Diagnosing infection in the ICU. A new dawn?

Kyiv 2016
Infection and Sepsis

- It’s a bit of a problem and we don’t seem to be doing very well
  - Incidence is increasing
  - No new interventions since antibiotics
  - Rise in multi-drug resistant bacteria

- To manage a condition we need to know what to treat
Everything starts with the definition

- Sepsis is an ancient Greek term
- It means ‘decomposition’
- …and they described it perfectly:
  - ‘A local lesion, heated by humor afflux, makes the whole body become feverish. One can die because of this….’
  - ‘A darkening and a faster sedimentation of the form component of blood’
Feverish, tachycardic and unwell

So let's imagine......

What you do about it depends a little in which century you live
Two golden ages of sepsis

14th Century
- Make an assumption they are septic (Greek definition)
- Put to bed and wash with vinegar
- Blood letting
- Eat bread, fruit and veg
- Try
  - Tie a hen around their waist
  - Drink their urine
  - Warm treacle and beer

21st Century
- Make an assumption they are septic (give antibiotics)
- Put to bed and wash with chlorhexidine
- Tolerate a Hb > 60g/l
- Start early nutrition
- Try
  - Activated Protein C
  - Talactoferrin (breast milk)
  - Steroids
What has changed?

- The clinical definition of sepsis in ancient Greece or Kyiv today:
  - Is highly non-specific
  - Does not isolate when the septic process started
  - Let alone what is causing it
- Our understanding has improved markedly
  - Mitochondria
  - Reactive oxygen/nitrogen species
  - Cell death etc etc
- But still held back by diagnostic uncertainty
Not Rapid Pathogen Detection
The yield from blood cultures are negligible.
When we are sure...we are not

- **ARISE**: 1600 patients with severe sepsis, 38% cultures were positive
- **PROCESS**: 1351 patients with severe sepsis, 31% cultures were positive
- **ProMISE**: 1260 patients with severe sepsis, 56% able to identify a pathogen
- **SOAP study (observational European study)**: 1177 patients with infection, 468 had a pathogen identified (39%)
- **Canada/US**: 2,731 patients with Septic Shock – 37% had positive blood cultures (Kumar Crit Care Med 2006)
So why is that?

- Often prior use of antibiotic
- Viral aetiology
- Inappropriate culture technique
- Fragile organisms (e.g. pneumococcus)
- Patient is not septic!
- Sensitivity of blood culture is approximately 40%
  (specificity ~95%)
They make no difference

- 414 patients in ED with pneumonia
- Blood cultures taken and antibiotics started
- 7% blood cultures positive (26/414)
- Of those 26:
  - 11/26 continue empiric therapy, though 8 could de-escalate
  - 11/26 de-escalate
  - 4/26 broaden therapy

They make no difference

- 760 patients with community pneumonia, all had blood cultures
- 43 (5.7%) were positive
- Culture suggested a step down in antibiotics in 17
- Of those 17 only 6 followed the recommended course of action

Cambell et al. Chest; 2003
No other area tolerates this level of imperfection

- Cardiologists would not stent all with chest pain
- High sensitivity Troponin T 90% sensitivity with baseline
  - ST elevation on ECG 88-98% specific
- Stroke doctors would not thrombolyse everyone with a weak arm
- Oncologists would not give ‘chemotherapy’ to everyone with a mass on CT
- Why should we give antibiotics to everyone who may just be septic?
Perhaps because…

A retrospective cohort analysis of 760 patients with severe sepsis*

31% received inappropriate antibiotic treatment

In 58%, therapy was delayed

42% had resistance to the antibiotic administered

Patients who progress to septic shock have a 7.6% increase in mortality every hour while not on appropriate therapy**

How big a problem is empiric prescribing?

- Pneumonias comprise the largest single group (22.8%) of all hospital-acquired infections in UK.
- Standard empiric treatment is piptazobactam or carbapenems.
- Look at organism ID and susceptibility and these drugs achieve 85-86% coverage.
- But 49% of pathogens could have been covered by amoxicillin-clavulanate and 27% by ampicillin or amoxicillin.
- Thus, empirical piperacillin-tazobactam or imipenem amounts to under treatment in 14-15% of cases and over-treatment in 27-49%.
Not just the UK

- European study of 3,147 ICU admissions identified an infection (clinically or microbiologically defined) in 37%
  - 64% received an antibiotic
- In an Israeli teaching hospital infection could only be defined in 54% of cases where antibiotics were being used
  - Length of antibiotic course was the same if infection was defined (11.5 days) or undefined (10.7 days)
  - Even when clinician certainty was low, antibiotics continued
  - 658 antibiotic days could have been saved in the 4 month study period

Levin et al J.Hosp Med 2012
So what’s the big deal?
Quite a lot really…

- Simple diarrhoea, rash etc
- Drug induced nephritis and cholestatic liver impairment
- Mitochondrial impairment – potentiating organ dysfunction
- Destruction of gut flora (C. difficile infection)
- Anaphylactic reactions
- Pressure on bacteria to develop drug resistance
Antibiotic resistance

- The liberal use of broad spectrum antibiotics is leading to a rapid rise of highly resistant bacteria across the World.
- Ultimately one of the biggest challenges to healthcare in the coming decades.
Meropenem sales 2005-2010

Units per 1000 population

India

Egypt

Pakistan

Netherlands
UK from 2010-2013

46% rise in piptazobactam use

37% rise in meropenem use
E. Coli resistance to cephalosporins 2001-2013
Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study

**Netherlands**
- 43 patients
- MDR=10 (23%)
- XDR= 0 (0%)

**France**
- 206 patients
- MDR=67 (33%)
- XDR= 16 (8%)

**Spain**
- 70 patients
- MDR=29 (41%)
- XDR= 11 (16%)

**Greece**
- 288 patients
- MDR=219 (75%)
- XDR= 145 (50%)
Cost of multi-resistant bacteria

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Deaths per Year</th>
<th>Hospital Days</th>
<th>Societal Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td>500m</td>
<td>25,000</td>
<td>2.5m</td>
<td>Overall societal costs: €900 million, hosp. days. Approx. €1.5 billion per year</td>
</tr>
<tr>
<td>Thailand</td>
<td>70m</td>
<td>&gt;38,000</td>
<td>&gt;3.2m</td>
<td>Overall societal costs: US$84.6–202.8 mill. direct. &gt;US$1.3 billion indirect</td>
</tr>
<tr>
<td>United States</td>
<td>300m</td>
<td>&gt;23,000</td>
<td>&gt;2.0m</td>
<td>Overall societal costs: Up to $20 billion direct. Up to $35 billion indirect</td>
</tr>
</tbody>
</table>


...developing new antibiotics will not address this growing problem
There seems to be a conflict...

Drive to spot and treat sepsis

Vs

Drive to control antibiotic misuse
We desperately need to...

- Identify the pathogen faster and more reliably than you (or Sir Alexander Fleming) can.
- Identify the inflammatory response is to an infection.
  - Currently best markers are pro-calcitonin or C-reactive protein.
  - Both are rubbish.
- Field is now changing very fast indeed.
Where are we now?

- Post culture techniques
  - MALDI-TOF systems, Vitek 2, etc.
  - Common in many laboratories
  - Reduce time to identification and susceptibility

- Pre-culture techniques
  - Iridica, SeptiFast, T2 Biosystems
  - Able to deliver results within a few hours
  - New and currently not very common (at least not in the UK)
Any evidence?

Kerremans et al J. Antimicrob Chemother 2008

Prospective RCT of 1498 patients with positive culture from sterile compartments

Rapid pathogen detection (Vitek2) vs standard culture

Intervention group

- Identification reduced by 13h and 20h for susceptibility testing (P<0.001)
- Lower DDD of antibiotics.
- No difference length of stay and mortality

However, large number of protocol violations (~15%)
Any evidence?

- 290 patients with positive culture guided by the results from Vitek 2
- Compared to 284 historical controls (bit of a flaw!)
- Vitek 2 led to:
  - Reduced Time to ID and sensitivities 9.4 h (±1.2) vs 27.0 h (± 9.1) for the (P < 0.001)
  - Time result received within 48hr of culture of specimen: 81% vs 52%
  - Reduced time in ward 7.7 ± 14.6 vs 10.1 days ± 16.3 p=0.003
  - Decreased need for intubation 7.9% vs 14.4% p=0.017
  - Decreased number of investigations
  - Decreased costs €12,402 vs €15,990
Any evidence?

- Huang et al. (2013)
- A pre–post quasi-experimental study using a post culture MALDI-TOF system (Bruker Microflex) and Antimicrobial Stewardship Programme
- 256 pre–intervention and 245 post intervention.
- Time to organism identification: 84h vs 55.9h, P < .001
- Reduced time to optimal treatment: 90.3 vs 47.3 hours, P < .001
- Reduced 30 day mortality: 20.3% vs 12.7%, P = 0.021
- Reduced ICU LOS: 14.9 vs 8.3 days, P = 0.014
Having said that

- All these studies have fairly major methodological flaws
- Had to rely on an organism being cultured
- All had fairly long time to ID an organism and effect treatment
- But all showed some sort of benefit we would like to see and perhaps a taster of what is possible
What about pre-culture techniques?

- Promise of much faster turns around times
- Panels including bacteria, fungi or viruses
- Unaffected by antibiotics
- Impressive observational trials
- Concerns that DNA does not equal infection:
  - Dead bacteria
  - DNA Translocation
New PCR/ESI MS developed by Abbott
Can detect over 1,200 pathogens
- Bacteria
- Viruses
- Fungi
Limited, but expanding resistance profile
- MEC-A, VAN-A/B, KPC
Direct from blood, BAL, CSF etc
Result within 6-8 hours
IRIDICA

PCR/ESI-MS
Does it work?
Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in Bloodstream Infections, Pneumonia, and Sterile Site Infections

Jean-Louis Vincent, MD, PhD, FCCM; David Brealey, MD; Nicolas Libert, MD; Nour Elhouda Abidi, MD; Michael O’Dwyer, MD; Kai Zacharowski, MD; Malgorzata Mikaszewska-Sokolewicz, MD; Jacques Schrenzel, MD; François Simon, MD; Mark Wilks, PhD; Marcus Picard-Maureau, PhD; Donald B. Chalfin, MD, MPH; David J. Ecker, PhD; Rangarajan Sampath, PhD; Mervyn Singer, MD; the Rapid Diagnosis of Infections in the Critically Ill Team

Critical Care Medicine. August 2015
Methodology

To compare the performance of PCR/ESI-MS 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
Of the 625 blood samples...

<table>
<thead>
<tr>
<th></th>
<th>Culture</th>
<th>PCR/ESI-MS</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>

- PCR/ESI-MS has a yield 3x that of culture
- Positive blood culture rate similar to literature
Of the 625 blood cultures...

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

- Negative predictive value: 97%
- Positive predictive value: 24%
- Sensitivity: 81%
- Specificity: 69%
A little caution...

- Sensitivity and specificity are about comparing to a gold standard.
- Blood cultures are standard but they are not golden.
- This is a recurrent problem as we start to replace old biomarkers and definitions.
  - Creatinine – renal failure
  - Chest x-ray – pneumonia
  - CRP – sepsis diagnostics
Perhaps its picking up irrelevant DNA?
Organisms within the blood

<table>
<thead>
<tr>
<th>Organism</th>
<th>Iridica</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td></td>
<td></td>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Enterococcus faecium</td>
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<tr>
<td>Klebsiella pneumoniae</td>
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<tr>
<td>Candida albicans</td>
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<tr>
<td>Enterococcus faecalis</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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<td></td>
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<tr>
<td>Enterobacter cloacae complex</td>
<td></td>
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<tr>
<td>Streptococcus pyogenes</td>
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<td></td>
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<tr>
<td>Klebsiella oxytoca</td>
<td></td>
<td></td>
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<tr>
<td>Bacteroides fragilis/thetaiolaomicon</td>
<td></td>
<td></td>
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<tr>
<td>Citrobacter koseri</td>
<td></td>
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<tr>
<td>Haemophilus influenzae</td>
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<tr>
<td>Streptococcus mitis/pneumoniae</td>
<td></td>
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<tr>
<td>Morganella morganii</td>
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<tr>
<td>Candida glabrata</td>
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<tr>
<td>Fusobacterium nucleatum</td>
<td></td>
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<tr>
<td>Hafnia alvei</td>
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<tr>
<td>Stenotrophomonas maltophilia</td>
<td></td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
<td></td>
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<tr>
<td>Candida tropicalis</td>
<td></td>
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<tr>
<td>Finegoldia magna</td>
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<tr>
<td>Mycobacterium africanum/bovis/canetti/tuberculosis</td>
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<tr>
<td>Neisseria meningitidis</td>
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<tr>
<td>Raoultella ornithinolytica/planticola</td>
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<tr>
<td>Rothia mucilaginosa</td>
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<tr>
<td>Acinetobacter baumannii</td>
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<tr>
<td>Candida parapsilosis</td>
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<tr>
<td>Citrobacter freundii</td>
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<tr>
<td>Streptococcus oralis/pneumoniae</td>
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<tr>
<td>Enterobacter cancerogenous</td>
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<tr>
<td>Escherichia vulneris</td>
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<td></td>
</tr>
<tr>
<td>Gemella morbillorum</td>
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<td></td>
</tr>
<tr>
<td>Granulicatella adiacens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicobacter cetorum; Helicobacter pylori</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella varicola</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactobacillus acidophilus/amylolovus/crispatus</td>
<td></td>
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<tr>
<td>Lactobacillus fermentum</td>
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<tr>
<td>Lactobacillus gasseri</td>
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<tr>
<td>Lactococcus lactis</td>
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<tr>
<td>Micrococcus luteus</td>
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<tr>
<td>Prevotella denticola</td>
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<tr>
<td>Roseomonas gilardi</td>
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<tr>
<td>Shigella boydi</td>
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<td></td>
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<tr>
<td>Staphylococcus lugdunensis</td>
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<td></td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pseudopneumoniae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium paraputrificum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Organisms within the blood

- *Escherichia coli*
- *Staphylococcus aureus*
- *Enterococcus faecium*
- *Klebsiella pneumoniae*
- *Candida albicans*
- *Enterococcus faecalis*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae complex*
- *Streptococcus pyogenes*
- *Klebsiella oxytoca*
- *Bacteroides fragilis/thetaiotaomicron*
- *Citrobacter koseri*
- *Haemophilus influenzae*
- *Streptococcus mitis/pneumoniae*
- *Morganella morganii*
- *Candida glabrata*
- *Fusobacterium nucleatum*
- *Hafnia alvei*
- *Stenotrophomonas maltophilia*
- *Streptococcus pneumoniae*
- *Candida tropicalis*
Replicate sampling

- 169 had replicate blood sampling (e.g. 2 venepunctures)
  - PCR/ESI-MS concordance in 83%
  - Culture concordance in 55%
- 151 had sampling from 2 sites (e.g. respiratory & blood)
  - PCR/ESI-MS Concordance in 57%
  - Culture concordance in 12%
A panel of 3 doctors, independent of the trial, reviewed results.

They were asked to comment if the PCR/ESI-MS results would alter antibiotic prescription if they had known about the result.

442 summaries were reviewed.

42% of the time the PCR/ESI-MS result would have affected their decision.

Rising to 57% if the PCR/ESI-MS result was positive.
Final thoughts

If implemented carefully, these devices may revolutionise the way we manage infection and sepsis in a way we have not seen for decades.
кінець
(The End)
Of the 185 respiratory samples...

### Performance

<table>
<thead>
<tr>
<th></th>
<th>Culture</th>
<th>PCR/ESI-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>81 (44%)</td>
<td>117 (63%)</td>
</tr>
<tr>
<td>Negative</td>
<td>104 (56%)</td>
<td>68 (37%)</td>
</tr>
</tbody>
</table>

- **PCR/ESI-MS**
  - **Positive**
    - 68 (37%)
  - **Negative**
    - 13 (7%)

- **Culture**
  - **Positive**
    - 68 (37%)
  - **Negative**
    - 55 (30%)

- **Negative predictive value of 81%**
Where is the *Staph. Epi*?

- Presumed contaminants (excluded from analysis)
## UK Blood Stream Isolates 2011-2012

<table>
<thead>
<tr>
<th>Group of bacteria</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>9.7%</td>
</tr>
<tr>
<td>Staphylococcus aureus (MSSA)</td>
<td>7.8%</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>7.1%</td>
</tr>
<tr>
<td>Non-pnuogenic streptococci</td>
<td>6.4%</td>
</tr>
<tr>
<td>Other gram-negative</td>
<td>6.3%</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>4.3%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4.2%</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>4.2%</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>4.2%</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>3.1%</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>2.2%</td>
</tr>
<tr>
<td>Staphylococcus aureus (MRSA)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>1.5%</td>
</tr>
<tr>
<td>Group B Streptococci</td>
<td>1.4%</td>
</tr>
<tr>
<td>Group A Streptococci</td>
<td>1.4%</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>1.2%</td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>1.0%</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

*UK Blood Stream Isolates* 2011-2012
Samples taken

- Simultaneous samples for PCR/ESI-MS paired with:
  - Blood culture
  - BAL or endotracheal aspirate
  - Fluid from other sterile body cavities
    - CSF
    - Pleural
    - Ascitic
  - Excluding urine, sputum and faeces
- PCR/ESI-MS samples were frozen and batch analysed
- Clinicians blinded to result
8 European Centres

- University College London Hospitals, London
- Barts Health, London
- Hospital Erasme, Brussels
- Hôpitaux Universitaire Genève
- Hôpital Militaire du Val de Grace, Paris
- Child of Christ Hospital, Warsaw
- Universitätsklinikum Frankfurt
- Hôpital St Louis, Paris
Results

- 543 patients recruited – 529 included in analysis
- >900 samples taken
  - 625 blood samples
  - 88 broncho alveolar lavages
  - 96 tracheal aspirates
  - 11 CSFs
  - 36 intra-peritoneal fluid
  - 14 pleural fluid
  - 13 tissue
  - 37 other samples
Characteristics

- **Age**: 60.4 ± 18.8 years
- **Gender**
  - Male: 61.2%
  - Female: 38.8%
- **Source of ICU admission**
  - Emergency Department: 32%
  - Ward: 25%
  - Theatres: 16%
- **Immune status**
  - Competent: 83.4%
  - Incompetent: 16.6%
- **Antibiotics**
  - Started following enrolment: 22.1%
  - Within the last 30 days: 75.4%
- **SOFA**
  - 7.9 ± 4