New Diagnostic approaches and Antimicrobial Management of Infectious Diseases: An Overview from Kuwait

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Faculty of Medicine
Kuwait University
Outline

• Introduction
• Antimicrobial usage in the 21st Century
• Need for new diagnostic approaches
• What infections are priorities for such approaches??
  – Sepsis
  – Pneumonia
• Impact on antimicrobial management of ID
• Overview from Kuwait
In 1969 Surgeon General William H. Stewart declared in a message to the US Congress:

“It is time to close the book on infectious diseases...

.... The war against pestilence is over.”
Definition of New Antibiotics

“New Antibiotic: Anything that we introduce to bacteria and going to see resistance to!”
Antibiotic therapy if indiscriminately used may turn out to be medical flood that temporarily cleans and heals but ultimately destroys life itself

Felix Marti-Ibanez, 1955
...As Antibiotic Options Decline
The Situation in 2004

BAD BUGS, NO DRUGS
As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews

Infectious Diseases Society of America
http://www.idsociety.org/badbugsnodrugs.html
The Situation Worsens
Years Later

- **Bad Bugs, No Drugs: No ESKAPE**
  - Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp

- **Dry pipeline**
  - Some important molecules for MRSA
  - Few novel molecules for other ESKAPE pathogens
  - No new drugs for infection due to MDR Gram (-) bacilli (e.g., A baumannii and P aeruginosa)
  - Few advantages over currently available therapies

Rice LB. *J. Infect Dis.* 2008;197:1079
Defining ESKAPE?

Highlighting troublesome bacteria with the ability to “escape” the effects of current antimicrobial agents…

ESCAPE

Enterococcus faecium
Staphylococcus aureus
Clostridium difficile
Acinetobacter baumannii
Pseudomonas aeruginosa
Enterobacteriaceae
The $10 \times 20$ Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020
THE ANTIMICROBIAL RESISTANCE CHALLENGES
If and when antibiotics are indicated, the philosophy is now based on attempting to get it right first time.
Does Inappropriate antimicroboidal therapy result in antibiotics resistance???

OR

Antibiotic resistance leads to inappropriate therapy???
VICIOUS CYCLE ???
COMBAT DRUG RESISTANCE

No action today, no cure tomorrow

7 APRIL 2011 WORLD HEALTH DAY
What could be the actions today???
Antimicrobial Stewardship

The process of appropriate usage of antimicrobial agents aiming at prevention of antimicrobial resistance
Rational use of antibiotics

Education

Infection Control

Proper Laboratory Diagnosis

De-escalation

Vaccination
1. Role of new and rapid diagnostic tools in the early diagnosis of sepsis
SEPSIS

= Infection

+ Systemic inflammation
Sepsis

Worldwide:
30,000,000 cases / year

USA:
1.000.000 / year


Germany:
~125.000 - 300.000 / year

Mortality rate increases with increasing severity.

Mortality rate is:
- 7% in patients with SIRS
- 16% in patients with Sepsis
- 20% in patients with Severe Sepsis
- 46% in patients with Septic Shock

Rangel-Frausto et al. (JAMA 1995)
The Golden Hour

And

The Silver Day
We ought to spend more time to search for an accurate diagnosis rather than search for the Magic Bullet for the treatment of Sepsis"  

Roger Bone, 1996
Prompt Diagnosis of Sepsis: Unachievable goal
Experience from Kuwait
A. Molecular diagnosis of sepsis
Conventional culture system

1. < 50% positive
2. TAT 48-72 hrs
Evaluation of the comparative performance of Verigine Blood Culture Nucliec acid System to Conventional Techniques in a Tertiary-care Hospital in Kuwait

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¹ Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait.
² Laboratory Department, Ibn Sina Hospital, Kuwait
The diagnosis of bacteremia and sepsis is a priority in a Clinical Microbiology Department as they carry high mortality (20-50%).

Early correct antibiotic treatment is correlated with higher survival rates.

This is the main reason why broad spectrum antibiotics are usually administered until the microbiology results are known.
Once the bacterial pathogen is known, treatment can be adjusted to a more specific antibiotic therapy.

A key predictor of mortality rates in patients with severe bloodstream infection is the time to identification of the causative pathogen and initiation of targeted therapy.
Rapid identification of blood isolates is important in patient management as well as antimicrobial stewardship.
The Verigene Gram-positive and Gram negative Blood Culture (BC-GP, BC-GN)) system (Nanosphere, USA) is a qualitative, multiplexed automated nucleic acid in vitro diagnostic test for the direct identification of Gram-positive and Gram negative bacteria and their genetic resistance markers. With a TAT of 2 hrs
Verigene BC-GP and BC-GN identifiable targets
NB. Of the staphylococci only *S. aureus*, *S. epidermidis* and *S. lugdunensis* can be identified as the other staphylococci are not present in the database.

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus Spp.</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Streptococcus Spp.</td>
<td>S. anginosus. Group</td>
</tr>
<tr>
<td>Micrococcus Spp.</td>
<td>S. agalactiae</td>
</tr>
<tr>
<td>Listeria Spp.</td>
<td></td>
</tr>
<tr>
<td>Resistance</td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>Mec A.</td>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Van A.</td>
<td></td>
</tr>
<tr>
<td>Van B.</td>
<td>Enterococcus faecium</td>
</tr>
</tbody>
</table>

**Gram-Positive Blood Culture (BC - GP) Tests:**
<table>
<thead>
<tr>
<th>Targets</th>
<th>Organism/Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Targets</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>Citrobacter</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>Proteus</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella oxytoca</em></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aerogenes</em></td>
</tr>
<tr>
<td></td>
<td><em>Serratia marcescens</em></td>
</tr>
<tr>
<td>Resistance Marker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CTX-M</td>
</tr>
<tr>
<td></td>
<td>VIM</td>
</tr>
<tr>
<td></td>
<td>KPC</td>
</tr>
<tr>
<td></td>
<td>IMP</td>
</tr>
<tr>
<td></td>
<td>NDM</td>
</tr>
<tr>
<td></td>
<td>OXA (48/23/40/58)</td>
</tr>
</tbody>
</table>

N.B. *Stenotrophomonas maltophilia* cannot be identified as it is not present in the data base.
Objectives

- To evaluate the performance of Verigene (BC-GP and BC-GN) nucleic acid test for the direct identification of Gram-positive and Gram-negative bacteria from positive blood culture bottles in comparison with Gene-Xpert system (Cepheid, USA) for Gram-positive bacteria and with the conventional culture technique for both Gram-positive and Gram-negative bacteria.
- To evaluate the performance of Verigene (BC-GP) and (BC-GN) for the detection of resistant markers directly from positive blood culture bottles in comparison with conventional culture technique.
- To evaluate the impact of rapid detection of the causative pathogens from blood on the management of patients.
Materials and Methods

- All the demographic data including the age, sex, patient location, underlying clinical condition, clinical and laboratory data suggesting sepsis, initial empirical therapy, adjusted therapy and outcome of the patients were collected.

- For Gram-positive bacteria:
  - All blood culture bottles (Bactec, Bekton Dickinson, USA) showing Gram-positive cocci by Gram stain were processed in:
    - Verigene for BC-GP according to the manufacturer’s instructions
    - GeneXpert (Cepheid, USA) for BC-GP (only for Gram-positive cocci in clusters)
  - All the positive blood culture bottles were simultaneously cultured by conventional methods for both ID as well as susceptibility using Vitek II, and Vitek MS (Biomerioux, France)
Materials and Methods

• For Gram-negative bacteria:
  – All blood culture bottles showing Gram-negative bacilli by Gram stain were processed in:
    • Verigene for BC-GN according to the manufacturer’s instructions
  – All the positive blood culture bottles were simultaneously cultured by conventional methods for both ID as well as susceptibility using Vitek II, and Vitek MS

• A total of 11 QC strains of different streptococci were included in the evaluation
Results

A. Gram-positive
A total of 63 patients with positive blood culture for Gram-positive cocci were included in the evaluation.
Table 1: Comparison between results of Verigine and conventional culture for Gram-positive bacteria

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th>Virigine</th>
<th>Conventional culture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><strong>S.epidermidis</strong></td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td><strong>S.homonis</strong></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>S.hemolyticus</strong></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other Staphylococci</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td><strong>Enterococcus fecalis</strong></td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Enterococcus fecium</strong></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Streptococcus mitis</strong></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Streptococcus spp.</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Micrococcus spp.</strong></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gram-positive cocci (QC strains)</td>
<td>Verigine</td>
<td>Conventional</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><em>Enterococcus fecium</em></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3: Comparison between Verigine, Cephid Gene Xpert and conventional culture for *Staphylococcus* spp.

<table>
<thead>
<tr>
<th><em>Staphylococcus</em> spp.</th>
<th>Verigine</th>
<th>Gene Xpert</th>
<th>Conventional culture</th>
<th>% Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin sensitive</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S.epidermidis</em></td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td><em>S.homonis</em></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td><em>S.hemolyticus</em></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 4: Comparison between Verigine and conventional culture for detection of resistance markers for *Staphylococcus* spp.

<table>
<thead>
<tr>
<th>Conventional Culture</th>
<th>Verigine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin sensitive <em>staphylococcus aureus</em></td>
<td>TN 11</td>
<td>FP 2</td>
</tr>
<tr>
<td>Methicillin-resistant coagulase-negative <em>Staphylococci</em></td>
<td>FN 2</td>
<td>TP 1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>
Table 5: Comparison between Verigine and conventional culture for detection of resistance markers for *Enterococcus* spp.

<table>
<thead>
<tr>
<th>Conventional Culture</th>
<th>Verigine</th>
<th>VAN A and B negative</th>
<th>VAN A and B positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin sensitive <em>Enterococcus fecalis</em></td>
<td>TN</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Vancomycin-sensitive <em>Enterococcus fecium</em></td>
<td>FN</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus fecium</em></td>
<td>FN</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
A total of 63 patients with positive blood culture for Gram-negative cocci were included in the evaluation. 3 of them were Stenotrophomonas maltophilia. Not detected.
Table 6: Comparison between results of Verigine and conventional culture for Gram-negative bacteria

<table>
<thead>
<tr>
<th>Gram negative</th>
<th>Verigine</th>
<th>Conventional culture</th>
<th>% Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>24</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>15</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>8</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>7</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td><em>Pseudomonas</em> <em>oryzihabitans</em></td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td><em>Enterobacter</em> <em>spp.</em></td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td><em>Proteus</em> <em>spp.</em></td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 7: Comparison between Verigine and conventional culture for detection of resistance markers for Gram-negative bacteria

<table>
<thead>
<tr>
<th>Bacteria (No.)</th>
<th>Verigine</th>
<th>Conventional culture</th>
<th>% Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E.coli (24)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESBL</td>
<td>10</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Non-ESBL</td>
<td>14</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td><strong>klebsiella pneumoniae (8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESBL</td>
<td>4</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Non-ESBL</td>
<td>4</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td><strong>Enterobacter spp (2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESBL</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Non-ESBL</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td><strong>Serratia marcescens (1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESBL</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Non-ESBL</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa (7)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem resistant</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Non-carbapenem resistant</td>
<td>7</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td><strong>Acinitobacter spp. (15)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem resistant</td>
<td>1</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Non-carbapenem resistant</td>
<td>9</td>
<td>4</td>
<td>44</td>
</tr>
</tbody>
</table>
Table 8: Impact of rapid identification of Gram-positive bacteria on the modification of the empirical antibiotic therapy

<table>
<thead>
<tr>
<th>Gram positive bacteria</th>
<th>De-escalate</th>
<th>Escalate</th>
<th>Continue same antibiotic</th>
<th>Stop antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>11</td>
<td>2</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>Streptococcus mitis</em></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 9: Impact of rapid identification of Gram-negative bacteria on the modification of the empirical antibiotic therapy

<table>
<thead>
<tr>
<th>Gram-negative bacteria</th>
<th>De-escalate</th>
<th>Escalate</th>
<th>Continue same antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>2</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>0</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>
Molecular diagnosis of sepsis

TAT 2 hrs
B. Procalcitonin as a septic marker
Biomarkers for stratification of septic patients
• **To** achieve early and accurate detection of sepsis
• **To** differentiate infection from noninfectious SIRS
• **To** prognosticate clinical outcome
Hospitals and particularly ICUs have a great need for markers which are specific and reliable indicators of Sepsis!
Expectations on an innovative Sepsis Marker

Clinical aspects

• specific
  – Recognises only septic conditions (no false positives)

• Sensitive
  – Recognises all septic conditions (no false negatives)

Technical aspects

• Applicable in lab routine
• Available 24/7
• Short time to result
Procalcitonin
PCT

The Aminoacid-Sequence of Procalcitonin (PCT)

- N-ProCT
- Calcitonin
- Katacalcitonin
- Cleavage site of Endopeptidases

PAM = Peptidyl-Amidating Monooxygenase
PCT Levels increase with Extension of Infection and Severity of Disease

- Stable in Blood Samples
  - Store at Room Temperature
- Half-Life in Plasma:
  25–30hrs (1 Day)
  - Measure 1x per Day

TAT is 30 mints

Clinical condition
- Septic shock
- Severe sepsis
- Systemic infections (sepsis)
- Local infections
- Normal values

0,05
0,5
2
5

Sepsis/Sev.Sep/SS!
PCT

Controversies!!!
Pro-PCT
Rapid increase
Rapid decrease
Over 24 hrs

No increase in viral infection
Not influenced by steroidal and non-steroidal antiinflammatory agents

The increase is proportional to severity of sepsis and Sofa score

TAT is 30 mints

Intensive care Medicine, 2011, 37: 796-800
Anti-PCT
Will PCT level improve survival and reduce antibiotics exposure in ICU patients?

No big difference in survival between PCT and control
Will PCT level help to reduce antibiotic exposure??

YES

PCT had **2.7 more days without antibiotic exposure**

**Limitation of the study:**
53% PCT group were not treated according to protocol??
Case 1

• A 40 year-old male
• Admitted to the ICBU 35% burn on 18\textsuperscript{th} June, 2013
• Severe hypotension
• Started on Meropenem immediately
• On the 23\textsuperscript{rd} June blood grew MDR \textit{Acinitobacter baumanii} sensitive to colistin only
• Same bacteria grew in Wound, ETT
Case 1

Blood culture positive

<table>
<thead>
<tr>
<th>Date</th>
<th>Temp</th>
<th>WBC</th>
<th>PCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>19/6</td>
<td>38.5</td>
<td>12.7</td>
<td>3.61</td>
</tr>
<tr>
<td>20/6</td>
<td>37</td>
<td>10</td>
<td>7.77</td>
</tr>
<tr>
<td>21/6</td>
<td>38.5</td>
<td>12.89</td>
<td>4.8</td>
</tr>
<tr>
<td>23/6</td>
<td>38.5</td>
<td>14.7</td>
<td>4.8</td>
</tr>
<tr>
<td>24/6</td>
<td>31.6</td>
<td>17.2</td>
<td>10.3</td>
</tr>
<tr>
<td>25/6</td>
<td>17.2</td>
<td>21.1</td>
<td>10.3</td>
</tr>
<tr>
<td>26/6</td>
<td>6.8</td>
<td>16.2</td>
<td>6.6</td>
</tr>
<tr>
<td>27/6</td>
<td>6.6</td>
<td>16.5</td>
<td>6.6</td>
</tr>
<tr>
<td>29/6</td>
<td>4.2</td>
<td>16.4</td>
<td>4.2</td>
</tr>
<tr>
<td>30/6</td>
<td>2.8</td>
<td>21.6</td>
<td>4.2</td>
</tr>
<tr>
<td>4th July</td>
<td>2.2</td>
<td>0.18</td>
<td>2.2</td>
</tr>
<tr>
<td>11th July</td>
<td>37</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>

Meropenem

Colistin

WBC: White Blood Cells
PCT: Procalcitonin
Case 2

- 57 year subdural hematoma
- MICU
- Sepsis:
- Started on Pip/Tazo
- ETT
- Blood Culture
  - Both grew *Klebsiella pneumoniae* ESBL
- Shifted to Meropenem
Case 2

Meropenem

<table>
<thead>
<tr>
<th>Date</th>
<th>Temp</th>
<th>WBC</th>
<th>PCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd Aug</td>
<td>37.5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>6th Aug</td>
<td>38</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>8th Aug</td>
<td>38.4</td>
<td>16</td>
<td>66</td>
</tr>
<tr>
<td>9th Aug</td>
<td>37.2</td>
<td>9.76</td>
<td>32.65</td>
</tr>
<tr>
<td>11th Aug</td>
<td>37.6</td>
<td>9.7</td>
<td>11.88</td>
</tr>
<tr>
<td>14th Aug</td>
<td>37.1</td>
<td>8.9</td>
<td>5.58</td>
</tr>
<tr>
<td>15th Aug</td>
<td>37.2</td>
<td>8.8</td>
<td>0.08</td>
</tr>
</tbody>
</table>

- Temp
- WBC
- PCT

Legend:
- Temp
- WBC
- PCT
Prompt modification of therapy upon increase in PCT

Antimicrobial Stewardship
2. Role of new and rapid diagnostic tools in the early diagnosis of pneumonia
Pneumonia

Life-threatening acute infection of LRT

» incidence Germany 600.000 – 800.000 ¹

» up to 5% of patients admitted to a hospital for other causes develop a pneumonia ²

» fast progressing disease

American Thoracic Society / IDSA classifies

» community-acquired pneumonia (CAP)
   » acquired in the community without any history of medical intervention

» healthcare-associated pneumonia (HCAP)
   » occurs in a non-hospitalized patient with extensive healthcare contact

» hospital-acquired pneumonia (HAP)
   » occurs 48 hours or more after admission
   » ventilator-associated pneumonia (VAP) after endotracheal intubation

¹ Höffken et al, S3 Leitlinie CAP (2009)
Microbial etiology of pneumonia

Hospital-acquired pneumonia

- caused by a wide variety of pathogens
- spectrum depends on the circumstances pneumonia was acquired
- polymicrobial in 25 - 30%, depending on subtype
- common pathogens include
  - aerobic gram-negative bacilli
  - gram-positive cocci
- 30 – 40 % false-negative cultures
- hospitalized pneumonia
  - due to viruses / fungi significantly less common, except in immune compromised patient
  - bacteria often drug-resistant

Clinical relevant resistance in pneumonia

– It is not just MRSA ..... 

» β-lactam-resistance, including ESBL

» KPC-resistance

» Macrolide-resistance

» Quinolone-resistance

» Multi-drug resistance (MDR)
Challenges in testing respiratory tract infections
• Mortality rates reaches up to 36%
• Rapid and accurate diagnosis and effective initial treatment knowing:
  • What is the pathogen?
  • Which antibiotic to use?
  • Which antibiotic will fail?

Successful outcome

Reduces mortality

Reduces length of stay

Reduces resistance development

Reduces Cost
Empirical therapy for pneumonia

Inappropriate empiric therapy

- empirically based initial regimen wrong in up to 40 – 50% of cases \(^1\)
- associated with increased mortality,
- adequate initial treatment significantly reduces
  - mortality
  - LOS
  - costs per patient

- outcome benefits from faster diagnostics \(^3\)

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1 Kollef et al, Chest. 1999 Feb;115(2):462-74
CASE STUDY

• Female, 73 y

0 day

Empiric treatment

Dyspnoe
Fever
Chest pain

Chest radiograph
lung infiltrate
CRB-65 1

Mortality 1%

CAP
► Hospitalization

1 Short inpatient hospitalization
2 Severe pneumonia

14 day

Resp. insufficient

Adjusted treatment

Chest radiograph
progressive infiltrate
CRB-65 3
Mod. AST Score +
Mortality 30%

sCAP
► ICU

Sputum culture
fluoroquinolone resistant
P. aeruginosa

Fast molecular testing
Role of faster molecular testing in making difference in the standard of care management of pneumonia

In less than 4 hours

Health economic modeling of the impact of fast pneumonia testing
An Unmet Medical Need: Rapid Molecular Diagnostics Tests for Respiratory Tract Infections

Infectious Diseases Society of America®
Evaluation of P50 Pneumonia Application in the rapid diagnosis of pneumonia in a tertiary-care hospital in Kuwait

Dr. Aneesa Abdulla
Dr. Shama Shatti
Dr. Ahmed Behbehani
Professor Eiman Mokaddas
1. Unyvero™ A50 Analyzer: Universal Analyzer
2. Unyvero™ C8 Cockpit: Intuitive User Cockpit
3. Unyvero™ L4 Lysator: Universal Lysator
4. Unyvero™ Cartridge: Disposable for different clinical application
### Antibiotic Resistance Markers

| Marker | Structure          | Mechanism                  | Localization   |
|--------|--------------------|----------------------------|----------------|----------------|
| tem    | β-Lactamase        | Target inactivation/hydrolyzation | Plasmid        |
| shv    | β-Lactamase        | Target inactivation/hydrolyzation | Chromosome/Plasmid |
| ctx-M  | β-Lactamase/Cefotaxime | Target inactivation/hydrolyzation | Plasmid        |
| dha    | AmpC-β-Lactamase   | Target inactivation/hydrolyzation | Chromosome/Plasmid |
|Obc    | AmpC-β-Lactamase   | Target inactivation/hydrolyzation | Plasmid        |
| kpc    | Carbapenemase      | Target inactivation/hydrolyzation | Chromosome/Plasmid |
| oxa-51-like | Carbapenemase | Target inactivation/hydrolyzation | Plasmid        |
| mecA   | Penicillin binding protein | Target alteration | Chromosome |
| msrA   | Efflux pump        | Target discharge           | Chromosome     |
| ermA   | Erythromycin-methylase | Target modification | Chromosome and Plasmid |
| ermB   | Erythromycin-methylase | Target modification | Chromosome and Plasmid |
| ermC   | Erythromycin-methylase | Target modification | Chromosome and Plasmid |
| mefE/A/E | Efflux pump | Target discharge | Transposon |
| intI   | Integrate          | MDR marker                 | Chromosome and Plasmid |
| sulI   | DHPS               | Target alteration          | Plasmid        |
| gyrA83 | Gyrase A.          | Target mutation            | Chromosome     |
| gyrA87 | Gyrase A.          | Target mutation            | Chromosome     |
| parC   | Topoisomerase      | Target mutation            | Chromosome     |

### Beta-Lactams

- **Penicillin**
- **3rd Gen Cephalosporin**
- **Carbapenem**
- **Oxacillin/Methicillin**
- **Macrolide**
- **Lincomamide**
- **MDR**
- **Sulphonamide**
- **Fluoroquinolone**

### Bacterial Strains

- **Staphylococcus aureus**
- **Streptococcus pneumoniae**
- **Enterobacter sp.**
- **Escherichia coli**
- **Klebsiella pneumoniae**
- **Klebsiella oxytoca**
- **Morganella morgani**
- **Proteus sp.**
- **Serratia marcescens**
- **Haemophilus influenzae**
- **Pseudomonas aeruginosa**
- **Acinetobacter baumannii**
- **Stenotrophomonas maltophilia**
- **Moraxella catarrhalis**
- **Legionella pneumophila**
- **Chlamydia pneumoniae**
- **Pneumocystis jirovecii**
Multiplex PCR and array-based detection

**Pathogen DNA**

**Specific Amplification**

**Target Hybridization**

**Detection and Specific Control**

Step 1 - 60 seconds:
Transfer the patient sample into the Unyvero™ Sample Tube.

Step 2 - 30 seconds:
Place the Unyvero™ Sample Tube into the Unyvero™ Lysator.

Step 3 - 30 seconds:
After taking the Sample Tube out of the Lysator insert it and the Unyvero™ Master Mix Tube into the Unyvero™ Cartridge.

Step 4 - 20 seconds:
Load the Cartridge into the Unyvero™ Analyzer for further fully automated processing.

Answers:
Comprehensive results are available in <4 hours and will be displayed on the Unyvero™ Cockpit screen without any further operator interaction.
Objectives

• To evaluate the role of \textit{unyvero™} in the rapid diagnosis of pneumonia (Both CAP and HAP) and the detection of resistance markers in comparison with the conventional culture techniques

• To evaluate the impact of \textit{rapid molecular diagnosis of pneumonia} on the management of patients
Methods

• All patients with the clinical diagnosis of pneumonia both CAP, HAP and VAP from 3 ICU’s, one Organ Transplant Department, and KCCC/ Shaikha Badria Center for Cancer and Chemotherapy admitted to the hospital from November 2012 till April 2013 were included in the evaluation.

• 6 patients on mechanical ventilation with no evidence of pneumonia were included as surveillance

• All relevant clinical data were collected

• Sputum, ETT’s or BAL were inoculated into cartridge and processed as well by conventional culture technique
Results
A total of 45 patients were included in the evaluation

VAP
18

HAP
10

CAP
11

6 surveillance cases
• The detailed data on all the patients:
  - Underlying conditions
  - Clinical diagnosis
  - Signs of infection (e.g. fever, WBC, PCT)
  - Microbiology diagnostic findings by Unyvero compared to the conventional culture techniques for both ID as well as antimicrobial susceptibility testing results
  - Empirical antibiotic therapy
  - **Modification of antibiotic therapy based on Unyvero results in 4 hrs**
  - The final outcome of the patients.
Comparision between Unyvero and Conventional culture in the detection of different microrganisms
<table>
<thead>
<tr>
<th>Organism</th>
<th>Unyvero</th>
<th>Conventional Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>S. aureus</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Acinetobacter baumanii</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>E. coli</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Maroxella catarallis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pneumocystis jerowesii</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pantonia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Legionella pneumoniae</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Chamydia pneumoniae</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Not detected/ No growth</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Commensals</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
TAT for Unyvero
4hrs
For both ID and AST

TAT for the conventional culture technique is
48-72 hrs
Comparison of the detection of antibiotic resistance between Unyvero System and the conventional Culture
<table>
<thead>
<tr>
<th>Organism</th>
<th>Conventional culture</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td>2 1 1 1</td>
</tr>
<tr>
<td><em>Acinetobacter baumanii</em></td>
<td>4 4 4 4</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
<td>1 1 1 1</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>1 1 1 1</td>
</tr>
</tbody>
</table>

TAT 4 hrs
Impact of Rapid diagnosis of Pneumonia on the management of pneumonia cases
In 12 cases
6 VAP, 4 CAP, 2 HAP

Empirical AB X modified either the same day or within 24 hrs according to Unyvero results for both ID and resistance markers

With significant improvement after the modification
4 patients all immunocompromised *Legionella pneumophila* detected and treated accordingly

One *Chlamydia pneumoniae* detected in one cancer patient and treated accordingly
Case 1

- 52 years Kidney transplant
- Case of CAP (hospitalized)
- Unyvero in 4hrs:
  - *S. pneumoniae*
  - *Hemophilus influenzae*
- Empirical therapy:
  - Respiratory quinolone
  - No improvement
- Modification:
  - Add ceftriaxone
- Marked improvement

Conventional culture
After 48 hrs
*Haemophilus influenzae*
Case 2

- 57 years Kidney transplant
- A case of VAP
- Unyvero in 4 hrs:
  - *Acinetobacter baumanii*
  - *Pseudomonas aeruginosa*
- Resistance Markers:
  - Int1, sul1 AND Oxa 51
- Empirical therapy:
  - Meropenem
- Modification upon resistance markers the same day:
  - Add colistin

Conventional culture after 72 hrs *Acinetobacter baumanii*
Resistant to meropenem
Sensitive to colistin
Case 3

- 27 years patient in neurology ward
- A case of HAP
- Unyvero in 4 hrs:
  - *S.pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Legionella pneumophila*
  - *Stenotrophomonas maltophilia*
  - *S.aureus*
- Resistance markers:
  - None
- Empirical therapy:
  - Tazocin
- Modification of therapy:
  - Add respiratory quinolone for *Legionella pneumophila*

Conventional culture after 72 hrs
- Proteus mirabilis
- Pseudomonas aeruginosa
- Sensitive strain
Case 4

- 53 years patient in SB
- A case of lymphoma
- Unyvero in 4 hrs:
  - *Acinetobacter baumanii*
  - *Stenotrophomonas maltophilia*
  - *Pneumocystis jiroveci*
- Resistance Markers:
  - Oxa 51
  - CTX-M
  - Tem
- Empirical therapy:
  - Meropenem
- Modification:
  - Add colistin
  - Cotrimoxazole

**Conventional techniques**

After 72 hrs

*Acinetobacter baumanii* only

Sensitive to meropenem
Acknowledgement
Conclusion
Management of Infectious Diseases
In the era of antimicrobial resistance, are new antibiotics the solution???
Culture result

De-escalate
Proper laboratory diagnosis

Effective antimicrobial agent

Treatment success

Lab result after 2-5 days

Lab Results not matching with the empirical therapy

Wrong ID

Wrong Susceptibility

Treatment failure
Effective directed antimicrobial agent (difficult to grow, however clinical important pathogens and MDRO's)

Treatment success

Rapid Laboratory diagnosis

Less antimicrobial resistance

Antimicrobial Stewardship
Timing Line
Diagnosing Sepsis and Pneumonia

Time waits for no body
Tomorrow is too late

Thank You