This depends a little on your point of view…

Glass half full

Glass half empty
Trial of Early, Goal-Directed Resuscitation for Septic Shock

Effects of Fluid Resuscitation With Colloids vs Crystalloids in Critically Ill Patients Presenting With the Route of Early Nutritional Support in Critically Ill Adults

Trial of Early, Goal-Directed Resuscitation for Patients With Severe Sepsis or Septic Shock

New England Journal of Medicine
A cup of hospital tea

P < 0.00000000000001

Adjusted hazard ratio, 0.94 (0.79–1.11); P = 0.46
P = 0.63 by log-rank test

Hazard ratio, 1.25 (95% CI, 0.88–1.76)
P = 0.20
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
Let's 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.

- ATP → ADP → AMP → Adenosine
- CD39
- CD73

Alveoli

- Pro-inflammatory
- Increase vascular permeability

- Anti-inflammatory
- Decrease vascular permeability
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...
CD73 is found in human lung and can be induced.
CD73 activity decreases permeability

**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.
...and in ARDS patients

Survival %

All 37 IFN-b treated patients

Control: 32% mortality

IFN-β: 8% 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.
  - It's not there just for biochemistry labs to measure!
- They made a human recombinant ALP to replace it.
- But how does it work?
Seem familiar?
Results were promising…
In the supplemental....

<table>
<thead>
<tr>
<th>Non-renal Clinical Endpoints</th>
<th>Placebo</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length ICU stay: days, mean (SD)</td>
<td>25 (18)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Length hospital stay: days, mean (SD)</td>
<td>47 (36)</td>
<td>31 (26)</td>
</tr>
<tr>
<td>Length of ventilator support: days, median (95% CI)</td>
<td>21 (4-26)</td>
<td>5 (4-29)</td>
</tr>
<tr>
<td>SOFA Score change 0-7 days: mean (SD)</td>
<td>4 (3)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>
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 let's figure out who is 'truly' septic
- Let's figure out what the organism is
- Let's 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

McHugh et al, submitted 2014

Sepsis
SIRS
SeptiCyte
Validation of SeptiCyte® Lab as a molecular signature for the discrimination between sepsis and “SIRS”
Other biomarkers and combinations?

- Procalcitonin
- sTREM1
- CD64

- 300 consecutive patients admitted to a French ICU
- 79 further patients from a second ICU for validation
- Samples taken within 12 hours of admission
- PCT, TREM1, and CD64 measured
- Each independently predictive of sepsis
- Bioscore constructed
  - 1 point for each test scoring above the optimal cutoff

...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)
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
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...

<table>
<thead>
<tr>
<th></th>
<th>Culture</th>
<th>IRIDICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>68 (11%)</td>
<td>228 (36%)</td>
</tr>
<tr>
<td>Negative</td>
<td>557 (89%)</td>
<td>397 (64%)</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Culture</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>55 (9%)</td>
<td>173 (28%)</td>
</tr>
<tr>
<td>Negative</td>
<td>13 (2%)</td>
<td>384 (61%)</td>
</tr>
</tbody>
</table>

- 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 Staphylococcus 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*
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

........................................... 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