Diagnostic technologies to guide the use of narrow spectrum therapeutics

Herman Goossens
Laboratory of Medical Microbiology
VAXINFECTIO
University of Antwerp
Background

• Assume technologies to rapidly detect phenotype and/or genotype
• Assume technologies for targeting initial treatment, modifying existing treatment, or to aid patient enrollment in clinical trials
• This will determine required specifications (sensitivity, specificity, NPV, PPV, TAT, software, hardware...) of the technologies

My problem with new technologies (and this title): to put the cart before the horse
Agenda

• Diagnostic technologies
• Challenges to develop these technologies
• Use of rapid diagnostics:
  – to aid patient enrollment (real value and huge need!)
  – to guide antibiotic treatment (more controversial)
• Opportunities, Conclusions and Future
Conventional diagnostic microbiology is slow

- Day 1: Culture microscopy
- Day 2: Pure culture
- Day 3: Identification susceptibility
- Day 4: Identification susceptibility
Integrated sample prep with minor or almost no sample handling

Pros
• Fully automated process
• Less hands-on time
• Fully controlled workflow

Cons
• Often validated for only a single sample type

Cepheid: Xpert® Carba-R
• Insert swab into sample reagent vial and vortex
• Transfer the sample reagent to the cartridge
• Insert cartridge and start assay

Biocartis: Idylla
• Less than 2 minutes hands-on time per sample
• Works for tissue slices (even paraffinized), blood, urine, stool, sputum or tissue
• All reagents in cartridge
Sample preparation
Biocartis: Polaris

Capable of handling 5 or 10 ml of whole blood
Selective cell lysis releases internalised bacteria and removes blood cells
Allows detection of up to 1 CFU/ml

Multiple targets
bioMérieux: FilmArray
Reverse transcriptase
Turn RNA into cDNA
TAT: 1 hour

Lucigen Dx: developmentl product
OmniAmp™ Polymerase amplifies both DNA and RNA

Tsunami of instruments
Fast systems

Alere: i
Isothermal amplification: NEAR
15 min Influenza test

Xagenic: X1
Nanostructured microelectronic sensors:
20 mins; 50 targets test

Handheld devices

Micronics: PanNAT
1 hour 3 targets test
H: 20 cm / Depth= 34.5 cm /
Width: 12 cm

Epistem: Genedrive
1 hour real-time PCR test
NEXT GENERATION SEQUENCING
Challenges for developing rapid diagnostic tests

- Unclear medical needs
- Huge technical challenges
- Lack of guidance for (regulatory) evaluations
- Lack of proven clinical benefit
- Unclear which samples should be collected
- Role in antibiotic stewardship is controversial
- Many barriers for use
- Guidelines de-emphasize diagnostic microbiology

H. Goossens, Lancet Infectious Diseases Commission on Antibiotic Resistance, part 3, 18 December, 2013
Many different samples

**Nasopharyngeal swabs**
Relatively high pathogen load
Presence of commensals

**Urine**
Relatively high pathogen load
Normally sterile

**Stool**
Relatively high pathogen load
Presence of commensals

**Endotracheal aspirates and sputum**
Relatively high pathogen load
Presence of commensals
Large variation in consistency

**Whole blood**
Very low pathogen load
Normally sterile
Many different targets

Acute community-acquired pneumonia (adults)

Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Legionella pneumophila, Legionella spp., oral anaerobes (aspiration), Neisseria meningitidis, Moraxella catarrhalis, Mycoplasma pneumoniae, (very rare-Yersinia pestis, Bacillus anthracis, Francisella tularensis, Pseudomonas pseudomallei), Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Actinomyces spp., Cryptococcus neoformans, Chlamydia pneumoniae, Chlamydia psittaci, rubeola virus, varicella virus, influenza virus (A, B, C), adenovirus, Nocardia asteroides, Sporothrix schenckii, Penicillium marneffei, Geotrichum spp., Histoplasma duboisii (rare)

Pneumonia in immunocompromised host


Bronchitis

Haemophilus influenzae, Haemophilus parainfluenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Neisseria spp., Klebsiella spp., Pseudomonas spp., obligately aerobic gram-negative rod-shaped bacteria

Ref: Clinical Microbiology Procedures Handbook. 3rd Ed. Section 2. p. 2.1.3
Colonization vs Infection

BACTERIA

− Certain bacteria (e.g. *S. pneumoniae, H. influenzae, M. catarrhalis*) can cause CA-LRTI but also colonize healthy individuals

− Quantitative changes might determine the aetiology of these bacteria in CA-LRTI

− No molecular cut-offs available to distinguish colonization from infection

VIRUSES:

− Presence of respiratory viral agents based on conventional tests is commonly associated with respiratory symptoms

− What is the role of low copy numbers of (DNA) viruses and would quantitative PCR improve diagnostics?
Rapid diagnostics to aid patient enrollment
(real value and huge need: narrow-spectrum drugs will benefit immediately)
Why is the pipeline empty?

A *P. aeruginosa* - Focused VAP Programme

- Standard non-inferiority Phase 3 study\(^1\)
  - Need 336/arm or 672 evaluable patients total
- If only 10% yield *P. aeruginosa*,
  - We need 6,720 patients ... for ONE trial!

\(^1\)Assumes 80% success rates, 10% margin, and 90% power.

Courtesy: John Rex
Why VAP/\textit{P. aeruginosa}.

- VAP is a rare disease
- \textit{P. aeruginosa} is a rare causative organism of VAP
- High mortality
- Often toxic combination therapy
- Several \textit{Pseudomonas}-specific drugs in the pipeline
- Several ND4BB trials
Needs of pharmaceutical companies to aid enrollment of patients in clinical trials

• Identification of one or more **bacterial species** in a clinical specimen
• Detect **resistant organisms** in a clinical specimen
• Detect **resistant genes** (in isolates or even in a clinical specimen)
This need creates a schism between pharmaceutical and diagnostic companies

• Pharmaceutical companies interested in:
  – tests that target a limited number of organisms (e.g. *Pseudomonas* or *Acinetobacter* or MRSA) in a specific sample (e.g. in ETA), that can be used for targeting the patient (RUO for ex-US clinical studies or IUO)
  – tests with different requirements:
    • Detection of infection: sufficient to detect cutoff levels that correlate with infection (sensitivity less critical)
    • Detection of colonization: detection of any number of organisms (very high sensitivity required)
• Diagnostic companies interested in:
  – developing multi-plexed tests
  – tests that can be cleared for use (US-IVD or CE-IVD)
  – wide broad range of applications
Examples of clinical trials in IMI where rapid diagnostics are needed

- Phase II RCT with anti-α-toxin staphyloccocal antibody MEDI4893 for prevention of HABP/VABP (MedImmune):
  - Diagnostic test needed: rapid detection of *S. aureus* in ETA

- Phase II RCT trial with anti-pseudomonas antibodies MEDI3902 for prevention of HABP/VABP (MedImmune)
  - Diagnostic test needed: rapid detection of *P. aeruginosa* in ETA
S. aureus ETA Rapid Dx Weighting
Rapid Diagnostic for POCT for *Pseudomonas aeruginosa* colonization in endotracheal aspirates in patients on a mechanical ventilator

**Required diagnostic specifications:**

- High sensitivity ($<10^2$ cfu/mL) to identify patients as they become colonized (versus infected/pneumonia)
- High specificity also desired
- Validated for endotracheal aspirate samples (ETA)
- Minimal hands on time ($<30$ min) for specimen processing
- Rapid turn-around time for result ($<2$ hr)
- Test can be run on demand without need for batching
- Test can be performed outside of microbiology (ICU or step down unit)
- Low cost ($<40$)

- Supply up to 100 instruments to sites across Western Europe
- Service and Technical support for the instruments and assay kits
- Supply ~x,xxx tests between 2016 and 2020
CEPHEID ANNOUNCES DIAGNOSTIC COLLABORATION WITH MEDIMMUNE AND COMBACTE TO FACILITATE CLINICAL TRIALS OF NEW MONOClonAL ANTIBOdIES TO PREVENT SERIOUS INFeCTIOUS DISEASES

GeneXpert Systems and Xpert Tests Expected to Enhance Efficiency of Clinical Trials

SUNNYVALE, CALIF. — January 13, 2016 — Cepheid (Nasdaq: CPHD) today announced a collaboration with MedImmune, the global biologics research and development arm of AstraZeneca, and COMBACTE, a European public/private partnership set up to promote the development of new drugs in the anti-infectives field, to develop a series of rapid diagnostic tests to identify Staphylococcus aureus (S. aureus) and Pseudomonas aeruginosa (P. aeruginosa) in respiratory secretions of mechanically ventilated patients. These tests will be used to help identify patients for MedImmune’s MEDI4893 and MEDI3902 clinical programs, which are being conducted within the COMBACTE consortium to explore the use of biologics in preventing ventilator associated pneumonia (VAP) infections in intensive-care-unit (ICU) patients.
More examples (not exhaustive!)

• Phase III RCT of minocycline in subjects with HABP/VABP caused by *Acinetobacter baumannii complex* (Medicines Company)
  – Diagnostic test needed: rapid detection of *A. baumannii* in ETA

• Phase III Randomized trial with S-649266 for the treatment of severe Infections caused by Carbapenem-resistant Gram-negative bacteria (Shionogi)
  – Diagnostic test needed: rapid detection of CR-organisms and/or Carbapenemase genes
Performance characteristics of rapid diagnostic tests for patient enrichment in clinical trials

• Often unclear what test is needed and how the test will be used to aid patient selection

• Performance characteristics:
  – High sensitivity, specificity and PPV (rule-in tests: high probability that positive test is correct and that you can start the antibiotic; also rule-out?)
  – Rapid turn-around-time (limit prior therapy to minimum
  – On demand
  – Easy to use, minimal hands on time, simple readout
  – All-in-one test that permits testing at the point of care
Lessons learned

- Increased demand of pharmaceutical companies to perform test outside of microbiology lab, but:
  - Micro lab (feels) excluded
  - Purchasing and logistical challenges (product delivery)
  - Challenge to organise and track training of HCW
  - Maintenance, quality controls and test support
  - Miscommunication between pharmaceutical company, diagnostic company, micro lab, and CRO

- Often unclear whether the new test will be developed into a labeled product and who will pay

- Potential regulatory needs discussed too late (e.g. validation studies and EQA)
Rapid diagnostics to guide antibiotic treatment

(VABP/HABP)
User Requirement Specification for VAP (Ideal and Minimal)

- Intended use, medical decision to be influenced, place of use, patient criteria (algorithm)
- Targets
- Sensitivity, specificity, NPV, PPV, reproducibility, reproducibility near clinical threshold, type of analysis, reading system
- Type of specimen, sample prep, waste disposal ...
- End user profile, training required ...
- Biosafety requirement, instrument requirement, power requirement, maintenance required ...
- Test stability, storage requirements, self-life of reagents, controls ...
- Cost (of manufacturing, to end user...) and expected sales
- Regulatory and legal pathway (EU, US)
- Competitive landscape
- Regions of commercialization, market segmentation
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Compliant treatment (n=129)</th>
<th>Non-compliant treatment (n=174)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival through day 28 (total population)</td>
<td>65% (3)</td>
<td>79% (4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline CPIS &lt;7</td>
<td>68% (6)</td>
<td>80% (4)</td>
<td>0.063</td>
</tr>
<tr>
<td>Baseline CPIS ≥7</td>
<td>63% (6)</td>
<td>78% (5)</td>
<td>0.037</td>
</tr>
<tr>
<td>Survival through day 28 (patients with <em>Pseudomonas</em> spp infection*)</td>
<td>55% (9)</td>
<td>82% (9)</td>
<td>0.064</td>
</tr>
<tr>
<td>Resource use, after pneumonia (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation support (total population)</td>
<td>8 (3–15)</td>
<td>9 (2–18)</td>
<td>0.44</td>
</tr>
<tr>
<td>Length of stay in ICU (total population)</td>
<td>12 (7–22)</td>
<td>13 (5–20)</td>
<td>0.57</td>
</tr>
<tr>
<td>Length of stay in hospital (total population)</td>
<td>16 (9–28)</td>
<td>17 (10–26)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mechanical ventilation support (survivors to day 14)</td>
<td>8 (2–18)</td>
<td>9 (2–18)</td>
<td>0.81</td>
</tr>
<tr>
<td>Length of stay in ICU (survivors to day 14)</td>
<td>14 (7–23)</td>
<td>13 (5–21)</td>
<td>0.15</td>
</tr>
<tr>
<td>Length of stay in hospital (survivors to day 14)</td>
<td>18 (11–32)</td>
<td>18 (10–28)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Data are Kaplan-Meier % (SE) estimates of survival or median (IQR), unless otherwise stated. ICU=intensive-care unit.
*We isolated *Pseudomonas* spp for 50 patients (33 patients in the compliant group and 17 in the non-compliant group).

Table 5: Treatment outcomes, grouped by empirical treatment compliance

Kett et al, Lancet Infect Dis 2011;
Vicious circle within the HCA-pneumonia guidelines

Start Combination Therapy in Septic Shock if Suspicion of MDR Gram-Negative Organism

<table>
<thead>
<tr>
<th>Delay Between Documented Hypotension and 1st Appropriate Antibiotic in Combination Therapy</th>
<th>Sample Size, n</th>
<th>Mortality Rate n of Deaths/Total n of Patients (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day mortality</td>
<td>4662</td>
<td>Unadjusted</td>
<td>Monotherapy: 1277/2948 (43.3%) Combination Rx: 461/1714 (26.9%)</td>
<td>0.57 (0.51 - 0.63)</td>
</tr>
<tr>
<td></td>
<td>Propensity score adjusted</td>
<td>2446</td>
<td>Monotherapy: 444/1223 (36.3%) Combination Rx: 355/1223 (29.0%)</td>
<td>0.77 (0.67 - 0.88)</td>
</tr>
</tbody>
</table>

Matched cohort 28-day mortality stratified by delay between documented hypotension and 1st appropriate antibiotic in combination therapy

<table>
<thead>
<tr>
<th>Delay Between Documented Hypotension and 1st Appropriate Antibiotic in Combination Therapy</th>
<th>Sample Size, n</th>
<th>Mortality Rate n of Deaths/Total n of Patients (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000-1</td>
<td>1186</td>
<td>Monotherapy: 332/925 (35.8%) Combination Rx: 67/261 (25.7%)</td>
<td>0.68 (0.53 - 0.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>1.001-4</td>
<td>1147</td>
<td>Monotherapy: 332/925 (35.8%) Combination Rx: 68/222 (30.6%)</td>
<td>0.84 (0.65 - 1.09)</td>
<td>0.19</td>
</tr>
<tr>
<td>4.001-10</td>
<td>1147</td>
<td>Monotherapy: 332/925 (35.8%) Combination Rx: 67/222 (30.2%)</td>
<td>0.82 (0.63 - 1.07)</td>
<td>0.14</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1147</td>
<td>Monotherapy: 332/925 (35.8%) Combination Rx: 74/222 (33.3%)</td>
<td>0.89 (0.69 - 1.15)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Outcome in VAP Patients with 3-Hour Prolonged Infusion of 2 g Meropenem and 2 g Cefepime, plus Tobramycin and Vancomycin

Comparison of mortality, appropriate antibiotic therapy, length of stay, and number of superinfections in patients treated by the clinical pathway vs the historical control

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Historical control (n = 74)</th>
<th>Clinical pathway* (n = 94)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection-related</td>
<td>16 (21.6)</td>
<td>8 (8.5)</td>
<td>0.029</td>
</tr>
<tr>
<td>Appropriate antibiotic therapy, n (%)</td>
<td>36 (48.6)</td>
<td>53 (71.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Length of stay measurements, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection-related</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>26.1 (18.5)</td>
<td>11.7 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Median (25th-75th %)</td>
<td>23 (12-34)</td>
<td>10.5 (6-16)</td>
<td></td>
</tr>
<tr>
<td>Superinfections, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pathogens</td>
<td>26 (35.1)</td>
<td>15 (16.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>MDR pathogens</td>
<td>20 (27.0)</td>
<td>9 (9.6)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*: De-escalation: tobramycin 77%, β-lactam 66%, vancomycin 79%

Rapid VAP Assay based on RCA (RAPP-ID)

- **Target organisms:**
  - *P. aeruginosa*, *Acinetobacter*
  - *S. maltophilia*
  - *Enterobacteriaceae*

- **Resistance genes:** SHV, TEM, CTX-M, VIM, KPC, NDM, OXA, mecA

- **Specimen:** endotracheal aspirate (used in most centres)

- **TAT:** < 2 hours
  - Allow first dose of broad-spectrum antibiotics and de-escalate

- **Therapeutic aim:**
  - Not for diagnosis of disease (VAP)
  - Antibiotic stewardship:
    - Not for ruling in certain pathogens
    - To rule out certain pathogens to reduce of polymyxins, tigecycline, vancomycin, aminoglycosides and linezolid (high NPV: high probability that negative test is correct and that you can stop the antibiotic or change to narrow-spectrum antibiotic)
Proposed algorithm for late-onset VAP “to rule-out” allowing a first dose

Suspicion of VAP
Risk factors of MDR pathogen (ATS-IDSA)

Initial antibiotic treatment:
Carbapenem + aminoglycoside + linezolid or vancomycin

Rapid test for *P. aeruginosa* / *A. baumannii* / Enterobacteriaceae / *meca* / carbapenemase genes

(+) Enterobacteriaceae;
(-) carbapenemase genes

De-escalate
- Stop anti-MRSA antibiotic
- Stop aminoglycoside

(+) *P. aeruginosa* and carbapenemase genes

Modify
- Stop anti-MRSA
- Add colistin
- Stop aminoglycoside
Performance characteristics of rapid diagnostic tests to guide narrow spectrum antibiotics

- Depends on the (severity of) disease and specimen:
  - Late VABP: High sensitivity and NPV (rule-out test)

- Depends on targeted organism:
  - *S. pneumoniae*: molecular methods more sensitive than culture

- Depends on prevalence of disease:
  - NPV drops as prevalence rises and need higher sensitivity and specificity

- Depends on how the test will be used:
  - Alone or in combination with other tests (i.e. in an algorithm)

- Depends on how the results will be used
  - If first dose is allowed, turn-around-time can be several hours
Benefits of a rapid diagnostic test to target antibiotic treatment

• Shorten the period of empiric therapy
• Reduce antibiotic selective pressure and hence resistance
• Decrease broad-spectrum toxic antibiotics and hence morbidity and mortality
• Reduce cost (drug use, morbidity, mortality, LOS)
Agenda

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  – to guide antibiotic treatment (more controversial)
• Opportunities, Conclusions and Future
Antibacterial resistance projects funded at national level between 2007-2013 by priority topic with total funding

Kelly et al, Lancet Infect Dis 2015; published online 18 December
**Funding Opportunities: The 3 Diagnostics Prizes**

<table>
<thead>
<tr>
<th></th>
<th>Longitude Prize 2014</th>
<th>Horizon 2020 Antibiotics Inducement Prize</th>
<th>2014 US AMR Diagnostics Prize</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prize Fund</strong></td>
<td>£10M ($16M)</td>
<td>€1M ($1.3)</td>
<td>$20M</td>
</tr>
<tr>
<td><strong>Opens for Submissions</strong></td>
<td>Fall 2014</td>
<td>2015</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Award Date</strong></td>
<td>2020</td>
<td>Late 2016</td>
<td>TBD</td>
</tr>
<tr>
<td><strong>Prize Statement</strong></td>
<td>“...will reward a solution that enables doctors, nurses and patients to better target their treatment, and helps ensure that right antibiotic is used at the right time.”</td>
<td>“...will be awarded to the most significant development towards an accurate point-of-care solution which can prove a sustained reduction in the number of unnecessary courses of antibiotics prescribed for an upper respiratory tract infection, in the primary care setting of different European countries.”</td>
<td>The launch of a $20 million to facilitate the development of a rapid diagnostic test to be used by health care providers to identify bacterial infections at the point of patient care.</td>
</tr>
</tbody>
</table>

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Conclusions

• New technologies will continue to emerge
• New diagnostics will become more accepted
• Rapid diagnostics will allow development of narrow-spectrum antibiotics (rule-in)
• New diagnostics will mainly impact on modifying antibiotic treatment (rule-out)
• New diagnostics may have limited impact on empiric treatment of severe infections (golden hour)
Future: we need a Roadmap

- To help reaching a consensus regarding a set of needs and the technologies required to satisfy those needs
- To provide a mechanism to help forecast technology developments
- To provide a framework to help plan and coordinate technology development.
- To develop sustainable business models which result in long-term investments, sustainable innovation and public/private partnership
- To develop URS for different diseases, algorithms, ...

Funding: public private partnership EU-US?
Thank You