Emerging pathogen- Candida auris
Therapeutics- Inhaled antibiotics
Diagnostics- Procalcitonin
Simultaneous Emergence of Multidrug-Resistant Candida auris on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses

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Emergence of Candida auris: An International Call to Arms

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Candida auris

- Emerged in 2009
  - Japan
  - Retrospectively identified 1996 Sth Korea

- Initial case reports in South Korea, India, Pakistan, South Africa, Kuwait, Venezuela

- USA & UK 2013

- 2017- 20 NHS trusts in UK reporting cases; 3 hospitals with outbreaks, difficult to control
**C. auris - significance**

- > 50% multidrug resistant (fluconazole > AMB > echinocandin)

- High mortality - 70% with candidaemia

- Propensity for hospital outbreaks & clonal spread

- Misidentification common
  - Rhodorotula glutinis, Saccharomyces cerevisiae
  - Candida sake, Candida famata, Candida haemuloni
Further insights

- 54 isolates from 3 continents
  - Clinical information
  - Antifungal susceptibility testing
  - Whole genome sequencing

Lockhart et al Clin Infect Dis 2017; 64(2): 134-40
Clinical aspects-C. auris

- 41% diabetic
- 51% recent surgery
- 73% CVC
- 41% receiving systemic antifungal Tx when C. auris isolated

- Days (median) admission-infection: 19 (IQR 9,36)
- 61% blood stream infection
- 59% mortality
Resistance-C. auris

- 93% fluconazole
- 54% voriconazole (MIC $\geq 2$)
- 35% AMB
- 7% echinocandins
- 6% 5FC

- 41% resistant x 2 antifungal classes
- 4% resistant x 3 antifungal classes
Whole genome sequencing-C. auris

- 4 distinct clades
  - Japan
  - India/Pakistan
  - South Africa
  - Venezuela

Simultaneous emergence in multiple geographic regions

? why
Hypotheses

• A case of missed diagnosis?
  • Interrogation and analysis of database pre-2009 not identifying cases

• Antifungal selection pressure?
  • Widespread use of antifungals since 1990s
  • More rapid emergence in private sector (Sth Africa)

• Exogenous reservoirs, Intrininsic virulence&resistance?
  • Intraregional spread well described
  • Nosocomial outbreaks including ICUs
POINT:
Should Inhaled Antibiotic Therapy Be Used Routinely for the Treatment of Bacterial Lower Respiratory Tract Infections in the ICU Setting?
Yes

Richard G. Wunderink, MD, FCCP
Chicago, IL
Rationale

- Other strategies have failed to show success in treating HAP/VAP including:
  - Combination therapy
    - Beta-lactam + FQ
    - Beta-lactam + AG
  - Extended duration
    - Tx > 15 days increase superinfection with AMR organisms
  - PK/PD optimisation
    - Dori vs Imipenem study
    - RCT, metaanalysis have not shown clear benefit

Case for aerosolized AntiBx

- Levels in lung logs greater than with IV
- Reduced systemic toxicity

Evidence base:
- Initial RCT (tobramycin) vs SOC (1990s)
  - No difference in clinical cure but higher rates bacterial eradication (68% vs 31%)
- Aerosolised ceftazidime + tobramycin showing trend towards greater treatment success and less AM resistance
- Pilot studies showing better sterilisation airway secretions
- MDR GNR- better outcomes with aerosolised colistin than IV combinations (not RCTs)
COUNTERPOINT:
Should Inhaled Antibiotic Therapy Be Used Routinely for the Treatment of Bacterial Lower Respiratory Tract Infections in the ICU Setting?
No

Marin H. Kollef, MD, FCCP
Rationale

- The case against IV therapy is based on poorly designed studies, where IV drugs under-dosed in the critically ill, examples
  - Tigecycline (dosing off-label at 100mg bd shown to be improve cure rates)

- Consequences
  - Insufficient drug delivery lung epithelium
  - Not attaining mutation prevention concentration at the target site
Technical limitations - aerosol Tx

• Which device?
  • Diversity of commercial nebulizers with > 10 fold variation in delivery of aerosol
  • Vibrating mesh nebuliser (VMN) attractive option
    • Consistent particle size
    • Aerosol output 2-3 x greater than jet nebulisers
    • Can be used without changing ventilator settings
  • However uncertain whether even VMN can overcome effects of sputum antagonism
Evidence to support “no case”

- **Metaanalysis** showing insufficient evidence to support aerosolised antiBx for VAP/VAT (305 patients, 6 studies for inclusion)
  

- **Metaanalysis** showing improved cure and microbiological eradication using aerosolised colistin for VAP, though quality of evidence in 16 studies “low” or “very low”
  
Research questions, proposal

<table>
<thead>
<tr>
<th>1. Which type of BLRTI to treat with aerosolized antibiotics?</th>
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<tbody>
<tr>
<td>Ventilator-associated pneumonia (VAP)</td>
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<tr>
<td>Ventilator-associated tracheobronchitis (VAT)</td>
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<tr>
<td>Prophylactic administration to prevent VAP, VAT, and the emergence of antimicrobial resistance</td>
</tr>
</tbody>
</table>
2. Which antibiotic to aerosolize and at what dose?
   - Amikacin: 400 mg every 12 h
   - Aztreonam: 75 mg every 8 h
   - Ceftazidime: 15 mg/kg every 3 h
   - Colistin: 1 to 2 million units (80 to 160 mg) every 12 h
   - Tobramycin: 300 mg every 12 h
Research questions, proposal

3. Should combination aerosolized antibiotic treatment be used?

Amikacin 300 mg and fosfomycin 120 mg every 12 h
4. What is the optimal delivery device for aerosolized antibiotics in ventilated patients?

- Ultrasonic nebulizer
- Jet nebulizer
- Breath-enhanced jet nebulizer
- Vibrating mesh nebulizer
| 3 d |
| 5 d |
| 7 d |
| 10 d |
6. What outcomes should be used to determine the clinical effectiveness of aerosolized antibiotics in ventilated patients?

<table>
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<tr>
<th>30-day all-cause mortality</th>
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<tr>
<td>Clinical cure</td>
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<tr>
<td>Microbiological eradication</td>
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<tr>
<td>Ventilator-free d</td>
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<tr>
<td>Prevention of acquired antibiotic resistance</td>
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<tr>
<td>Reduction in the Clinical Pulmonary Infection Score</td>
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</table>
Effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock (Review)

Andriolo BNG, Andriolo RB, Salomão R, Atallah ÁN
Study

- 10 studies, 1215 participants
- \(\geq 18\) yrs with sepsis, severe sepsis, septic shock

Previous systematic reviews - inclusion criteria
- Critically ill adults & neonate (Kopterides 2010)
- Adults from ED, ICU, primary care (Schuetz 2011)
- Severe sepsis (Prkno, 2013)
Primary Outcome(1)-Mortality

PCT directed therapy vs comparator

- Mortality at longest follow-up no significant difference OR 0.81 [95% CI 0.65, 1.01]
- Mortality at 28 days no significant difference OR 0.87 [95% CI 0.59, 1.28]
- Mortality at ICU discharge no significant difference OR 1.03 [95% CI 0.50, 2.11]
- Mortality at hospital discharge no significant difference OR 0.98 [95% CI 0.75, 1.27]
Primary Outcome(2)-Duration AntiBx

PCT directed therapy vs comparator

- Time receiving antiBx (mean, days) **significant difference** -
  1.28 days [95% CI -1.95, -0.61]
Secondary Outcomes

PCT directed therapy vs comparator

- Hospital length of stay, trend towards reduced stay in PCT group (median diff of 2-11 days) but not statistically significant
- No significant diff in mean days of ICU stay
- No difference in SOFA scores during ICU, at day 3, at day 5 & max score
- No difference in APACHE II
- No difference in reinfection rate
- No difference in duration mechanical ventilation
Conclusion

- Evidence of low to moderate quality does not support the use of procalcitonin-guided antimicrobial therapy to minimize mortality, reinfection, clinical severity, mechanical ventilation, or duration of antimicrobial therapy of patients with sepsis, severe sepsis or septic shock. However, the reader should consider the possibility of insufficient sample power for all outcomes.
Conclusion

- since 2012, one of the main existing guidelines for dealing with severe sepsis and septic shock (Dellinger 2013) has included recommending procalcitonin to support clinicians while they decide whether or not to discontinue empirical antimicrobial therapy for patients with septic conditions. However, Dellinger 2013 assumes low quality of available evidence for this recommendation.