The Year in Infectious Diseases

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Treatment of latent tuberculosis

- preventive chemotherapy

  ... for subjects with conversion from TST/TIGRA-negative to positive or for TST/TIGRA-positive patients with enhanced risk of (early) disease manifestation/reactivation (overt pulmonary disease within 2 years after infection) (~5-10/100 person-years)

  current standard: (6-) 9 (-12) months INH daily

  problems: compliance, INH resistance
Treatment of latent tuberculosis
Treatment of latent tuberculosis

- **Martinson et al.**
  - 4-arm trial
    - 1x weekly rifapentine+INH (900 mg each) for 12 weeks (DOT)

~1000 HIV-positive subjects (South Africa, no HAART)
Primary endpoint tuberculous disease: similar in the 4 arms (<3/100 person years)
Untoward effects: more frequent with daily INH continuously
Treatment of latent tuberculosis

- Martinson et al.
  - 4-arm trial
    - 1x weekly rifapentine+INH (900 mg)

  *Rifapentine*
  - also known as cyclopentyl rifampicin
  - available as 150 mg tablets
  - long half-life, active metabolite
  - "orphan" drug in the EU

- ~1000 HIV-positive subjects (South Africa, no HAART)
- Primary endpoint tuberculous disease: similar in the 4 arms (<3/100 person years)
- Untoward effects: more frequent with daily INH continuously
Treatment of latent tuberculosis

- **Martinson et al.**
  - 4-arm trial
    - 1x weekly rifapentine+INH (900 mg each) for 12 weeks (DOT)
    - 2x weekly rifampicin+INH for 12 weeks (DOT)
    - daily INH continuously (self-supervised)
    - daily INH for 6 months (="standard of care") (self-supervised)
  - ~1000 HIV-positive subjects (South Africa, no ART)
  - Primary endpoint tuberculous disease: similar in the 4 arms (<3/100 person-years)
  - Untoward effects: more frequent with daily INH continuously
Sterling et al.

- 2-arm trial
  - 1x weekly rifapentine+INH (900 mg each) for 12 weeks (DOT)
  - daily INH for 9 months („standard of care“)
- Almost 8,000 patients (3% HIV-positive), follow-up 33 months, completion rate 82% vs 69%
- Tuberculous disease similar (3/100 person-years)
- More grade 3/4 adverse drug reactions with INH, in particular hepatotoxicity (9 versus 18/100 person-years)
Tuberculosis/HIV coinfection

- Timing of ART?
Timing of ART?

- 2 recent trials

- early vs delayed:
  2 vs 8 weeks, and <2 vs 8-12 weeks

Blanc et al *NEJM* 2011; 365: 1471
Havlir et al *NEJM* 2011; 365: 1482
Timing of ART?

- Results:
  - Blanc et al: "early" better (case fatality 18 vs 27%)
  - Havlir et al: "early" better for pts with <50 CD4 cells/µL (AIDS/deaths 16 vs 27%)

- IRIS more frequent with early ART

Blanc et al *NEJM* 2011; 365: 1471
Havlir et al *NEJM* 2011; 365: 1482
• ... the paper describing in detail the “ZEPHyR” trial (linezolid for MRSA pneumonia) is now out there!!
S. aureus

- Linezolid for MRSA pneumonia

Wunderink et al CID 2012; 54:621
S. aureus & vancomycin

... NO new convincing data on clinically useful effects of vancomycin dosing optimization and on the relevance of high trough level targets
S. aureus & vancomycin

- ... from the “ZEPHYR” trial

<table>
<thead>
<tr>
<th>Vancomycin trough levels (day 3)</th>
<th>(0-7.9 \mu g/mL)</th>
<th>(8-12.3 \mu g/mL)</th>
<th>(12.4-17.4 \mu g/mL)</th>
<th>(&gt;17.4 \mu g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17/35 (48.6)</td>
<td>17/37 (46.0)</td>
<td>15/33 (45.5)</td>
<td>15/33 (45.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vancomycin MIC</th>
<th>(&lt;1 \mu g/mL)</th>
<th>(1 \mu g/mL)</th>
<th>(\geq 2 \mu g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10/16 (62.5)</td>
<td>77/122 (61.5)</td>
<td>3/8 (37.5)</td>
</tr>
<tr>
<td></td>
<td>7/14 (50.0)</td>
<td>64/134 (47.8)</td>
<td>7/13 (53.8)</td>
</tr>
<tr>
<td></td>
<td>-22.8 to 47.8</td>
<td>1.6 to 25.8</td>
<td>-59.5 to 26.8</td>
</tr>
</tbody>
</table>

Wunderink et al CID 2012; 54:621
**S. aureus & vancomycin**

**Kullar et al, Detroit:**

*Conclusions.* In light of the high failure rates associated with this antimicrobial, optimizing the pharmacokinetic/pharmacodynamic properties of vancomycin by targeting higher trough values of 15–20 mg/L and AUC$_{24h}$/MIC ratios $\geq$400 in selected patients should be considered.

**Moore et al, Detroit:**

*Conclusions.* The results demonstrated that daptomycin was associated with a better outcome compared with vancomycin for the treatment of BSIs due to MRSA with higher vancomycin MICs. These findings support the recommendations of recent guidelines, which suggest consideration of the switch to alternative agents when the isolate has a high vancomycin MIC or when patients are not improving during receipt of therapy.
S. aureus & vancomycin MICs

... the Australian experience

Antibiotic Choice May Not Explain Poorer Outcomes in Patients With Staphylococcus aureus Bacteremia and High Vancomycin Minimum Inhibitory Concentrations

Natasha E. Holmes,1 John D. Turnidge,2,3 Wendy J. Munckhof,4,5 James O. Robinson,6 Tony M. Korman,7,8 Matthew V. N. O’Sullivan,9 Tara L. Anderson,10,11 Sally A. Roberts,2 Wei Gao,12 Keryn J. Christiansen,13,14 Geoffrey W. Coombs,13 Paul D. R. Johnson,1,15,16,9 and Benjamin P. Howden1,12,15,17,9
S. aureus & vancomycin MICs

... the Australian experience

- N=523 S. aureus bacteremia (324 MSSA)
- 34% vanco MIC >1.5 µg/mL (E-test) (26% MSSA)
- Multivariable analysis:
  
mortality associated with ↑ age & ↑ vanco MIC in both MRSA and MSSA !!
and independent of vancomycin treatment

Holmes et al JID 2011; 204:340
β-Lactam extended infusion

- systematic reviews/metaanalyses inconclusive

Kasiakou et al *Drugs* 2005; 65:2499

Roberts et al *Crit Care Med* 2009; 37:2071

Tamma et al *BMC Infect Dis* 2011; 11:181
Slow initial β-lactam infusion and oral paracetamol to treat childhood bacterial meningitis: a randomised, controlled trial

Tuula Pelkonen, Irmeli Roine, Manuel Leite Cruzeiro, Anne Pitkaranta, Matti Kataja, Heikki Peltola
β-Lactam extended infusion: meningitis study

- Single-center (Angola)
- Children 2 months – 13 years of age
- Study design: cefotaxime therapy during initial 24 h:
  - continuous infusion vs i.v. bolus (every 6 h)
- Second randomization: paracetamol vs placebo

Pelkonen et al Lancet Infect Dis 2011; 11:613
Pen/βLI for ESBL infection?

- So far, their use not encouraged based on:
  - problems with in vitro testing (MIC breakpoint, inoculum effect, detection with automated systems)
  - some unfavourable clinical experience published

→ limited clinical experience with them
→ carbapenem overuse ?!
Pen/βLI for ESBL infection?

... the Spanish experience

β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum β-Lactamase–Producing Escherichia coli: A Post Hoc Analysis of Prospective Cohorts

Jesús Rodriguez-Baño,1,* María Dolores Navarro,1 Pilar Retamar,1 Encarnación Picón,1 Álvaro Pascual,1,3 and the Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group
Pen/βLI for ESBL infection?

Empirical therapy cohort (n=103)
- Treated with BLBLI (n=72)
  - 37 Amoxi/Clav
  - 35 Pip/Tazo
- Treated with carbapenem (n=31)

Definitive therapy cohort (n=174)
- Treated with BLBLI (n=54)
- Treated with carbapenem (n=120)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BLBLI (n = 72)</th>
<th>Carbapenem (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median y (IQR)</td>
<td>69 (59-80)</td>
<td>60 (52-78)</td>
<td>.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>29 (40.3)</td>
<td>11 (35.5)</td>
<td>.6</td>
</tr>
<tr>
<td>Nosocomial acquisition</td>
<td>26 (36.1)</td>
<td>24 (77.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Charlson index, median, (IQR)</td>
<td>2 (1-5)</td>
<td>2 (1-5)</td>
<td>.6</td>
</tr>
<tr>
<td>Cancer</td>
<td>21 (31.9)</td>
<td>11 (35.5)</td>
<td>.7</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>5 (6.9)</td>
<td>5 (16.1)</td>
<td>.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (2.8)</td>
<td>3 (9.7)</td>
<td>.1</td>
</tr>
<tr>
<td>Urinary or biliary tract as source</td>
<td>52 (22.2)</td>
<td>18 (58.1)</td>
<td>.1</td>
</tr>
<tr>
<td>ICU admission</td>
<td>7 (9.9)</td>
<td>2 (6.7)</td>
<td>.7</td>
</tr>
<tr>
<td>Severe sepsis or shock at presentation</td>
<td>14 (19.4)</td>
<td>9 (29.0)</td>
<td>.2</td>
</tr>
<tr>
<td>Pitt score, median (IQR)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>.7</td>
</tr>
<tr>
<td>CTX-M enzyme</td>
<td>57 (80.3)</td>
<td>25 (86.2)</td>
<td>.4</td>
</tr>
<tr>
<td>Definitive therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>32 (44.4)</td>
<td>30 (93.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BLBLI</td>
<td>34 (47.2)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Empirical Therapy Cohort</td>
<td></td>
<td>P</td>
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<tr>
<td>-------------------------------------</td>
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<tr>
<td></td>
<td>BLBLI (n = 72)</td>
<td>Carbapenem (n = 31)</td>
<td></td>
</tr>
<tr>
<td>Mortality, no. of deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>2 (2.8)</td>
<td>3 (9.7)</td>
<td>.1⁶</td>
</tr>
<tr>
<td>Day 14</td>
<td>7 (9.7)</td>
<td>5 (16.1)</td>
<td>.3</td>
</tr>
<tr>
<td>Day 30</td>
<td>7 (9.3)</td>
<td>6 (19.4)</td>
<td>.1</td>
</tr>
<tr>
<td>Hospital stay after BSI, median (IQR), d</td>
<td>12 (8–28)</td>
<td>13 (9–25)</td>
<td>.7⁶</td>
</tr>
</tbody>
</table>
Table 3. Mortality at 30 Days in Patients Who Received Empirical Therapy With an Active β-Lactam/β-Lactam Inhibitor, According to Minimum Inhibitory Concentration of the Antimicrobial Used

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>BLBLI (n = 72)</th>
<th>Carbapenem (n = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Inhibitory Concentration, mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>0/10</td>
<td>0/8</td>
<td>1/4</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>...</td>
<td>1/12</td>
<td>2/25</td>
</tr>
</tbody>
</table>

Data are expressed as No. of patients who died/No. of patients treated.
Pen/βLI for ESBL infection?

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  - 35 Pip/Tazo
- Treated with carbapenem (n=31)

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<tbody>
<tr>
<td>Age, median y (IQR)</td>
<td>67 (56–83)</td>
<td>76 (55–78)</td>
<td>.3b</td>
</tr>
<tr>
<td>Male sex</td>
<td>34 (63)</td>
<td>70 (58.3)</td>
<td>.5</td>
</tr>
<tr>
<td>Nosocomial acquisition</td>
<td>18 (33.3)</td>
<td>67 (55.8)</td>
<td>.006b</td>
</tr>
<tr>
<td>Charlson index, median, (IQR)</td>
<td>2.5 (1–5)</td>
<td>3 (1–5)</td>
<td>.5b</td>
</tr>
<tr>
<td>Cancer</td>
<td>15 (27.8)</td>
<td>43 (35.8)</td>
<td>.2</td>
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<td>3 (6.6)</td>
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<td>.1</td>
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<td>Neutropenia</td>
<td>6 (11.1)</td>
<td>7 (5.8)</td>
<td>.1c</td>
</tr>
<tr>
<td>Urinary or biliary tract as source</td>
<td>42 (77.8)</td>
<td>79 (65.8)</td>
<td>.1</td>
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<td>4 (7.4)</td>
<td>18 (15.4)</td>
<td>.1</td>
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<td>6 (14.8)</td>
<td>32 (26.7)</td>
<td>.08</td>
</tr>
<tr>
<td>Pitt score, median (IQR)</td>
<td>1 (0–2)</td>
<td>1 (1–2)</td>
<td>.04b</td>
</tr>
<tr>
<td>CTX-M enzyme</td>
<td>43 (82.7)</td>
<td>95 (81.2)</td>
<td>.8</td>
</tr>
</tbody>
</table>
Significant in multivariable analysis of survival:

- Pitt score
- Severe sepsis/shock
- NOT: BLBLI
Antiviral therapy for HCV

- Chronic HCV infection – a significant burden (~150 Mio)
- Poor response with pegylated IFNα + ribavirin: <50% “SVR” in genotype 1 virus infection
- Development of direct-acting antiviral agents initially focussed on inhibitors of the NS3 protease and the RNA-dependent RNA polymerase NS5B
Antiviral therapy for HCV

Boceprevir
- Poordas et al *NEJM*: ~67% vs 40% *
- Bacon et al *NEJM*: ~60% vs 20% #

Telaprevir
- Jacobson et al *NEJM*: ~70% vs 40% *
- Zeuzem et al *NEJM*: Δ 25-50% #

*previously untreated subjects  # retreatment
Antiviral therapy for HCV

- Expensive
- Many side effects (anemia, rash etc)
- Complex interactions with ART

Vision:
- all-oral IFN-free regimens
- better tolerable
- less expensive
Antiviral therapy for HCV

Preliminary Study of Two Antiviral Agents for Hepatitis C Genotype 1

Anna S. Lok, M.D., David F. Gardiner, M.D., Eric Lawitz, M.D., Claudia Martorell, M.D., Gregory T. Evers, M.D., Reem Ghalib, M.D., Robert Reindollar, M.D., Vinod Rustgi, M.D., Fiona McPhee, Ph.D., Megan Wind-Rotolo, Ph.D., Anna Persson, Ph.D., Kurt Zhu, Ph.D., Dessislava I. Dimitrova, M.D., Timothy Eley, Ph.D., Tong Guo, Ph.D., Dennis M. Grasela, Pharm.D., Ph.D., and Claudio Pasquinelli, M.D., Ph.D.

- **Drugs:**
  - Daclatasavir, a first-in-class, highly selective NS5A replication complex inhibitor
  - Asunaprevir, a highly active NS3 protease inhibitor
Antiviral therapy for HCV

HCV RNA Levels, Group A

Daclatasvir + asunaprevir

Follow-up

Week

0 1 2 3 4 6 8 10 12 16 20 24 PT14 PT18 PT24 PT36 PT48

LLOQ

LLOD

HCV RNA (log_{10} IU/ml)
HIV prevention

“... currently, we think that about 4–6 new people get infected for every person we treat ...”

Dr. M.S. Cohen
HIV prevention

- ART as used until today ?
  - Reduced but continued transmission (e.g. the Henan Chinese Discordant Couples Study [Lu et al J AIDS 2010])
  - Continued HIV shedding among women with below detectable plasma viral load [Cu-Uvin et al AIDS 2010]
HIV prevention

- Early ART?

Science 23 December 2011:
Vol. 334 no. 6063 p. 1628
DOI: 10.1126/science.334.6063.1628

NEWS

BREAKTHROUGH OF THE YEAR
HIV Treatment as Prevention
Early ART for HIV prevention

- the Cohen trial (HPTN 052)
Early ART for HIV prevention

- 1,763 HIV-discordant couples; 1:1 immediate vs delayed ("standard") ART

Results:
- ↓96% linked HIV transmission
… what about other antivirals?

作者：Cao ZX, Guo YM, Yang T, et al.
… what about other antivirals?

- Traditional chinese herbal medicine vs oseltamivir for H1N1 influenza
… what about other antivirals?

- Traditional Chinese herbal medicine vs oseltamivir for H1N1 influenza

- **Maxingshigan-Yinqiaosan**
  - 12 different herbs
  - incl. „mormon tea“ (*Ephedra* genus)
  - decoction
… what about other antivirals?

- Traditional chinese herbal medicine vs oseltamivir for H1N1 influenza
  - **Maxingshigan-Yinqiaosan**
    - 12 different herbs
    - incl. „mormon tea“ (*Ephedra* genus)
    - decoction
Maxingshigan-Yinqiaosan

- PCR-confirmed influenza, n=410
- 4-arm trial:
  control : oseltamivir : M-Y : M-Y+oseltamivir
- Open-label treatment for 5 days
- Primary endpoint: fever
- Results:
Maxingshigan-Yinqiaosan

- Results (fever [h]):
  - control : oseltamivir : $M$-$Y$ : $M$-$Y$+oseltamivir
  |   |   |   |   |   |
  | 26 | 20 | 16 | 15 |   |
the median viral titer in throat swabs at enrollment was similar, and a rapid decrease in virus shedding was observed in all 4 groups $(P < 0.001)$

Changes in virus shedding from baseline to day 5 did not differ by treatment group $(P = 0.69)$
Use of antibiotics was similar among all groups at baseline (4.9% to 7.8%; $P = 0.88$) but was much more frequent in the control group after enrollment (34.3% vs. 15.7% in the oseltamivir group, 9.7% in the maxingshigan–yinqiaosan group, and 7.8% in the combination therapy group; $P < 0.001$).