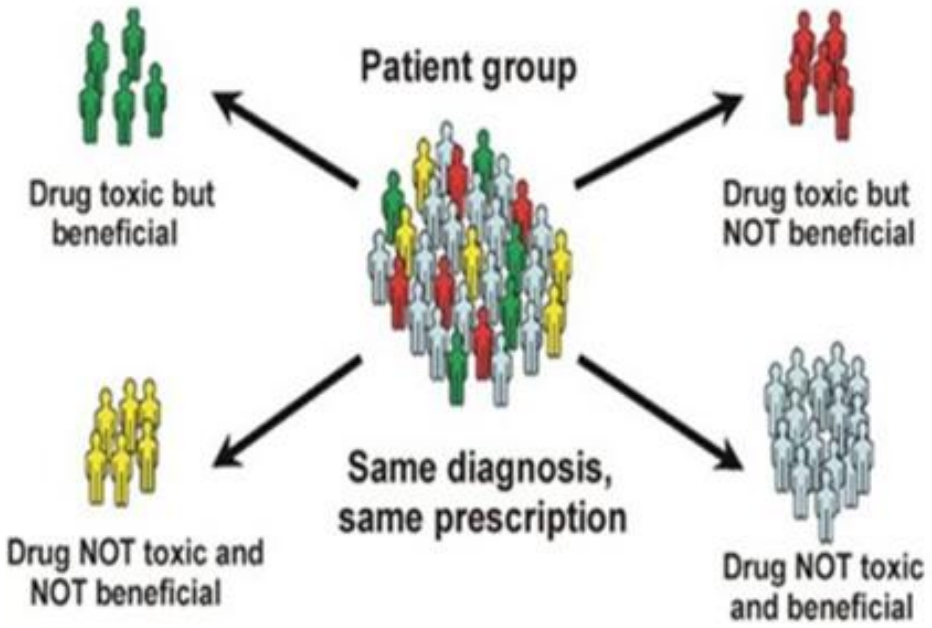
So why do the trials show no significant difference?

So why do the trials show no significant difference?



Patients with ARDS are not all the same

Lancet Respir Med. Author manuscript; available in PMC 2015 Aug 1.
Published in final edited form as:
Lancet Respir Med. 2014 Aug; 2(8): 611–620.
Published online 2014 May 19. doi: 10.1016/S2213-2600(14)70097-9

PMCID: PMC4154544
NIHMSID: NIHMS618882
PMID: 24853585

Latent Class Analysis of ARDS Subphenotypes: Analysis of Data From Two Randomized Controlled Trials

Carolyn S. Calfee, M.D., MAS,[1] Kevin Delucchi, PhD.,[2] Polly E. Parsons, M.D.,[3] B. Taylor Thompson, M.D.,[4,5] Lorraine B. Ware, M.D.,[6] Michael A. Matthay, M.D.,[1,7] and the NHLBI ARDS Network

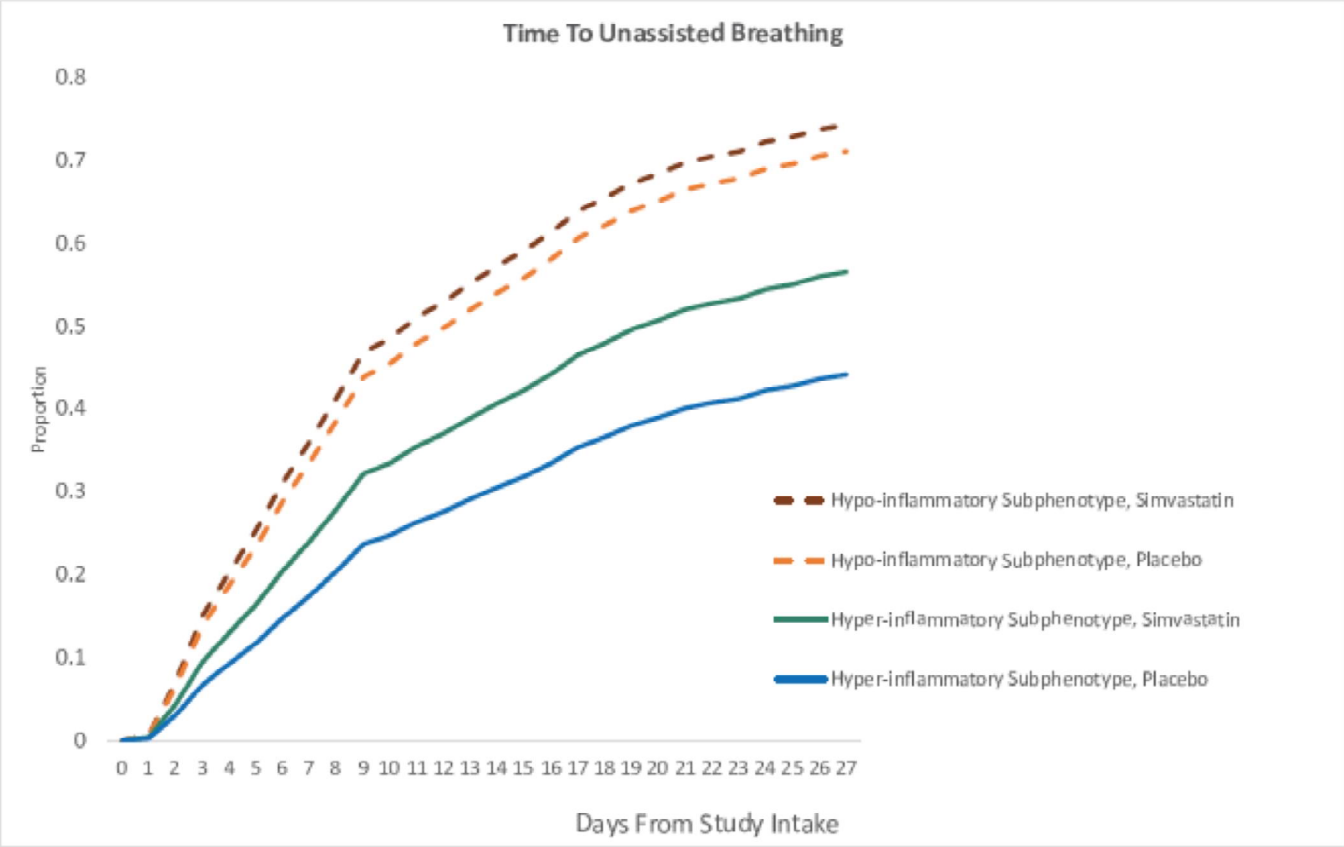
	"Hypoinflammatory" ARDS Class 1	"Hyperinflammatory" ARDS Class 2	p-value
90d Mortality	19%	51%	<0.001
Ventilator Free Days	18.4	8.3	<0.001
Organ Failure Free Days	16.5	8.4	<0.001

Subphenotypes in ARDS

	Class 1 (n=354)	Class 2 (n=186)	p-value
28 Day Mortality, n (%)	59 (17%)	73 (39%)	<0.0001
90 Day Mortality, n (%)	78 (22%)	87 (46%)	<0.0001
Ventilator-Free Days, median (25-75%)	18 (0-23)	2 (0-17)	<0.0001
Non-pulmonary organ failure-free days, median (25-75%)	27 (21-28)	15 (0-25)	<0.0001

Class 1 subphenotype – non-hyperinflammed
Class 2 subphenotype - hyperinflammed

Simvastatin treatment is associated with shorter duration of ventilation in class 2



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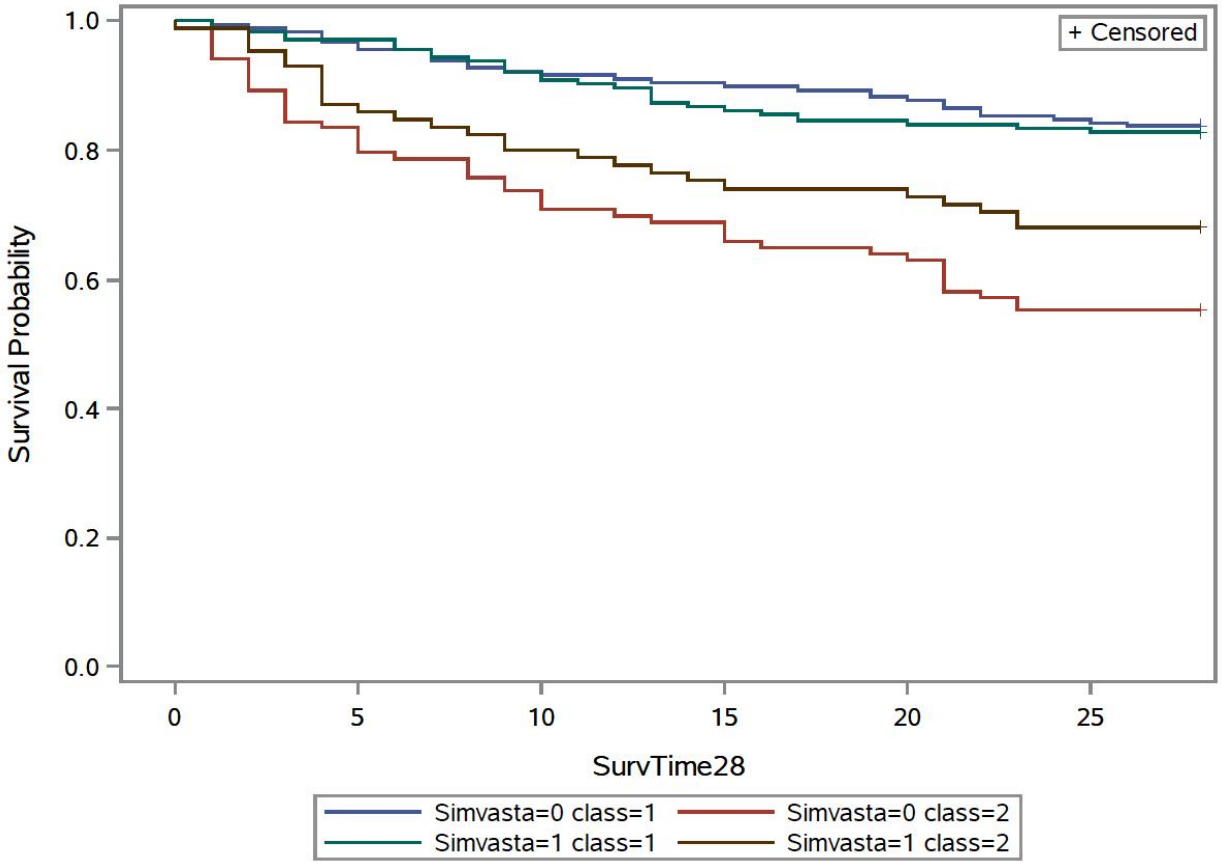
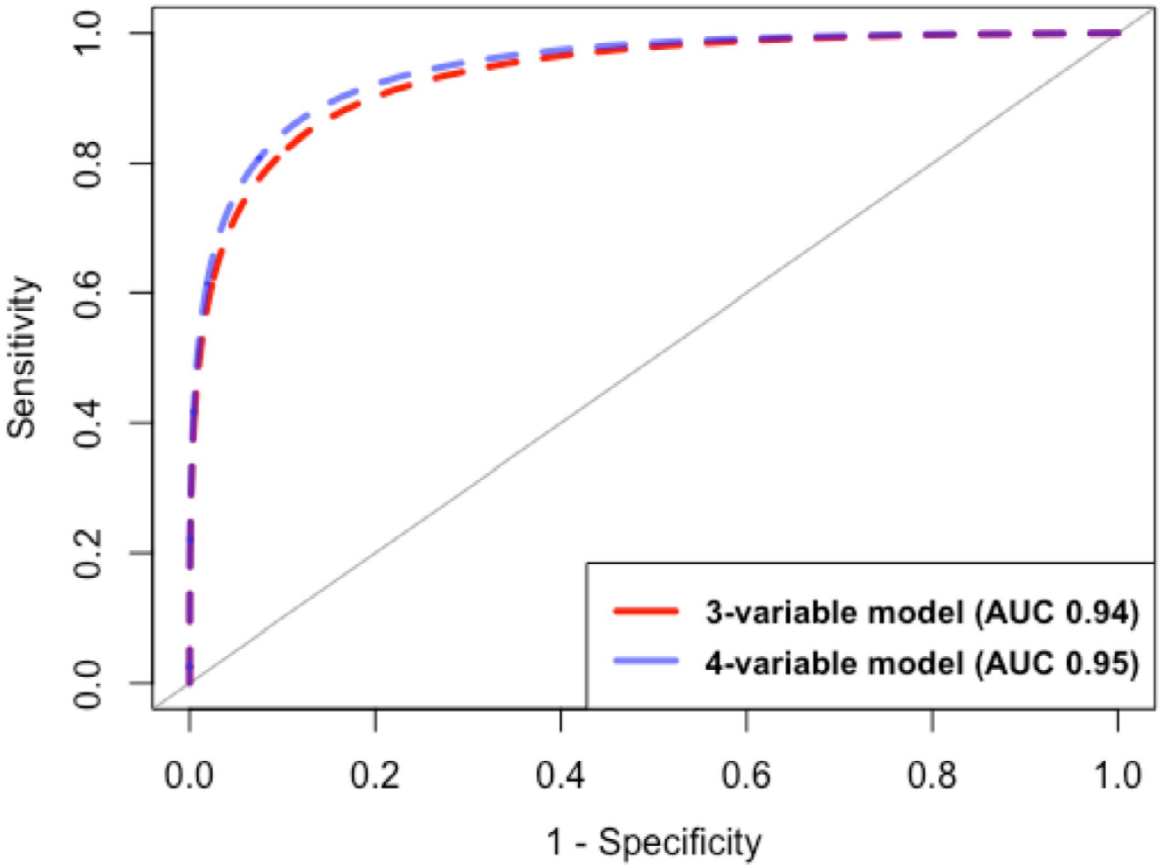
Simvastatin is associated with increased survival in class 2



Limitations

- Post hoc analysis
- Full latent class analysis dependent on a wide range of biomarkers and clinical data
- Can it be simplified?
- Can it be used to prospectively define a hyperinflammed and non-hyperinflammed cohort in ARDS?

Simplification



Parsimonious 4 variable model

- sTNFR1
- IL-6
- HCO_3^-
- vasopressor use

Pratik et al. Lancet Resp. Med. 2019 (in press)

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Prospective identification?

- HCO_3^-
- vasopressor use
- sTNFR1
- IL-6

Prospective identification?

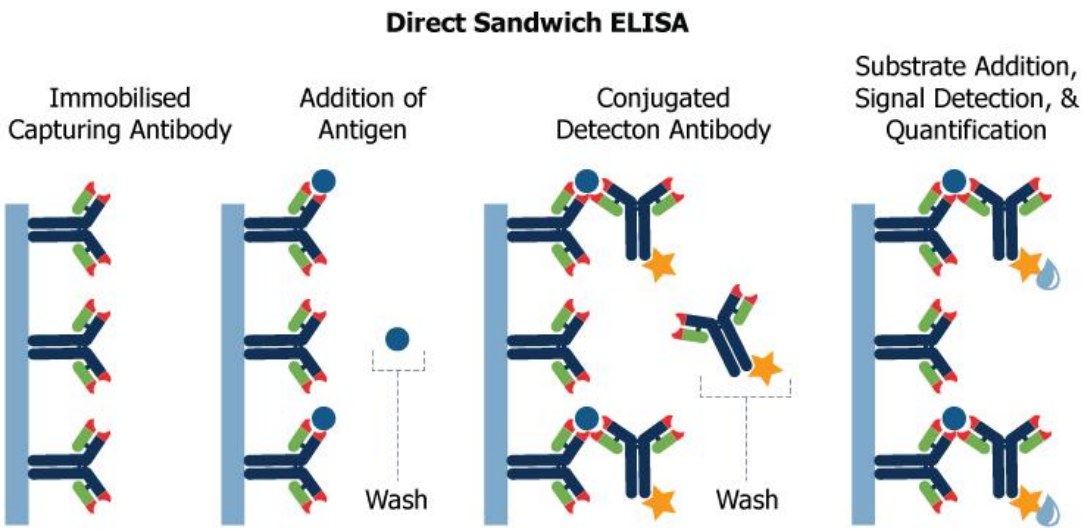
- HCO_3^-
- vasopressor use
- sTNFR1
- IL-6

Prospective identification?

- HCO_3^-
- vasopressor use
- sTNFR1
- IL-6

Currently measured by immunoassay

ELISA



Issues

- Time (overnight incubation and 8 hours)
- Accuracy / what it measures
- Costs (1 plate = 40 samples)
- Laboratory trained personnel

Faster solutions

- Automated and faster results
- Designed for multiple samples
- Laboratory grade environment
- Skilled personnel
- Costs

Faster solutions

- Automated and faster results
- Designed for multiple samples
- Laboratory grade environment
- Skilled personnel
- Costs

STUDY
PHIND
Phenotypes IN ARDS

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PHIND

Collaboration with Randox

Develop point of care (POC) assay to measure IL-6 and sTNFR1 in plasma

2.1 System Components

The Evidence MultiSTAT system comprises of six main components:

- Touch Screen User Interface
- Reagent Cartridge Loading Bay
- Computer (internal)
- Robotics (internal)
- Incubator (internal)
- CCD Imaging Unit (internal)

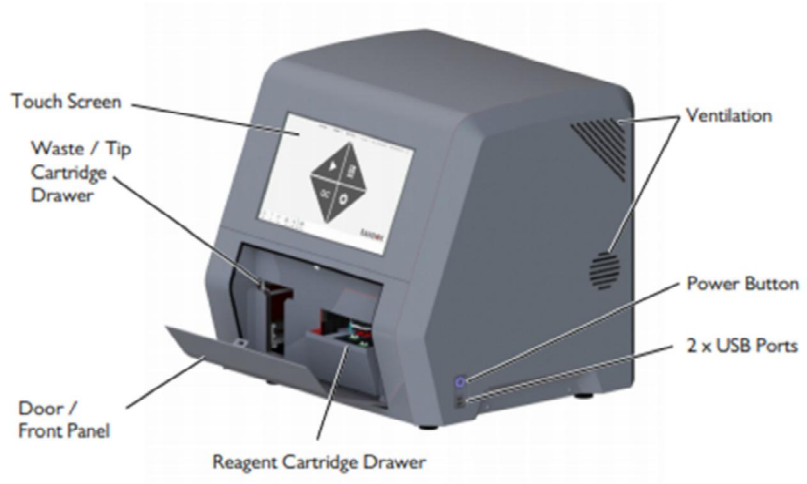

Figure 2-1 Evidence MultiSTAT Analyser

STUDY PHIND Phenotypes IN ARDS

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PHIND

- Multi-centre, prospective cohort study (n=480)
- Use assay, along with serum HCO_3^- and requirement for vasopressors, to assign subphenotype
- Assess clinical outcomes in prospectively defined sub-phenotypes (28 day mortality)
- End of study compare assignation using POC assay against traditional lab ELISAs

STUDY PHIND Phenotypes IN ARDS

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PHIND – expected outcomes

- Prospectively confirm existence of the subphenotypes in ARDS
- Confirm if prospective identification is possible using POC assay and parsimonious model
- Proceed to Stratified-HARP: randomize patients in the hyperinflammed group to simvastatin vs placebo
- Explore potential for other precision studies in both phenotypes
- Further mechanistic work to understand endotypes

STUDY PHIND Phenotypes IN ARDS

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PHIND – progress

- Completing final validation of POC assay on existing samples

- Installation of POC analysers in 20 ICUs beginning

STUDY PHIND Phenotypes IN ARDS

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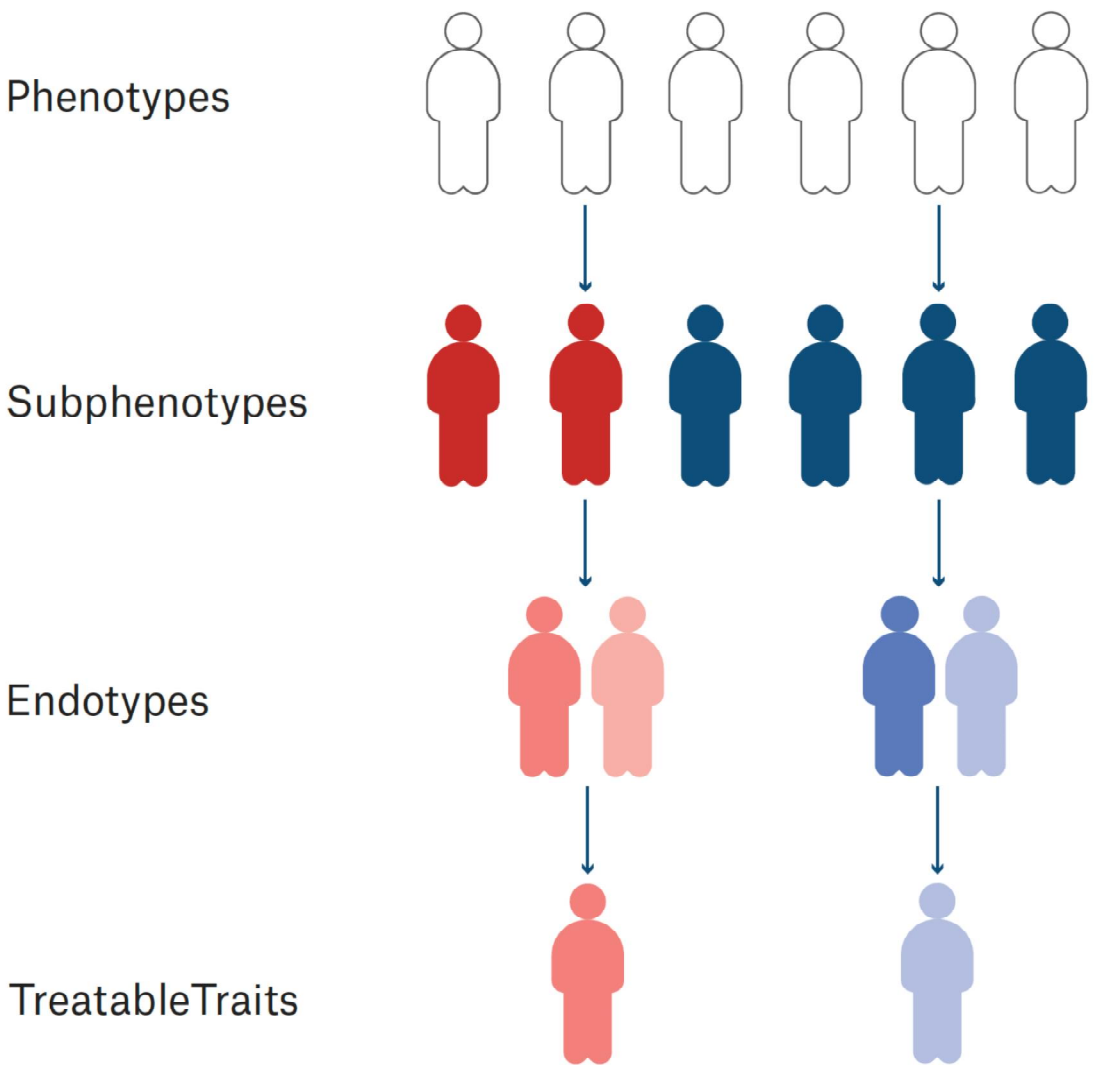
Can subphenotypes help us identify treatable traits?



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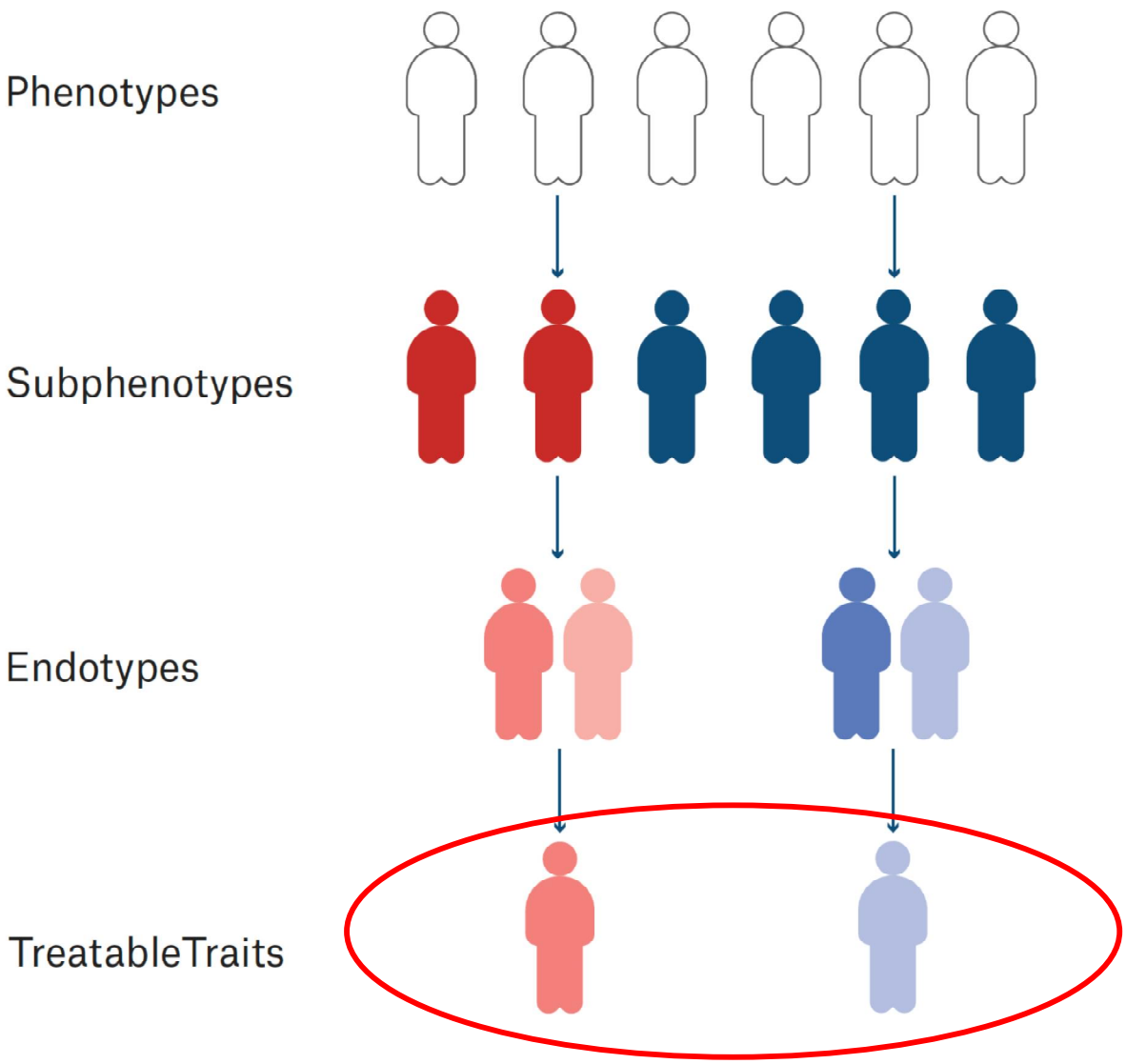
Can subphenotypes help us identify treatable traits?



Enrich clinical trials with population most likely to benefit from specific intervention

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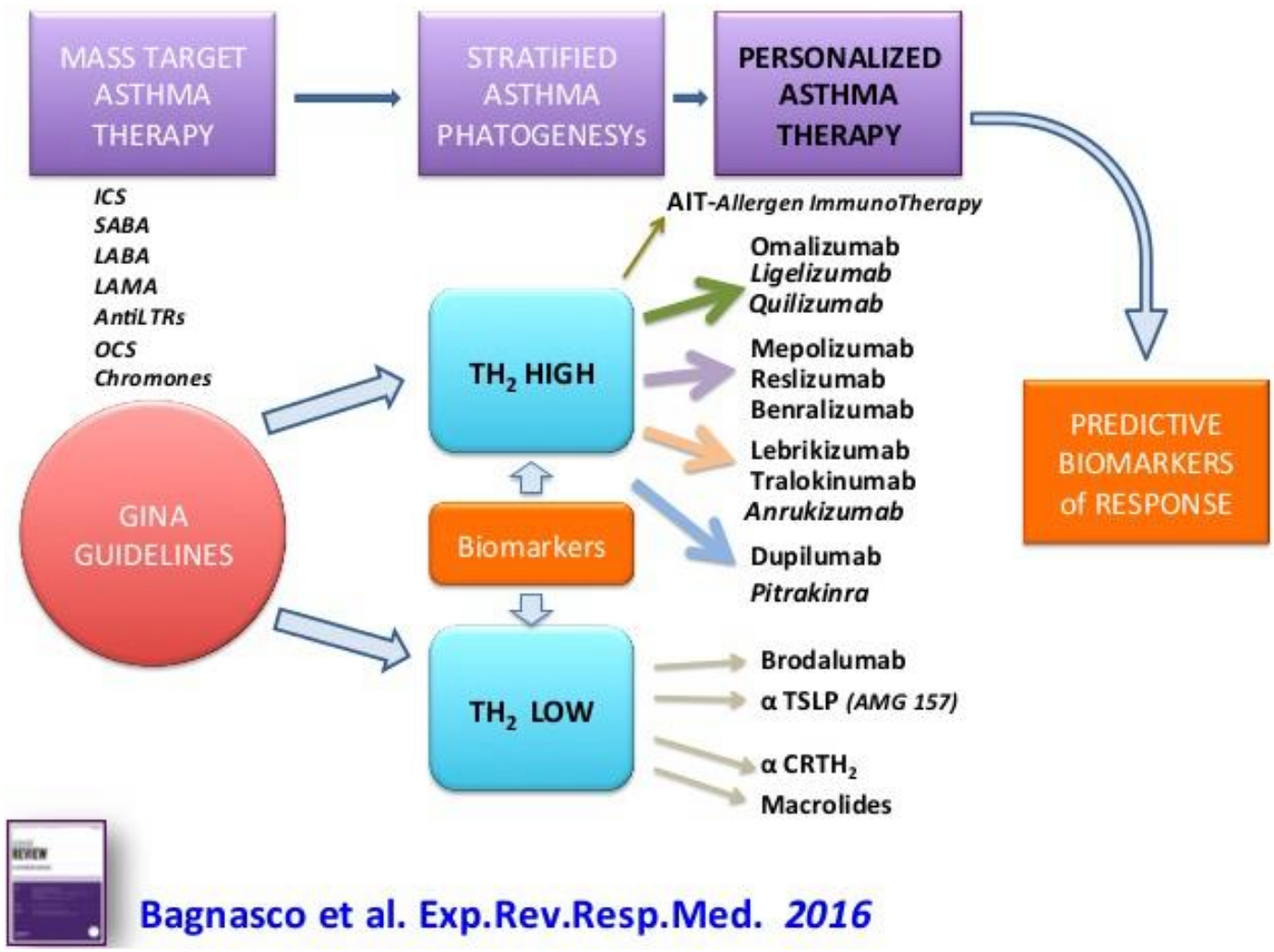
An accepted strategy in other disciplines



An accepted strategy in multiple disciplines

Challenges

- Defining pre-clinical models and human models which reflect subphenotypes in ARDS
- Determining if models more useful in testing novel therapeutic agents in specific subphenotypes
- Mechanistic studies to understand biology of given endotypes to predict targets for intervention

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Acknowledgments

Danny McAuley
Murali Shyamsundar
ALI lab and clinical research group
SNODs
NI CRN nurses
Carolyn Calfee
Michael Matthay
Kevin Delucchi
Pratik Sinha

RANDOX

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