Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

MELIOIDOSIS: MANAGING ACUTE AND CHRONIC INFECTION

Summary of the impact:

Sustained research by the University of Oxford's Mahidol Oxford Tropical Medicine Research Unit in Thailand (MORU) has been the driving force behind the current World Health Organization recommendations for the management of acute and chronic infection in patients with melioidosis. This research has motivated improvements in treatments and provided new strategies to identify at-risk populations, enabling clinicians to make early diagnoses. Melioidosis is a major cause of severe illness in parts of Southeast Asia and there are increasing numbers of cases in India, China, and Brazil.

Underpinning research:

The University of Oxford's Mahidol Oxford Tropical Medicine Research Unit (MORU) is the world's leading authority on melioidosis and carries out wide-ranging research into the aetiology, diagnosis and treatment of this disease.

Building on its discovery of ceftazidime as the first effective treatment for melioidosis in 1989, MORU's research has driven sustained improvement in the management of melioidosis across Asia and South America over the past 25 years.

The identification of at-risk groups:
By undertaking surveys in northern Thailand MORU has shown that most adult patients have an underlying disease (mainly diabetes mellitus) predisposing them to melioidosis infection. MORU also found that malnutrition, due to poor dietary intake, significantly increases a persons likelihood of contracting a chronic melioidosis infection[1].

Rapid diagnosis:
In 2005 MORU published two rapid diagnostic tests for melioidosis, based on direct immunofluorescence (IF) of the causative bacterium, *Burkholderia pseudomallei*, making it possible to detect disease at an earlier stage[2]. The sensitivities of both IF tests were 66%, and the specificities were 99.5 and 99.4%, respectively. This showed that this new test was not only faster; it was also far more specific and sensitive than the former diagnostic test.

The treatment of acute infection:
In 1996, researchers from MORU showed that the carbapenem antibiotics imipenem and meropenem have the lowest minimum inhibitory concentrations (MIC) against *B. pseudomallei* and as such perform better than ceftazidime[3]. In a randomized, comparative trial from Thailand published in 1999, the Unit also showed that a high dose imipenem was equally as effective as ceftazidime for severe melioidosis, with fewer treatment failures in those given imipenem[4].

MORU has tested several other conventional treatments for melioidosis in clinical trials. In 2005 it asked whether the addition of Trimethoprim/Sulfamethoxazole (TMP-SMX), which has very good tissue penetration, would provide further benefit in mortality reduction compared with monotherapy with ceftazidime in acute disease. This question was addressed in randomized controlled trials of 449 patients with severe melioidosis in Thailand[5]. The in-hospital mortality rate was not significantly different between the treatment groups (25.1 compared with 26.6 percent with combination therapy, respectively) and showed no long-term benefit. At a median of 71 weeks, there was no difference between the two groups with regard to the combined end point of mortality

or culture-confirmed recurrent melioidosis (17.8 versus 18.3 percent) with ceftazidime alone[5]. This study has since led to changes in clinical practice, refining treatment and reducing the physical and financial costs associated with TMP-SMX in the acute setting.

Eradication of persistent infection:
Eradication therapy is necessary to prevent reactivation or relapse after an acute infection with melioidosis, and in 1999 MORU published the most important trial of treatment for this stage of the disease. In this trial it compared the efficacy of a combination of chloramphenicol (first four weeks only), TMP-SMX, and doxycycline versus doxycycline alone in eradicating chronic infection. It found that relapse cases were significantly higher with doxycycline alone[6]. In 2005, a randomized trial in Thailand found no benefit from adding chloramphenicol to (TMP-SMX) plus doxycycline regimen. This body of work has led to a simple and effective cure for chronic infection in many thousands of individuals.

References to the research:

1. Suputtamongkol, Y. *et al.* The epidemiology of melioidosis in Ubon Ratchatani, northeast Thailand. *Int J Epidemiol* **23**, 1082–1090 (1994).

   Primary paper from MORU showing that an underlying disease (mainly diabetes mellitus) and malnutrition, significantly increases a person's likelihood of contracting a chronic melioidosis infection.

2. Wuthiekanun, V. *et al.* Rapid immunofluorescence microscopy for diagnosis of melioidosis. *Clin. Diagn. Lab. Immunol.* 12, 555–556 (2005). doi: 10.1128/CDLI.12.4.555-556.2005.

   Two rapid diagnostic tests for melioidosis, published by MORU, based on direct immunofluorescence (IF) of bacteria, making it possible to detect disease faster and at an earlier stage.

3. Smith, M. D., Wuthiekanun, V., Walsh, A. L. & White, N. J. In-vitro activity of carbapenem antibiotics against beta-lactam susceptible and resistant strains of Burkholderia pseudomallei. *J. Antimicrob. Chemother.* **37**, 611–615 (1996).

   This research from MORU shows that the carbapenem antibiotics imipenem and meropenem perform better than ceftazidime.

4. Simpson, A. J. *et al.* Comparison of imipenem and ceftazidime as therapy for severe melioidosis. *Clin. Infect. Dis.* 29, 381–387 (1999).

   A randomized comparative trial showing that high dose imipenem is equally as effective as ceftazidime for severe melioidosis, with fewer treatment failures in those given imipenem.

5. Chierakul, W. *et al.* Two randomized controlled trials of ceftazidime alone versus ceftazidime in combination with trimethoprim-sulfamethoxazole for the treatment of severe melioidosis. *Clin. Infect. Dis.* **41**, 1105–1113 (2005). doi: 10.1086/444456

   A randomized controlled trial of 449 patients with severe melioidosis in Thailand.

6. Chaowagul, W. *et al.* A comparison of chloramphenicol, trimethoprim-sulfamethoxazole, and doxycycline with doxycycline alone as maintenance therapy for melioidosis. *Clin. Infect. Dis.* **29**, 375–380 (1999).

   A combination therapy trial showing that relapse cases were significantly higher with doxycycline alone.

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Details of the impact:

Melioidosis is a threat to human health throughout South and East Asia, Northern Australia, the Indian subcontinent and areas of South America. Due to rising life expectancy and an increase in predisposing conditions for melioidosis (such as diabetes mellitus), the annual incidence of human melioidosis in the Ubon Ratchathani province of Thailand has substantially increased from 4.4 per 100,000 people for the period 1987 to 1991, to 21 per 100,000 in 2012.

The number of people dying from melioidosis in northeast Thailand is now comparable to deaths from tuberculosis, and exceeds those from malaria, diarrhoeal illnesses and measles combined, diseases considered to be a high priority by funding agencies and global health organisations.

In north-eastern Thailand, melioidosis accounts for 20% of all community-acquired septicaemias, and causes death in 40% of conventionally treated patients. *B pseudomallei* is an environmental saprophyte found in wet soils. Melioidosis is characterised by formation of abscesses, especially in the lungs, liver, spleen, skeletal muscle, and prostate. In a third of paediatric cases in Southeast Asia, the disease presents as a parotid abscess. In northern Australia, 4% of patients present with brain stem encephalitis.

The work of The University of Oxford's MORU has primarily been to define strategies to reduce mortality from melioidosis and to develop evidence-based guidelines on the prevention of infection.

International Guidelines:
As a result of MORU's underpinning research into treatment regimes[5, 7], the World Health Organization's Centers for Disease Control and Prevention now recommend the use of ceftazidime or meropenem as an intravenous therapy for melioidosis[8].

The same recommendations can also be found on UpToDate®, an evidence-based clinical decision support system authored by physicians to help clinicians make the right decisions at the point of care. The articles cite the MORU studies as the primary evidence in support of treatment [9].

An important advance has come from MORU's research demonstrating the superiority of carbapenem antibiotics for severe acute disease[10]. UpToDate® have also included these observations, reporting on treatment in the Northern Territory of Australia where melioidosis is hyperendemic. According to UpToDate® all patients requiring intensive care unit (ICU) admission in the Northern Territory are treated with meropenem. Meropenem is used rather than imipenem because of fewer neurologic side effects. Without access to appropriate antibiotics (principally ceftazidime or meropenem), the septicaemic form of melioidosis has a mortality rate that exceeds 90%.[9]

UpToDate® cites the 1999 and 2005 MORU trials as the primary evidence for the recommended 3 month eradication therapy with TMP-SMX and doxycycline.

Clinical Practice:
The Unit's research has also identified nutritional support as a major determinant of the outcome of chronic melioidosis infection. This has led to new strategies to support patient nutrition and has improved survival rates.

Focus on high-risk individuals and rapid diagnosis is important in order to start treatment at an early stage. The introduction of immunofluorescent based assays to detect bacteria by microscopy of pus, sputum, and urine has been useful in Thailand. The time to diagnosis has been reduced to 30 minutes.

Sources to corroborate the impact:

7. Cheng, A. C. *et al.* Dosing regimens of cotrimoxazole (trimethoprim-sulfamethoxazole) for melioidosis. *Antimicrob. Agents Chemother.* **53**, 4193–4199 (2009) doi: 10.1128/AAC.01301-08.

The World Health Organization's Centers for Disease Control and Prevention now recommend the use of ceftazidime or meropenem as an intreveous therapy for melioidosis. This recommendation was based on MORU's findings.

8. Centers for Disease Control and Prevention (CDC) - Treatment – Melioidosis (Accessed 2013) . *cdc.gov* at Available at http://www.cdc.gov/melioidosis/treatment/index.html

The WHO's Centers for Disease Control and Prevention recommend Trimethoprim-sulfamethoxazole or Doxycycline as an alternative oral therapy for the treatment of melioidosis based on MORU's research.

9. Currie, B and Anstey, N. Treatment and prognosis of melioidosis. In UpToDate Basow, DS (Ed), UpToDate, Waltham, MA, 2013.(Accessed 2013). Website accessible to subscribers only (available on request). http://www.uptodate.com/contents/treatment-and-prognosis-of-melioidosis?source=search_result&search=melioidosis&selectedTitle=2%7E23

Recommendations for the introduction of TMP-SMX during initial intensive therapy on UpToDate® directly cite MORU studies.

10. Wuthiekanun, V. *et al.* Survey of antimicrobial resistance in clinical Burkholderia pseudomallei isolates over two decades in Northeast Thailand. *Antimicrob. Agents Chemother.* **55**, 5388–5391 (2011) doi: 10.1128/AAC.05517-11.

MORUs research demonstrating the utility of carbapenem antibiotics for severe acute disease.