Update in Melioidosis

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Ubon Ratchathani

(above) A small selection of different colony types
History

1911- First recorded in the world (Whitmore & Krishnaswami): Glander-like illness, *Bacillus whitmore*. 1 century +2 this year ‘2013’

1917 - More than 100 cases reported from Rangoon (Krishnaswami): *Bacillus pseudomallei*

1932 - Stanton and Fletcher named ‘melioidosis’ [Greek] ‘*melis*’= a distemper of asses, ‘*eidos*’ = resemblance


1992 *Burkholderia pseudomallei*
‘Time-bomb Disease’
Spotniz M. Medical World News 1966; 7:55.

- 100 cases among French forces in Indochina (1948-1954)
- Cases reported from veterans of World War II
- 343 cases in American soldiers fighting in Vietnam were reported to be melioidosis (1973)
- Many cases reported from American veterans years after exposure
Worldwide distribution of melioidosis
Incidence of melioidosis in Thailand

- Highest incidence of melioidosis: Ubon Ratchathani
- 21.3 cases/100,000 population (A cohort study of 2,243 melioidosis patients with culture-proven melioidosis)
- Overall incidence in Thailand: 12.7 cases/100,000 population
- The incidence increase from 8 (in 2000) to 21.3 (in 2006)
  - Male sex predominant
  - 80% adult case, age ranged 40-60 yr
  - 20% paediatrics cases (80% seroconversion by age 4)
  - Major risk factor: known or undiagnosed DM
- 80% of cases occur in rainy season
- 3rd most common cause of death among infectious diseases in Northeast Thailand (after HIV and tuberculosis)
Melioidosis in Ubon Ratchathani

Number of cases

Year


152  184  235  250  273  380  454  427  300  364  377  381
Melioidosis in Ubon Ratchathani

Per 100,000 population

Year

incidence rate
mortality rate
Community-acquired bacteraemia in NE Thailand

1. *E. coli* (23%)
2. *B. pseudomallei* (19%)
3. *S. aureus* (8%)
Causative bacteria

• *B. pseudomallei* – Genus *Burkholderia* >40 species

• *B. thailandensis* & *B. pseudomallei* found in soil in Thailand & Australia
Routes of infection

Inhalation

Direct inoculation

Ingestion
Routes of infection (cont.)

- Related to breast feeding from mothers with mastitis (Australia)
- Human to human transmission
- Nosocomial Infection from a suspected environment source
- Mother to child transmission (Neonatal melioidosis)
- Laboratory-Acquired Infection
Risk factors for melioidosis

- Diabetes - 23 to 60%
- Heavy alcohol use – 12 to 39%
- Chronic pulmonary disease - 12 to 27%
- Chronic renal disease - 10 to 27%
- Thalassemia – 7 %
- Glucocorticoid therapy - < 5 %
- Cancer - < 5%
Melioidosis in Ubon Ratchathani
## Demographic data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pediatrics 185 (%)</th>
<th>Adults 2,227 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>6 (0.01-10)</td>
<td>51 (41-61)</td>
</tr>
<tr>
<td>Male, number (%)</td>
<td>117 (63.2)</td>
<td>1,287 (57.8)</td>
</tr>
<tr>
<td>Occupation as rice farmer</td>
<td>44 (24.7)</td>
<td>1,743 (82.0)</td>
</tr>
<tr>
<td>Underlying diseases, number (%)</td>
<td>7 (3.8)</td>
<td>1,030 (46.3)</td>
</tr>
<tr>
<td>Diabetes/hyperglycemia</td>
<td>3 (1.6)</td>
<td>852 (38.3)</td>
</tr>
<tr>
<td>Known diabetes mellitus</td>
<td>1 (0.5)</td>
<td>554 (25.1)</td>
</tr>
<tr>
<td>Newly diagnosed diabetes mellitus</td>
<td>0</td>
<td>165 (7.5)</td>
</tr>
<tr>
<td>Acute hyperglycemia</td>
<td>2 (1.1)</td>
<td>133 (6.0)</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>1 (0.5)</td>
<td>37 (1.7)</td>
</tr>
<tr>
<td>Kidney diseases</td>
<td>0</td>
<td>146 (6.6)</td>
</tr>
<tr>
<td>Renal calculi</td>
<td>0</td>
<td>93 (4.2)</td>
</tr>
<tr>
<td>Chronic liver disease/cirrhosis</td>
<td>0</td>
<td>15 (0.7)</td>
</tr>
<tr>
<td>Heavy alcohol drinking</td>
<td>0</td>
<td>21 (1)</td>
</tr>
<tr>
<td>Duration hospital stay, median (IQR)</td>
<td>13 (6-19)</td>
<td>8 (3-16)</td>
</tr>
<tr>
<td>Death, number(%)</td>
<td>34 (18.7)</td>
<td>867 (40.0)</td>
</tr>
</tbody>
</table>
# Melioidosis and HIV infection

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive patients (n=8)</th>
<th>HIV-negative patients (n=561)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteraemia</td>
<td>5 (63%)</td>
<td>291 (52%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Median (IQR) duration of hospitalisation</td>
<td>8 (2-9.5)</td>
<td>14 (7-22)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (13%)</td>
<td>150 (29%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Recurrence of melioidosis infection</td>
<td>1 (13%)</td>
<td>50 (10%)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

![Graph showing cases of melioidosis and HIV infection over years](chart.png)
Organ involvement in melioidosis

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Thailand (%)</th>
<th>Australia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ubon (n=2,412)</td>
<td>(n=540)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>1,019(42.2)</td>
<td>298(59)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>912(37.8)</td>
<td>278(51)</td>
</tr>
<tr>
<td>Liver/spleen</td>
<td>414(17.2)</td>
<td>43(8)</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>370(15.4)</td>
<td>87(16.6)</td>
</tr>
<tr>
<td>Genitourinary infection</td>
<td>190(7.9)</td>
<td>76(14)</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>168(7)</td>
<td>20(4)</td>
</tr>
<tr>
<td>Neurological</td>
<td>19(0.9)</td>
<td>14(3)</td>
</tr>
</tbody>
</table>
Internal organ abscesses and other foci of infection

<table>
<thead>
<tr>
<th>Site</th>
<th>Thailand (%)</th>
<th>Australia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ubon (n=2,412)</td>
<td>(n=540)</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>4(&lt;1)</td>
<td>76(20)</td>
</tr>
<tr>
<td>Spleen</td>
<td>223(9)</td>
<td>28(5)</td>
</tr>
<tr>
<td>Liver</td>
<td>191(8)</td>
<td>15(3)</td>
</tr>
<tr>
<td>Kidney</td>
<td>33(1)</td>
<td>18(3)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>0</td>
<td>3(&lt;1)</td>
</tr>
<tr>
<td>Psoas muscle</td>
<td>5(&lt;1)</td>
<td>4(&lt;1)</td>
</tr>
<tr>
<td>Other abscess/myositis</td>
<td></td>
<td>8(1)</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td></td>
<td>3(&lt;1)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>18(&lt;1)</td>
<td>9(2)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>0</td>
<td>17(3)</td>
</tr>
<tr>
<td>Pericardium</td>
<td>8(&lt;1)</td>
<td>4(&lt;1)</td>
</tr>
<tr>
<td>Para intestinal mass</td>
<td></td>
<td>4(&lt;1)</td>
</tr>
<tr>
<td>Breast (mastitis)</td>
<td>1</td>
<td>3(&lt;1)</td>
</tr>
<tr>
<td>Epididymo-orchitis</td>
<td>1</td>
<td>3(&lt;1)</td>
</tr>
<tr>
<td>Mycotic aneurysm</td>
<td>1</td>
<td>2(&lt;1)</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>79(2)</td>
<td>0</td>
</tr>
</tbody>
</table>
Pulmonary manifestations
Chest radiographs

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zonal opacities</td>
<td>140 (52.6%)</td>
</tr>
<tr>
<td>Widespread opacity</td>
<td>96 (36.1%)</td>
</tr>
<tr>
<td>Cavitations</td>
<td>25 (9.4%)</td>
</tr>
<tr>
<td>Diffuse interstitial shadow</td>
<td>24 (9.0%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>46 (17.3%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>18 (6.8%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>4 (1.5%)</td>
</tr>
</tbody>
</table>
Pulmonary melioidosis

- 60% of culture-proven melioidosis
- More severe (shock, acidosis, renal failure, respiratory failure, thrombocytopenia and APACHE II score)
- Most common: zonal opacities
- Poorer outcomes (higher mortality, longer hospitalisation and longer fever clearance time)
- Pulmonary melioidosis carried 50% mortality, nearly 10 days fever clearance time, 20% of patients needed ≥1 month treatment
Neurological melioidosis

- Abscess +
- Meningitis
- Encephalitis
- Brain stem encephalitis -
- Myelitis -
Skin and soft tissue

- Blister, pustules
- Cellulitis
- Subcutaneous abscess
- Chronic ulcer
- Lymphadinitis, abscess
Melioidosis in Children
Melioidosis in Paediatric Patients

• Localized infection (2/3 of all reported cases): most common presentation

• Most common sites involved: skin and soft-tissue of the head and neck, including cervical and submandibular abscess and suppurative parotitis

• Septicaemic form usually presented with pneumonia and multiorgan failure
Site of infection

- Prospective study in 185 case (age <15 yrs)
- Sunpasitthiprasong Hospital, Ubon Ratchathani, 2000-2008
Melioidosis in ENT

- ENT manifestation is presented more in paediatrics cases than adults
- Seasonal variation (rainy season)
- Mainly localised disease
- Most common site: parotid gland
- Good prognosis, un-fatal outcome
- No resistant strains
Ocular involvement

hematogenous dissemination

direct traumatic deposition of the organism
Ocular involvement

- Orbital cellulitis
- Endophthalmitis
- dacryocystitis
Diagnosis in melioidosis

- The more delay in diagnosis, the poorer outcome
- Empirical antibiotic against *B. pseudomallei* in CLI pneumonia in endemic area and presence of risk factor
- No colonisation
- Limited use of serology in endemic area (IHA)
- PCR: quicker than culture, but less sensitive
Laboratory Diagnosis

- Microscopic
  - Culture and identification (gold standard)
    - Antibiotic susceptibility test
      - Interpretation and clinical outcome
Colony Morphology of *B. pseudomallei*

- Twenty different morphotypes were observed
- Morphotype A: 34%, B: 18%, C: 6%
- Relationship between morphotype & phenotype
TREATMENT OF MELIOIDOSIS
In vitro susceptibility
(MIC, MBC and time kill curve)

Sensitive to:
• Doxycycline, Co-trimoxazole
• Ceftazidime, Ceftriaxone
• Amoxicillin/clavulanate
• Meropenem, Imipenem
• Cefoperazone/sulbactam
• Azlocillin, Ticarcillin-clavulanate
• Aztreonam,
• Doripenem, Biapenem,
• Piperacillin-sulbactam, (no trial)

Resist to:
• Moxifloxacin, Tigecycline, Ertapenem
• Cefepime. Aminoglycoside
Treatment of melioidosis

• Antibiotic
  – Initial intensive therapy
  – Maintenance therapy
• Get rid of source: drainage, aspiration, surgical removal
• Supportive care
Treatment of melioidosis

• Antibiotic iv
  – Ceftazidime (120mg/kg/day)
  – Imipenem (50mg/kg/day)
  – Meropenem (75mg/kg/day)
  – Cefoperazone/sulbactam (25mg/kg/day)
  – Amoxy-clavulanate (160mg/kg/day) 2.4gm loading dose then 1.2gm every 6 hr
• G-CSF no difference in mortality rate

Acute Treatment of Melioidosis (ATOM)
Ceftazidime vs Meropenem
Initial Intensive Therapy

• Duration of initial intensive therapy should be 10-14 days

• Longer treatment in
  – Critically ill patients
  – Extensive pulmonary disease
  – Deep-seated collection or organ abscess
  – Osteomyelitis
  – Septic arthritis
  – Neurologic melioidosis

• Median fever clearance time: up to 14 days, take longer time in deep-seated abscesses
Treatment

Intensive phase

• First line treatment: Ceftazidime at least 10-14 days

• Carbapenem such as imipenem, meropenem: lower MIC and superior in vitro time-kill studies, but no survival advantage in clinical trial
  – Preserve as the second line treatment for those who do not response to ceftazidime
Eradication Phase Treatment

Trimethoprim-sulfamethoxazole” for 3-6 months (No need to combine with doxycycline)

Dose:

- Co-trimoxazone (TMP/SMX)
  
  $< 40\text{kg}$ \hspace{1cm} $2 \times 2$
  
  $40-60\text{kg}$ \hspace{1cm} $3 \times 2$
  
  $> 60\text{kg}$ \hspace{1cm} $4 \times 2$

- Co-amoxiclav (625) $2 \times 3$
  
  Co-amoxiclav (375) $2 \times 3$ + amoxicillin(500) $1 \times 3$

Duration: 20 wks
Antimicrobial resistance in melioidosis

- Parenteral antimicrobial drugs used to treat melioidosis
  - Ceftazidime
  - Amoxicillin-clavulanic acid
  - Imipenem/meropenem

- 24/4,021 patients in 21 yrs with one or more isolates resist to ceftazidime (n=8), co-moxiclav (n=4), both (n=12)

- Antimicrobial resistant to ceftazidime involving loss of penicillin-binding protein 3 in *B. pseudomallei*

- 2 cases with persistent positive blood culture after 15 days of proper antibiotic therapy

- No carbapenem resistant detected
Recurrent melioidosis

Recurrent

• 13% in 10 yrs (6% in the first year)
• 130 patients with 145 episodes (4 cases with 3 episodes and 7 cases with 2 episodes)
  – 25% died as direct result
• Relapse: 75%
  – Median time to relapse 228 days, 89% 1 yr
• Reinfection: 25%
  – Median time to reinfection 823 days
• No difference in outcome
Risk factors for recurrent melioidosis

Relapse associated with oral antibiotic ≤8wks
Reinfection: no risk

Patterns of organ involvement in recurrent melioidosis
• Similar patterns of disease during the first and second episode in both relapse and reinfection
Prevention and Vaccine Development

• Human vaccine is currently not available for melioidosis
• Animal model use: live attenuated, subunit, plasmid-based DNA, and killed whole-cell vaccine candidates
• Immunosuppressive therapy especially high dose steroids
Melioidosis

- **Area of agreement**: Diagnosis & Antimicrobial Rx
- **Area of controversy**: Seroconversion signal the presence of a quiescent bacterial focus & increase long term risk of melioidosis
- **Area for developing research**:  
  - Effective prevention programme  
  - Relative importance of different route of infection  
  - Marked differentiate in mortality in high income vs lower income countries  
  - Afford strategies to reduce death from severe sepsis
Ongoing study

- Comparison of 12 and 20 wk duration of eradication phase treatment

New studies

- New big study: application of latex agglutination to *Pseudomonas* spp. culture positive from blood specimen in Thailand
- New in-house isolator haemoculture tube
- Prospective study for TLR5 in melioidosis
- *B. pseudomallei* and *B. thailandensis* in soil and its inhibition
• DM & melioidosis occur whole year especially in rainy season
• All age groups, but mostly 40-60 years old
• Affect every organs
• Septicaemia and septic shock are common
• Ceftazidime is gold standard in initial phase
• TMP-SMX regime is required at least 20 weeks for eradication phase
• Recurrent infection occurs 10%, 2/3 relapse (first 12 month), 1/3 re-infection (after 12 month)
• Probable melioidosis must be treated with same regimen as definite melioidosis