The Latest Evidence in Critical Care

Kyiv 2016

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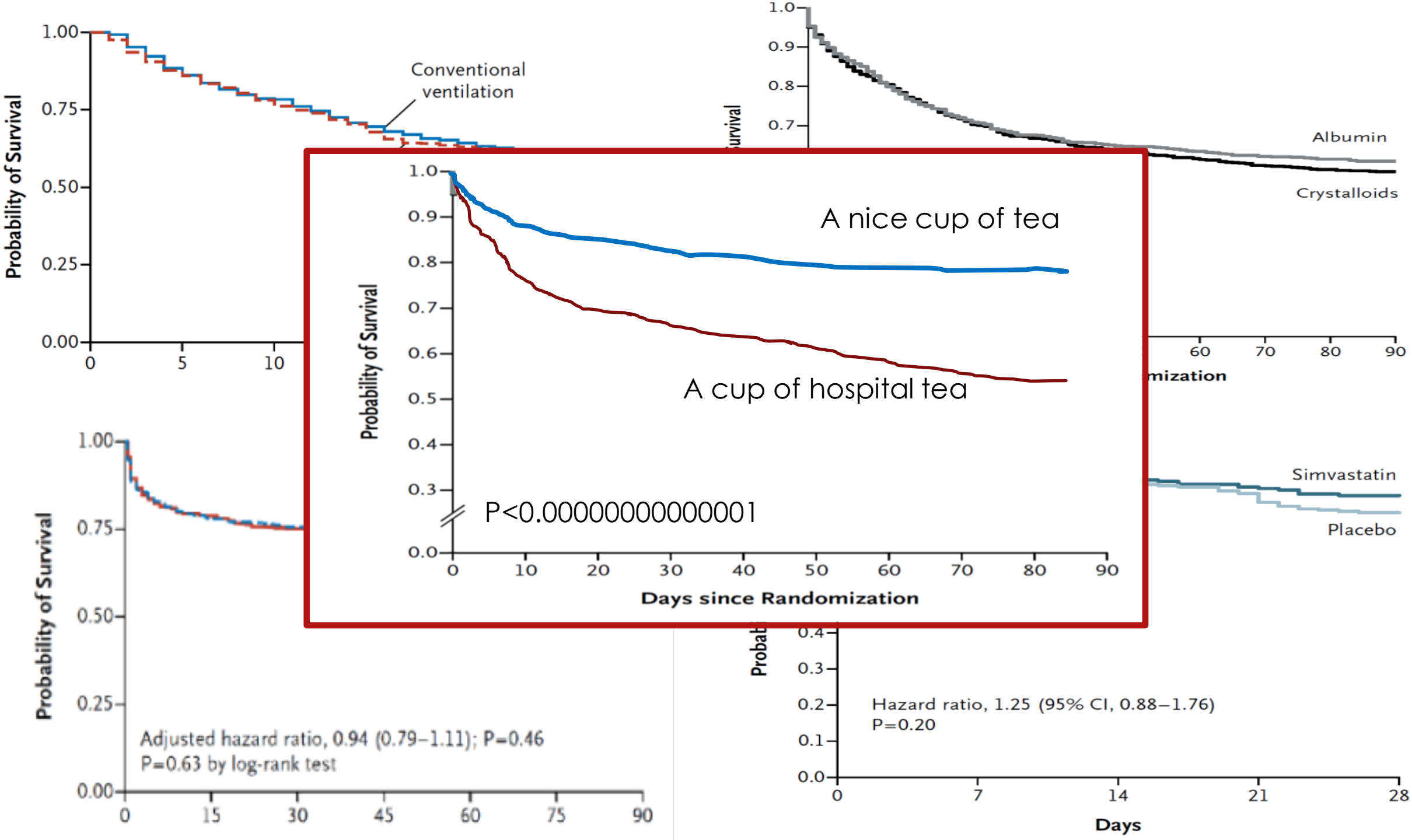
London, UK

This depends a little on your point of view…

Glass half full

Glass half empty


ORIGINAL ARTICLE
Albumin Replacement in Patients with Severe Sepsis or Septic Shock
Pietro Caironi, M.D., Gianni Tognoni, M.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., and Luciano Gattinoni, M.D., for the A
NEW ENGLAND JOURNAL of MEDICINE
JANUARY 10, 2008
ORIGINAL ARTICLE
Trial of the Route of Early Nutritional Support in Critically Ill Adults
Sheila E. Harvey, Ph.D., Francesca Parrott, M.Sci., David A. Harrison, Ph.D., Danielle E. Bear, M.Res., Ella Segaran, M.Sc., Richard Beale, M.B., B.S., Geoff Bellingan, M.D., Richard Leonard, M.B., B.Chir., Michael G. Mythen, M.D., and Kathryn M. Rowan, Ph.D., for the CALORIES Trial Investigators*
Research
Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Effects of Fluid Resuscitation With Colloids vs Crystalloids
ORIGINAL ARTICLE
Trial of Early, Goal-Directed Resuscitation for Septic Shock
Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*
ORIGINAL ARTICLE
Resuscitation for Patients with Early Septic Shock
The ANZICS Clinical Trials Group*
High vers
The NEW ENGLAND JOURNAL of MEDICINE
VOL. 370


Probability of Survival
1.00
0.75
0.50
0.25
0.00
0
5
10
Conventional ventilation
Albumin
Crystalloids
60
70
80
90
Simvastatin
Placebo
Adjusted hazard ratio, 0.94 (0.79–1.11); P=0.46
P=0.63 by log-rank test
15
30
45
75
Hazard ratio, 1.25 (95% CI, 0.88–1.76)
P=0.20
7
14
21
28
Days
A nice cup of tea
A cup of hospital tea
P<0.00000000000001
Days since Randomization

So what hope for the future?

- Truly believe there is hope
- Intelligent Luck
- Intelligent design

Intelligent Luck

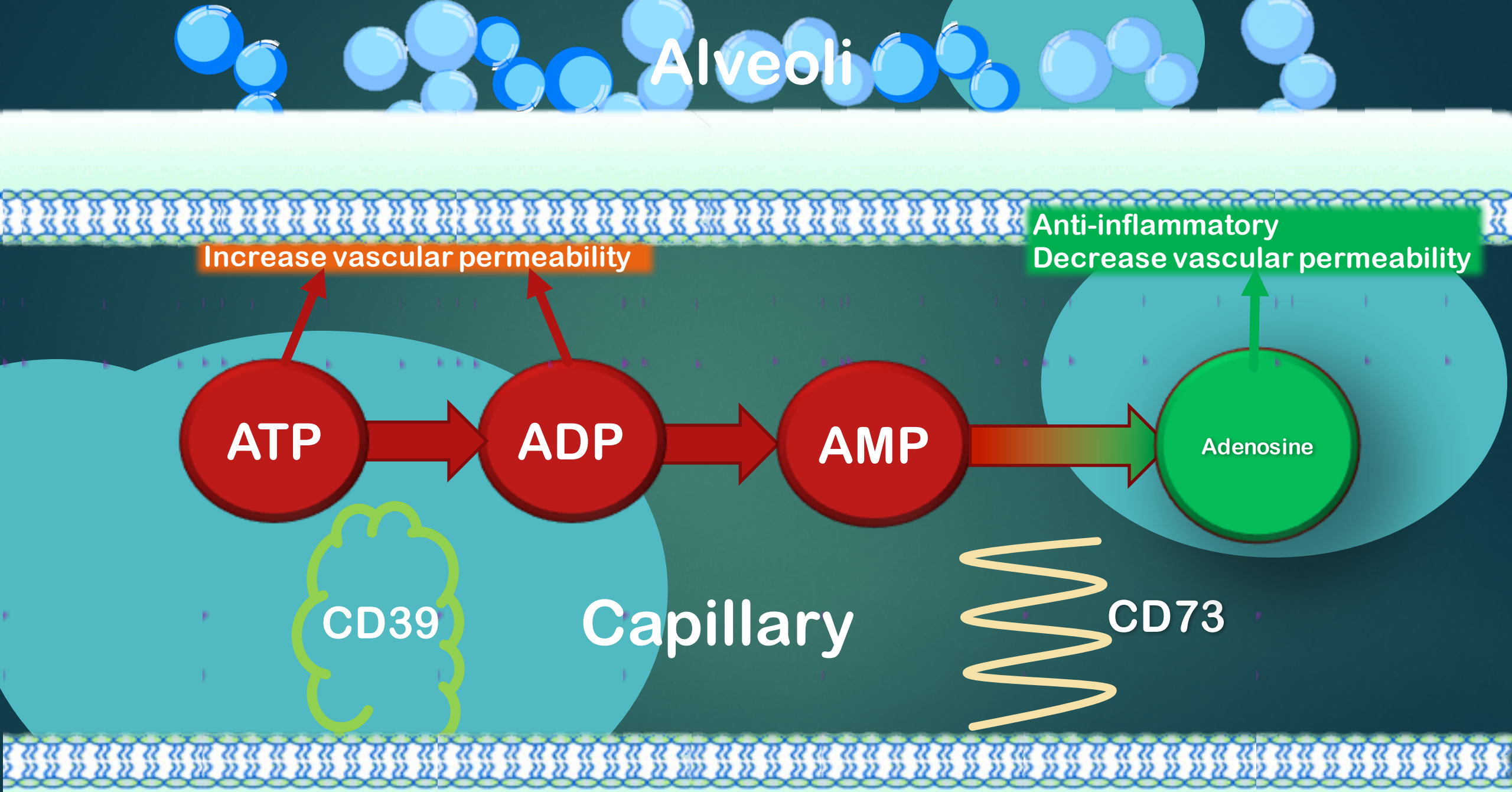
- We carry on as we are but hit on an absolutely core mechanism
- Advantages
  - We don’t have to admit we have been wrong
  - We do not need to redefine everything
  - Will keep the interventional ‘trial industry’ going
- Disadvantages
  - Those mechanisms are not clear
  - Luck usually takes time, it is expensive in the long run
  - Has yet to work for my lottery ticket

Intelligent design

- Start to re-define patient populations with more sensitive and specific markers (like myocardial infarction)
- Disadvantages
  - Have to start again
  - Have to admit we have been wrong
  - Need to identify and validate markers
- Advantages
  - Better understand our patients
  - Reduced heterogeneity
  - Increase chance of intervention actually working

Lets look at some luck

- ARDS, crudely characterised by capillary leak and fibrosis
- A highly heterogenous condition fraught with difficulty
  - Statins
  - HFOV
  - Activated protein C
  - B-agonists
  - Surfactant
  - Inhaled nitric oxide
  - Steroids
- Lots of postulated mechanisms but check this…



Extracellular purines (adenosine) regulate vascular homeostasis

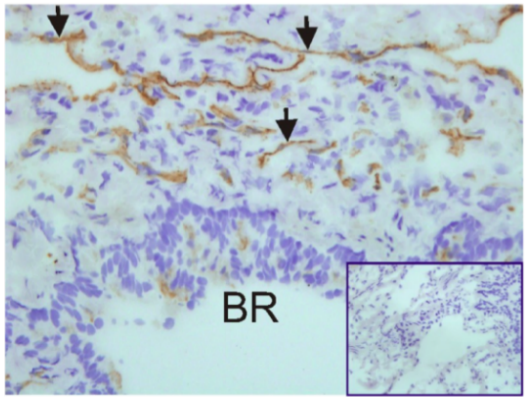
Can we stop the capillary leak?

- CD73 is lost in inflammation and adenosine used up by white cells
- Interferon Beta up regulates CD73
- IFN-β (used in MS) may be of potential in ARDS
- A small Finnish Biotech (Faron) and some academics got together to figure it out…

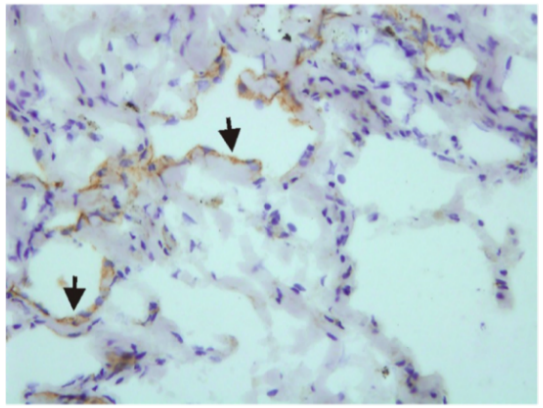
FARON
Pharmaceuticals

CD73 is found in human lung and can be induced

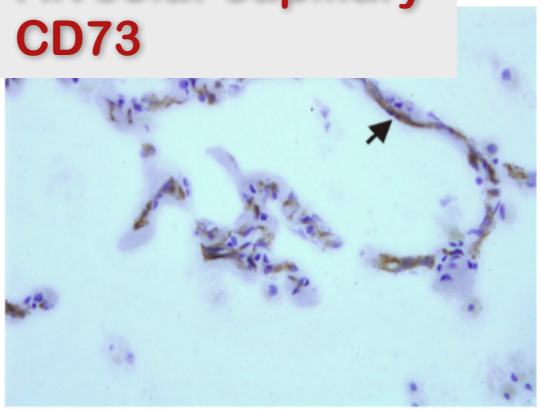
Peribronchiolar CD73



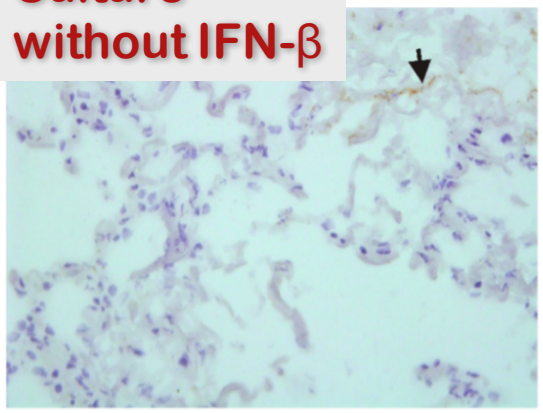
Culture with IFN-β



Alveolar capillary CD73

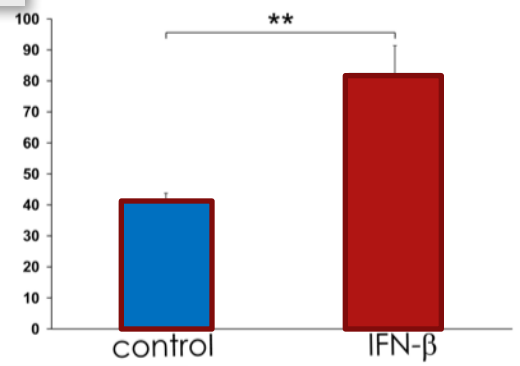


Culture without IFN-β

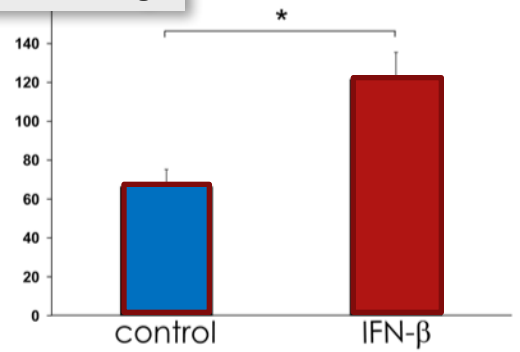


CD73 activity decreases permeability

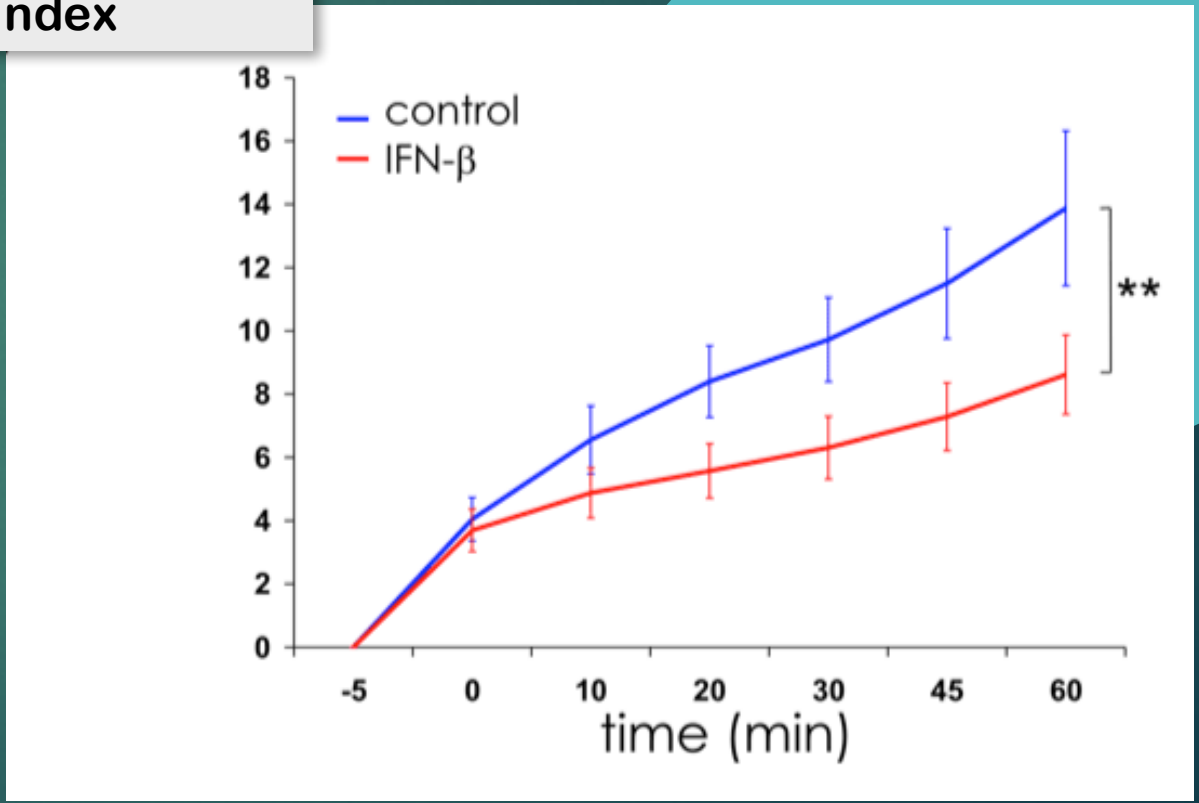
CD73



CD73 activity



Permeability Index



Now for patients

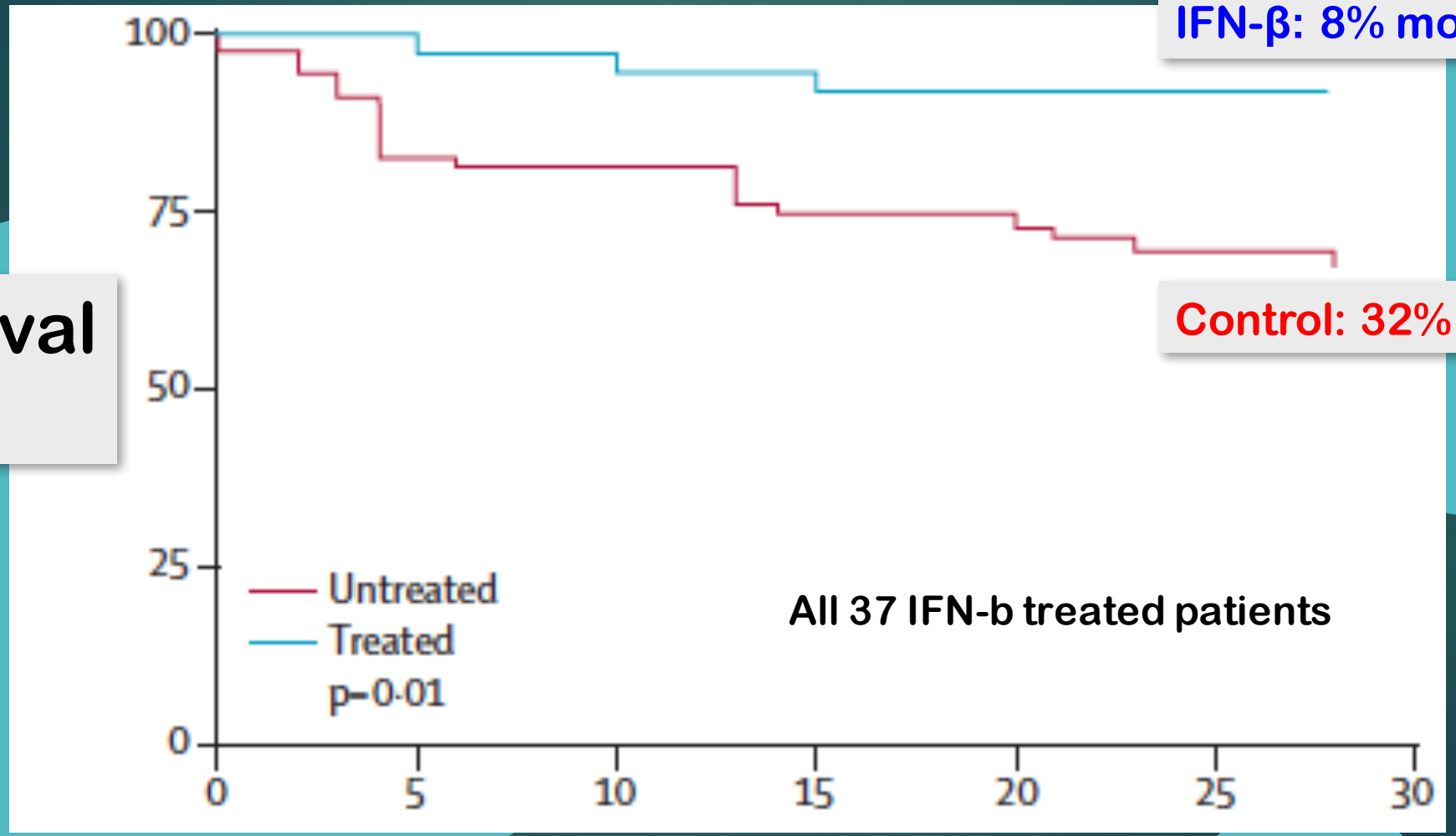
- Open label, dose ascending, safety and tolerability study
- Dose from 0.44µg to 22µg
- 37 patients treated & compared to 59 matched controls
- Well tolerated below 22µg, 10µg considered optimal.

Lancet Respir Med 2014

…and in ARDS patients

IFN-β: 8% mortality

Control: 32% mortality



Interestingly….

- At the end of the results section
  - 16% of IFN-β patients required RRT later on
  - 31% of control patients required RRT later
  - But the authors are interested in ARDS not kidneys

Very exciting!

- Results enabled funding for a phase III
- INTEREST study
- Over 50 centres around Europe
- 300 patients with moderate/severe ARDS
- Aim to reduce mortality and improve ventilator free days
- Meanwhile

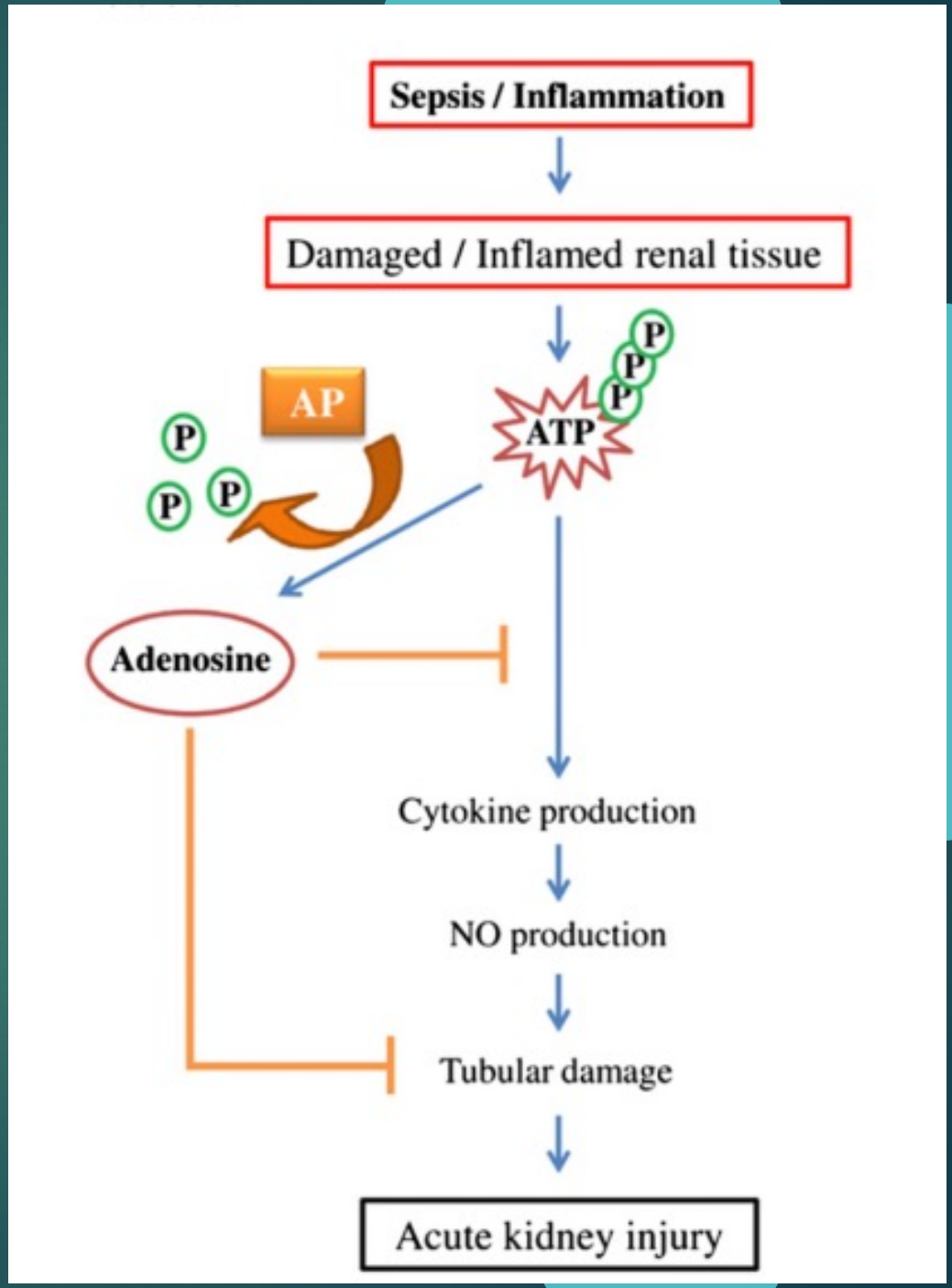
Interestingly….

- At the end of the results section
  - 17% of control and IFN-β patients on renal replacement therapy at enrolment
  - 16% of IFN- β patients required RRT later on
  - 31% of control patients required RRT later
  - No statistical significance
- Meanwhile….

in a galaxy far, far away (Netherlands)

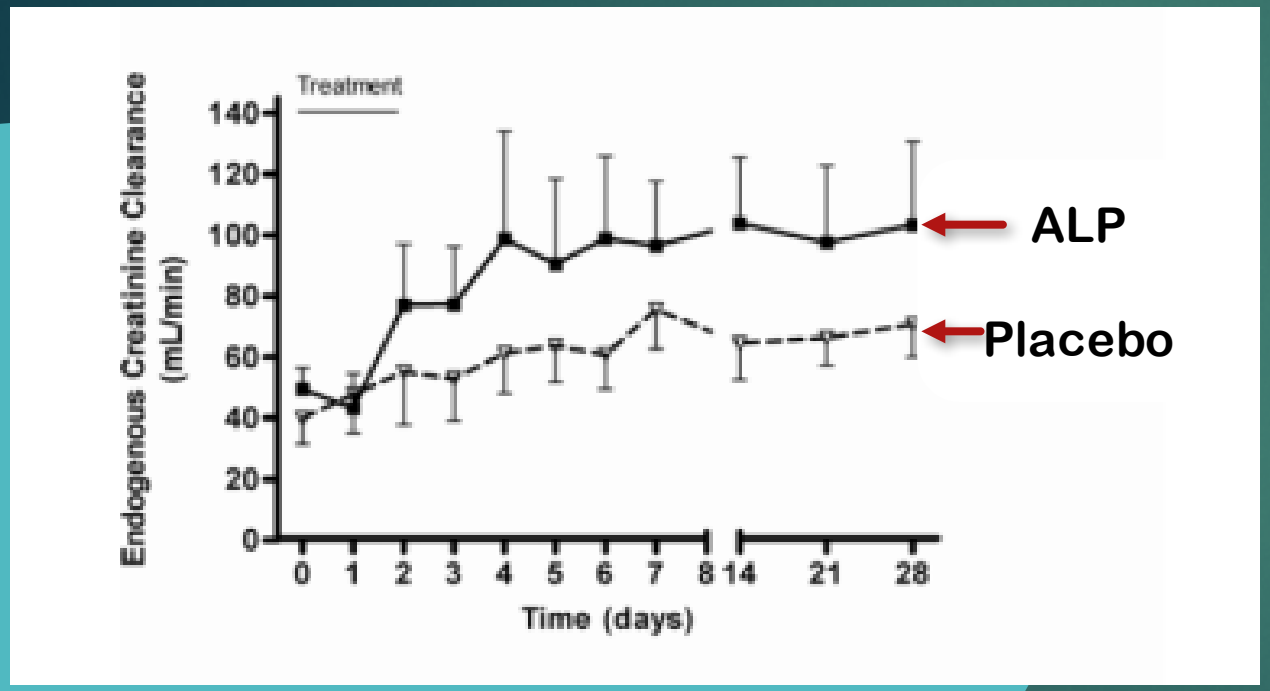
- A small biotech (AM-Pharma) and a group of nephrologists have an interest in sepsis induced AKI
- They noted alkaline phosphatase is depleted in the septic kidney
  - Its not there just for biochemistry labs to measure!
- They made a human recombinant ALP to replace it
- But how does it work?

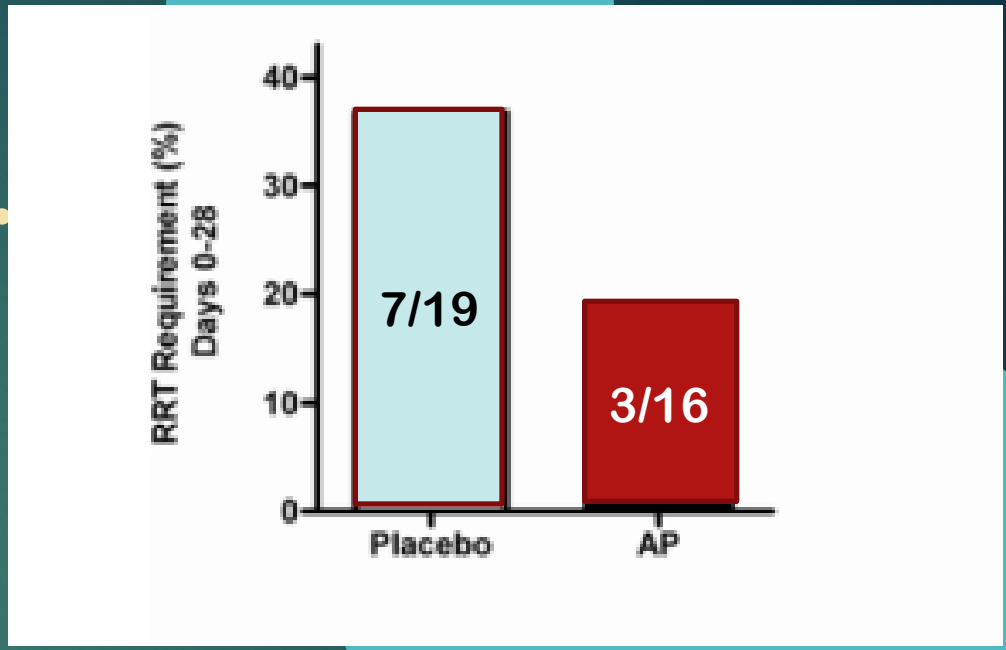
Seem familiar?

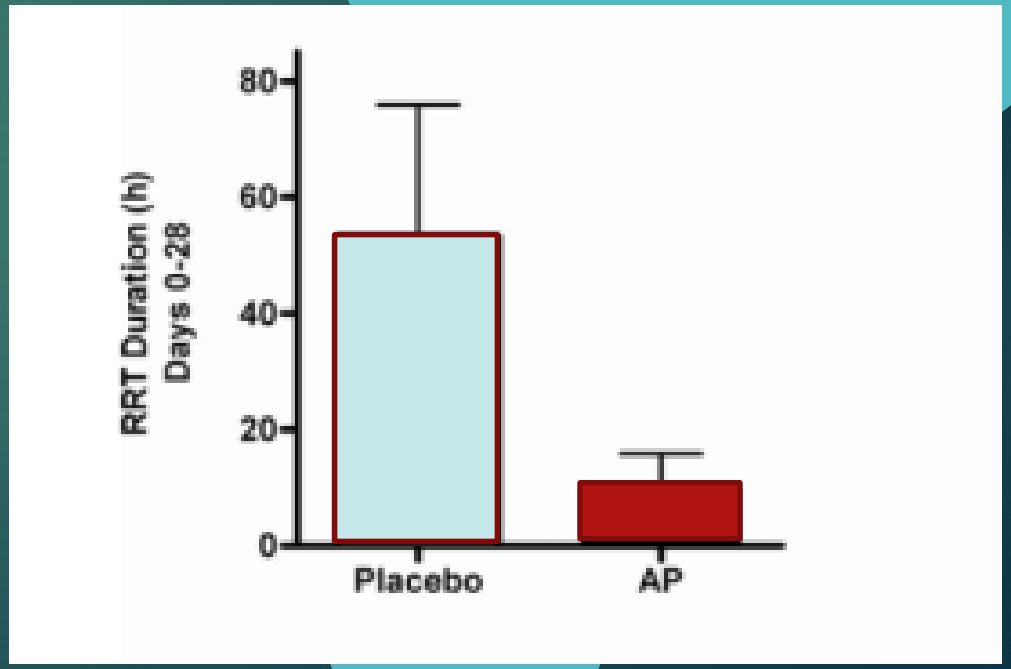


J Pharmacol Exp Ther 2013

Results were promising…







In the supplemental….

Non-renal Clinical Endpoints	Placebo	AP
Length ICU stay: days, mean (SD)	25 (18)	11 (8)
Length hospital stay: days, mean (SD)	47 (36)	31 (26)
Length of ventilator support: days, median (95% CI)	21 (4-26)	5 (4-29)
SOFA Score change 0-7 days: mean (SD)	4 (3)	6 (3)

Have they hit lucky?

- Could it be that both these groups of investigators have found a common key mechanism?
- Maybe purines are really key to organ dysfunction
- Neither group were aware of the other
- Unfortunately Evidence Based Medicine wants more

…over the top into the killing fields of the phase III trial

- Good luck to both for they will need it
- But someone has to win the lottery

What about intelligent design?

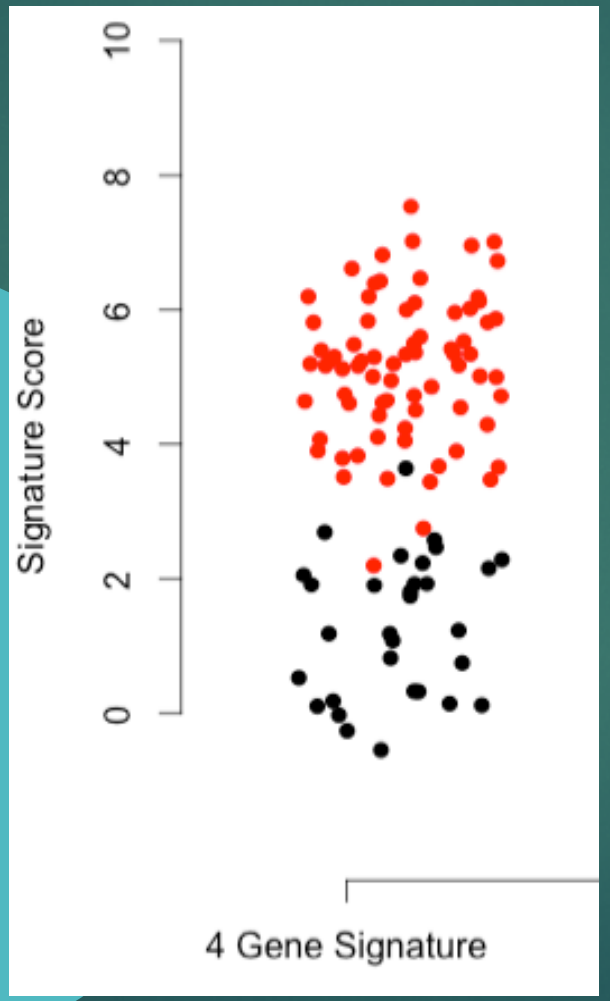
- As we talked about in the last lecture the OLD sepsis definitions are: Rubbish! (we need to see how the new ones do)
- The current biomarkers are no good
- We have no idea if someone is septic and for how long
- So lets figure out who is ‘truly’ septic
- Lets figure out what the organism is
- Lets figure it out quickly

Host response or sepsis detection

- Identify who is infected and who is not
- Most examine the host response
- Lots of work going into white cell transcriptomics
  - The bits of DNA been transcribed to RNA to make proteins
- Asking what the white cell thinks is going on
- One example is the SeptiCyte device
- Able to examine the transcriptome of 4 white cell genes

Sepsis Detection

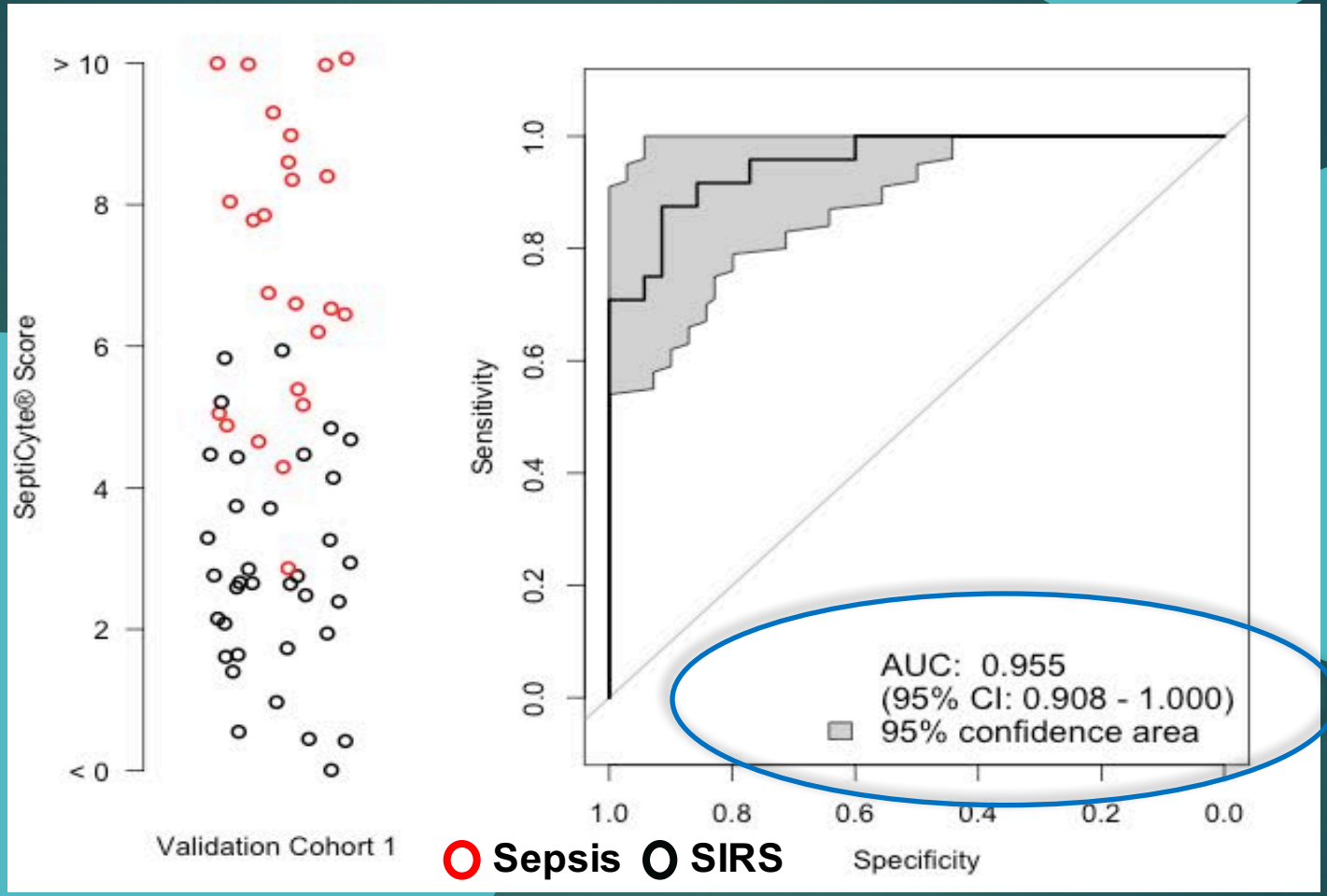
Sepsis
SIRS



SeptiCyte

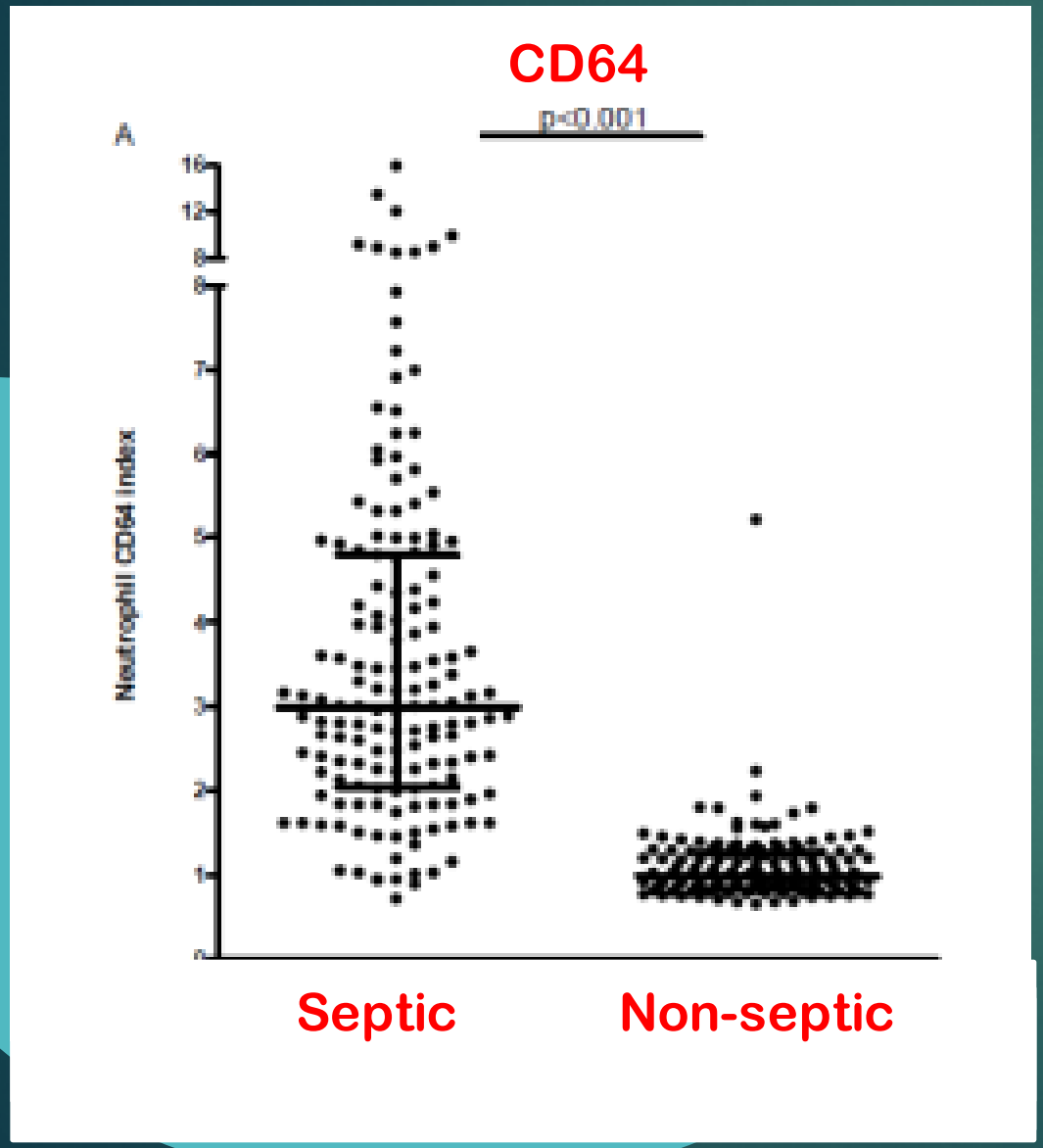
McHugh et al, submitted 2014

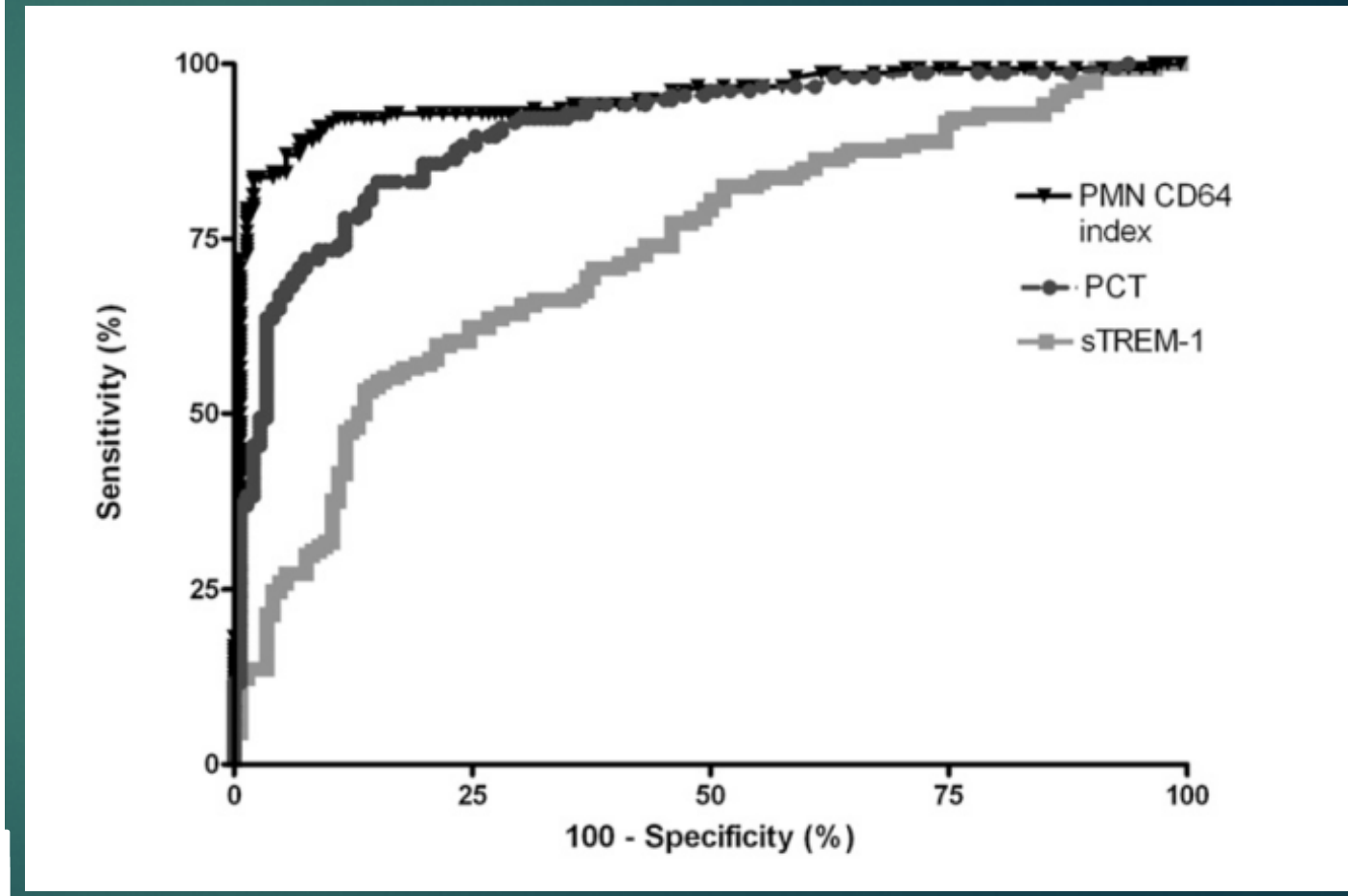
SeptiCyte Performance



Validation of SeptiCyte® Lab as a molecular signature for the discrimination between sepsis and "SIRS"

Other biomarkers and combinations?

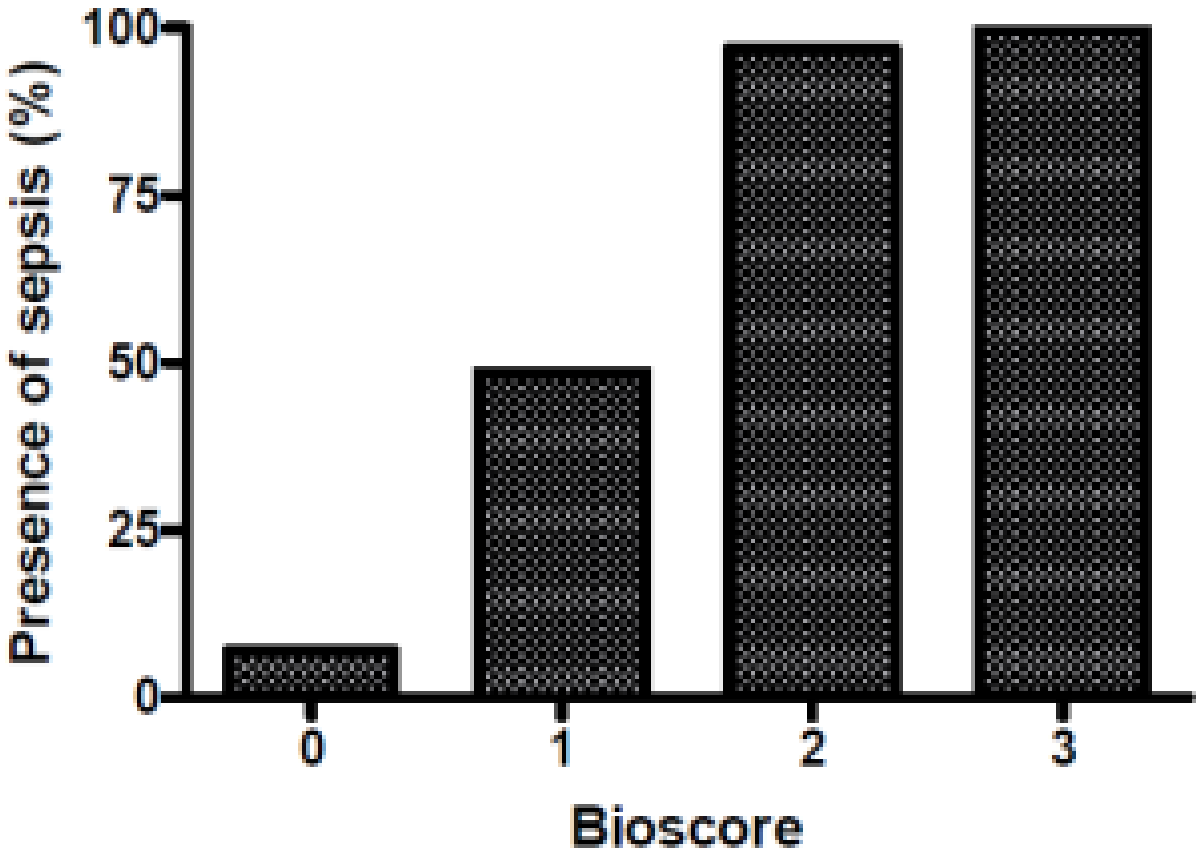




Gibot. Am J Respir Crit Care Med. 2012

Bioscore

…and when you combine the results



So if you know who has an infection/sepsis, what's the bug?

Rapid Pathogen Detection

The Iridica device (we talked about this earlier)

- New PCR/ESI MS
- Can detect over 1,200 pathogens
  - Bacteria
  - Viruses
  - Fungi
- Limited, but expanding resistance profile
- Direct from blood, BAL, CSF etc
- Result within 6-8 hours (no culture required)

RADICAL Study

- To compare the performance of PCR/ESI-MS device with standard hospital culture techniques
- A pragmatic prospective, observational trial
- Patient population: Any adult patient under the care of the critical care team being investigated for potential sepsis or pneumonia

Crit Care Med 2015

Characteristics

- Age 60.4 ± 18.8 years
- Gender
  - Male 61.2%
  - Female 38.8%
- Source of ICU admission
  - Emergency Department 44%
  - Ward 26.8%
  - Theatres 15%
- Immune status
  - Competent 83.2%
  - Incompetent 16.8%
- Antibiotics
  - Started following enrolment 28.9%
  - Within the last 30 days 71.2%
- SOFA
  - 7.9 ± 4

Of the 625 blood samples…

	Culture	IRIDICA
Positive	68 (11%)	228 (36%)
Negative	557 (89%)	397 (64%)

- IRIDICA has a yield 3x that of culture
- 12-15% of blood cultures are positive in UCLH and Barts Health
- Similar values reported at Intermountain Healthcare in Utah

Of the 625 blood cultures…

Performance		Culture	
		Positive	Negative
IRIDICA	Positive	55 (9%)	173 (28%)
	Negative	13 (2%)	384 (61%)

- Negative predictive value: 97%
- Positive predictive value: 24%
- Sensitivity: 81% Specificity: 69%

Let us imagine you have been given $20 million to trial a new drug for sepsis….

The following are all examples from the RADICAL trial

Would you enrol?...

- 59 yo man: Obesity, diabetes and hypertension
- Admitted with a septic arthritis (right knee)
- Treated with flucloxacillin
  - Blood cultures – nothing grown
  - knee fluid aspirated x 3 – nothing grown
- Deteriorated into multi organ failure
  - Co-amoxiclav, piptazobactam, oseltamivir, fluconazole, meropenem, moxifloxacin, clindamycin (3 days)
- Died
- PCR/ESI-MS: MecA carrying Staphyloccus aureas in all three knee samples

Young adult with pneumonia

- 22 year old admitted with pneumonia
- Develops Acute Respiratory Distress Syndrome (ARDS)
- Treated with co-amoxiclav, amikacin, piptazobactam and vancomycin
- Blood cultures and BAL were sterile
- Died after 8 days on the ICU
- PCR/ESI-MS: Blood, Candida glabrata

Haemoncology patient

- 63yo man with diffuse B-cell lymphoma
- Septic following chemotherapy and bone marrow transplant
- Long hospital and ICU stay
- Progressive respiratory failure
- Cultures (blood, respiratory, urine) all negative
- Ultimately died
- PCR/ESI-MS: Blood, Mycobacterium Tuberculosis!!!

A little extra…

- PCR/ESI-MS identified MEC A carrying organisms in the blood of 10 patients who died. Not detected by blood culture and not on appropriate antibiotics
- Patients where PCR/ESI-MS found an organism but culture negative had a significantly higher mortality

This is all a bit new

- Looks like we might be able to detect sepsis and identify the organism all within a few hours
- Using objective bio-markers
- Giving people the reassurance they are doing the right thing
- Would you propose a multi-million dollar sepsis drug development programme without this info?

This would be your publication if you do

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 VOL. 366 NO. 22

..... in Adults with Septic Shock

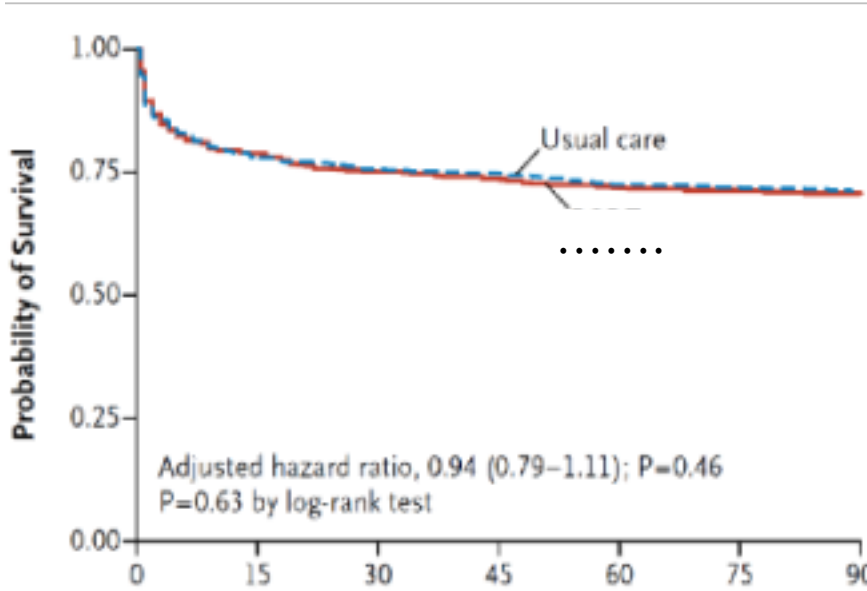
METHODS

In this randomized, double-blind, placebo-controlled, multicenter trial, we assigned .... patients with infection, systemic inflammation, and shock who were receiving fluids and vasopressors above a threshold dose for 4 hours to receive either

The primary outcome was death from any cause 28 days after randomization.

CONCLUSIONS

..... did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock.
ClinicalTrials.gov number, NCT00604214.)



Luck or Design

- Reality will be a bit of both
- It's a great time to be involved in Critical Care
- The big players are getting interested again
- I sincerely think/hope things will be very different in the next 10 years

Half full or half empty?

either way - room for more wine!!!

I would like to thank the following for providing me with a conflict of interest slide

The End