Speeding up the laboratory diagnosis of bloodstream infection

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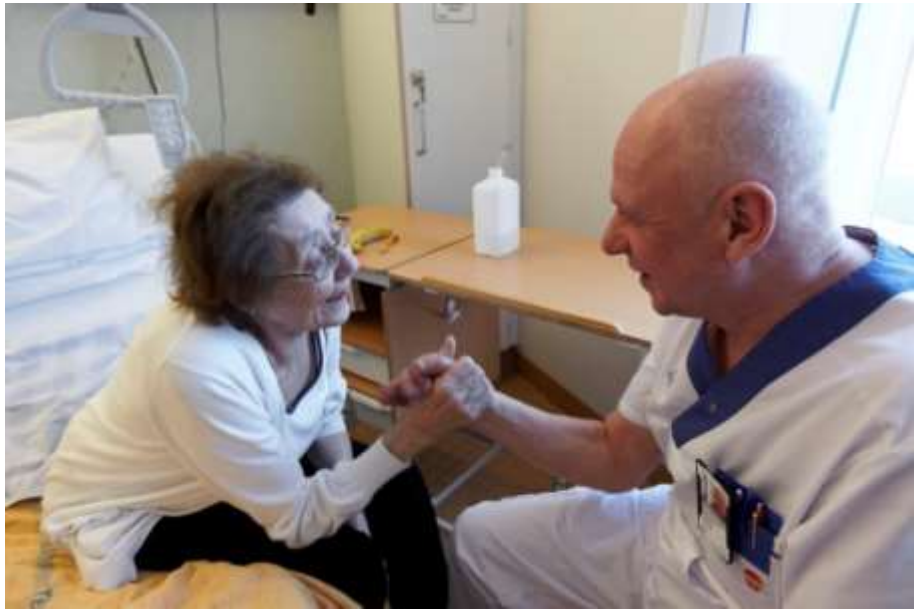
Disclosures

- Lectures for
  - Abbott Diagnostics (Sweden)
  - Astra Zeneca (Sweden)

- Research projects in collaboration with
  - BD
  - Qlinea
  - Luminex
  - BioMerieux/Biofire
  - Bruker Daltonics

Why?

- Increasing antibiotic resistance
- Improve antibiotic stewardship (Klein Breteler SJID 2011)
- Improve patient outcome (Kumar CCM 2006, Shorr CCM 2011, Kerremans JAC 2008)
- To save costs
  (Garcia-Vazquez SJID 2013)



The patient with sepsis

- Comes to the ER 24/7/365
- Is severely ill!
- Will benefit from rapid institution of antibiotics
- Is in some settings likely to be colonized with multiresistant bacteria

But!

- The patient does not always turn up at the ”correct” hospital
- The personnel do not always have the right incentives to handle the samples correctly
- The laboratory is not always open 24/7/365

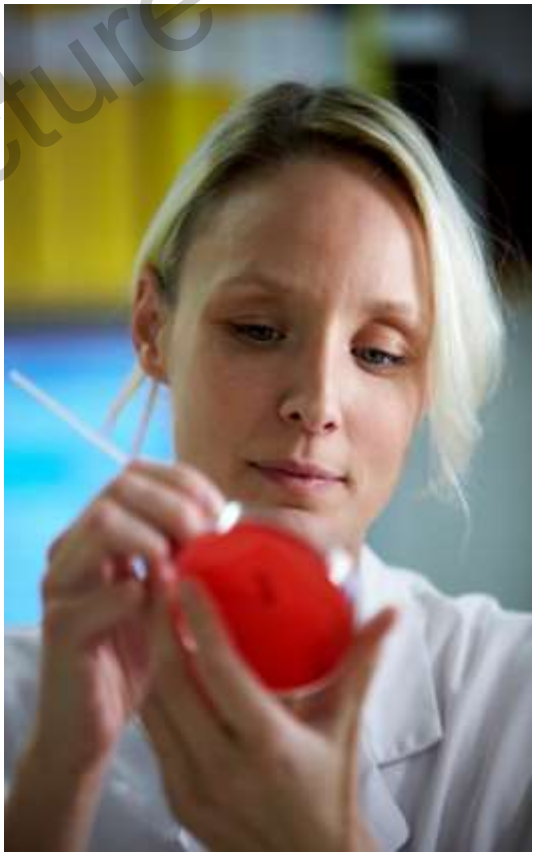
WHAT MAKES A RAPID TEST RAPID?

Pre analysis

- Knowledge
- Transports
- External Blood-culture cabinets
- Decentralized ER laboratories
- Electronic referrals

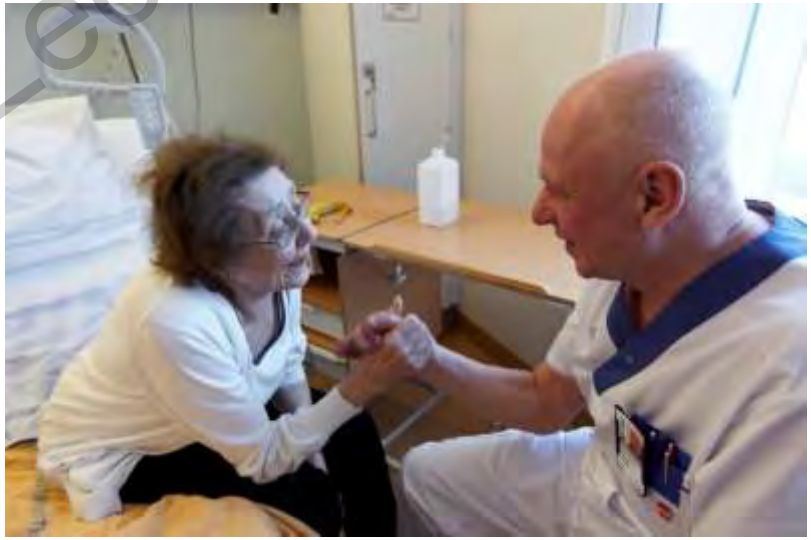
In the lab

- Opening hours
- Dedicated staff
- Knowledge
- Prioritize the diagnosis of sepsis
- Reports
  - Electronic
  - Transparent
  - Preliminary
  - Telephone



In the ward

- Electronic chart systems
- Knowledge
- Consultants available for instant discussion regarding antibiotic therapy



What you can do on monday

- Make your automated blood culture system available for the introduction of vials 24/7/365
  (van der Welden 2010, Schneiderhan 2013)

- ”Active culturing”

WHAT IS AVAILABLE TO GUIDE ANTIBIOTIC THERAPY?

In the Emergency Room

- History of the patient!
  - Visits abroad ?
  - Recent hospital stay?
  - Farmer?
  - etc

- Clinical Investigation

- CRP
- PCT
- WBC, neutrophils
- Lactate
- Etc…

Dynamic tests – To be followed over time!

RAPID SPECIES IDENTIFICATION

Rapid ID from Blood cultures using a molecular approach

- PCR for a range of pathogens
  - The most common pathogens
  - Some resistance genes
  - 1-6h to ID
- Broad range PCR
  - At least 2-6 hours to ID
  - Needs sequencing
- Quick-FISH (PNA-FISH)
  - Gram stain 10 min
  - Quick-FISH 20 min
  - The most common pathogens in smaller panels (Calderaro CMI 2013)

Rapid ID from Blood Cultures using MALDI-TOF

- MALDI-TOF direct method (Martiny EJCMID 2012)
  - 10-30 min
  - ID obtained in 66 - 99%
- ”Active culturing” and MALDI-TOF
  - Rapid incubation
  - 3 hours at its best to species ID

Martiny EJCMID 2012,
Lagacé-Wiens JCM 2012,
Klein JMM 2012,
Machen PLoS One 2014,
Schieffer JAM 2014

Impact of Rapid species ID using MALDI-TOF

- Time form BC to species ID
  - 84 → 56h (Huang CID 2013)
- Time to optimal antibiotics
  - 90 → 47h (Huang CID 2013)
  - 69 → 39 h (Dien Bard ePoster ECCMID 2015)
- 58h earlier report if:
  - introduction of BC vials 24/7
  - and MALDI-TOF 24/7 (Schneiderhan Clin Chem 2013)

Species ID before enrichment

Antigen tests

- Pneumococci (urine, CSF)
- Legionella (urine)
- Meningococci (CSF)

- Limited sensitivity
- Acceptable specificity
- Predicitive value?

Nucleic acid detection

- SeptiFast, Roche
- SepsiTest, Molzym
- Magicplex, Seegene
- Vyoo, Bionity
- Inhouse methods

- Limited sensitivity
- Limited panels
- Acceptable specificity
- Predicitive value?

NAT directly from blood

Benefit

- Could decrease time to Species ID
- Less problem with

Draw back

- Sensitivity?
  - 1 – 1.5 mL whole blood
- Will be batched → reduces

"SeptiFast appears to have higher specificity than sensitivity, but deficiencies in study quality are likely to render this body of work unreliable. Based on the evidence presented here, it remains difficult to make firm recommendations about the likely clinical utility of SeptiFast in the setting of suspected sepsis."

Dark et al Metaanalysis, Intensive Care Med 2015

Don´t forget!

- Gram stain
- Agglutination tests
- Rapid coagulase test
- Other culture results!

- And microbiologistics!!

RAPID SUSCEPTIBILITY TESTING

General aspects of AST

- Resistance detection ≠ Susceptibility testing
- So far no techniques with high sensitivity for detection of resistance mechanisms directly from blood sample
- All commercial and/or molecular systems are less dynamic to local epidemiology and treatment traditions

Molecular resistance detection

- Detects well known resistance mechanisms
  - MRSA
  - VRE
  - Carbapenemases and ESBLs
  - And more…
- Can be very useful in a high endemic setting
  - If not a resistant bacteria → optimize tx

Detection of Carbapenemases directly from positive BC

- MALDI-TOF (Hoyos-Mallecot JMM 2014, Johansson JMM 2014, Carvalhes JAC 2014)
- CarbaNP (Dortet CMI 2014)
- Arrays (Juiz IJAA 2014, Fishbein JCM 2012)
- PCR (Francis AJCP 2012, Hindiyeh JCM 2011)

Phenotypic AST

- Susceptibility testing

- DD or Gradient strip
  - 6-8h
    (Jonasson et al Poster ECCMID 2014, Sundqvist et al, manuscript, Eurostar project)
- Automated
  - 16h (5-16h)
    (Wimmer JCM 2012, Machen PLoS One 2014)

Disk Diffusion

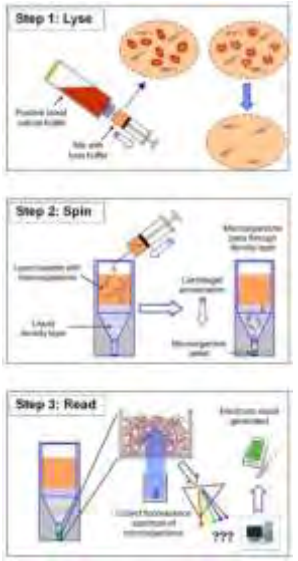
- Directly from BC-vials
  - Non-standardised inocloum
  - Over night incubation or short as below

- EuroStar Rapid Disk
  - EUCAST methodology
  - BUT! Short incubation time.
    - Enterobacteriaceae (6h)
    - Pseudomonas, Enterococci, *S.aureus* (8h)
    - *Haemophilus influenzae* and *Pneumococci* (8h)

Sundqvist et al Posters at ECCMID 2012, 2013, 2014
Manuscripts in progress

In pipeline

- Species ID
  - Intrinsic fluorescens (Walsh mBio 2013)



- AST
  - MALDI-TOF (Lange JCM 2014)
  - Microcalorimetry (Braissant et al JCM 2014)
  - Arrays (Braun PLoS One 2014)
  - Combined Broth Dilution and molecular detection → AST (Mezger JCM 2015, Beuving EJCMID 2015)

Future perspectives

- Molecular based detection from whole blood
  - Black box
  - Random access
  - Affordable
  - If accomplished: preliminary report in 6-8h?

- Culture (usually positive within 20h)
  - MALDI-TOF + rapid DD → definitive report in <30h?
  - Improvement possible?

But, to be rapid we need ”Microbiologistics”:

- Blood culture cabinets (also decentralized) available 24/7/365
- Microbiology open 24/7/365
- Skilled staff 24/7/365
- Not to forget other samples from the critically ill patient.
- Take control of the transport organization and the referrals!

Thank you