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Review

Treatment and prophylaxis of melioidosis☆

David Dance[a,b,*]

[a] Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao People's Democratic Republic
[b] Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, UK

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ABSTRACT

Melioidosis, infection with *Burkholderia pseudomallei*, is being recognised with increasing frequency and is probably more common than currently appreciated. Treatment recommendations are based on a series of clinical trials conducted in Thailand over the past 25 years. Treatment is usually divided into two phases: in the first, or acute phase, parenteral drugs are given for ≥10 days with the aim of preventing death from overwhelming sepsis; in the second, or eradication phase, oral drugs are given, usually to complete a total of 20 weeks, with the aim of preventing relapse. Specific treatment for individual patients needs to be tailored according to clinical manifestations and response, and there remain many unanswered questions. Some patients with very mild infections can probably be cured by oral agents alone. Ceftazidime is the mainstay of acute-phase treatment, with carbapenems reserved for severe infections or treatment failures and amoxicillin/clavulanic acid (co-amoxiclav) as second-line therapy. Trimethoprim/sulfamethoxazole (co-trimoxazole) is preferred for the eradication phase, with the alternative of co-amoxiclav. In addition, the best available supportive care is needed, along with drainage of abscesses whenever possible. Treatment for melioidosis is unaffordable for many in endemic areas of the developing world, but the relative costs have reduced over the past decade. Unfortunately there is no likelihood of any new or cheaper options becoming available in the immediate future. Recommendations for prophylaxis following exposure to *B. pseudomallei* have been made, but the evidence suggests that they would probably only delay rather than prevent the development of infection.

1. Introduction

Melioidosis is the name given to any infection caused by the saprophytic environmental bacterium *Burkholderia pseudomallei*, which is widespread in the soil and surface water in southeast Asia and northern Australia. The disease is being recognised with increasing frequency in known endemic areas [1,2] and new foci are regularly being identified [3,4].

The organism is intrinsically resistant to many antimicrobial agents, including those often used for the empirical treatment of sepsis in the tropics [5], and may be even more resistant when growing in biofilms [6–8] and in the anaerobic acidic conditions that might be found in vivo [9]. There is considerable evidence supporting current treatment recommendations, mainly derived from a series of large randomised clinical trials conducted in northeast Thailand since 1986, although there are also many unanswered questions. This review will summarise that evidence and the current recommendations and will consider some of the outstanding issues.

2. Treatment

The current convention is to view the treatment of melioidosis as comprising two phases: the first is the acute phase, the aim of which is to stop patients from dying of overwhelming sepsis; the second is the eradication phase, the aim of which is to kill any residual bacteria and to minimise the risk of the infection relapsing.

2.1. Acute phase (Table 1)

Until 1985, the usual treatment for the acute phase was a combination of chloramphenicol, doxycycline and trimethoprim/sulfamethoxazole (co-trimoxazole) (the 'conventional' regimen). However, the overall mortality was 37.9–61% and for patients with septicaemic infection and multiple foci it was as high as 87% [10]. Since there were new β-lactams available that showed

* Correspondence to: Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao People's Democratic Republic. Tel.: +856 2124 2168.
E-mail address: david.d@tropmedres.ac

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promising in vitro activity against *B. pseudomallei* [11], the first of several randomised prospective clinical trials of treatment for melioidosis was started in Ubon Ratchathani, northeast Thailand, in 1986 [12]. Patients were randomised to receive the conventional regimen or ceftazidime (120 mg/kg/day) according to a paired restricted sequential design. In total 161 patients were entered into the study, of whom 65 had culture-proven melioidosis and 54 of these were septicaemic. The overall mortality was 37% in those treated with ceftazidime compared with 74% in the conventionally treated group, a reduction of 50% [95% confidence interval (CI) 19–81%], suggesting that ceftazidime should be adopted as the acute-phase treatment of choice for severe melioidosis. Mortality in patients with septicaemic melioidosis was reduced from 76% to 43%, and in patients in whom melioidosis was not confirmed from 79% to 61%. Ceftazidime was given for a median of 8 days (range 7–28 days). Despite these encouraging results, it is worth noting that 4/20 patients and 1/9 patients still had positive blood cultures on Days 3 and 7 of treatment, respectively, and that 3 patients subsequently had bacteriologically confirmed relapses of melioidosis, indications of the recalcitrant nature of the disease.

A similar study, which also took place in northeast Thailand, was reported 3 years later [13] with broadly similar results. The study design differed in that ceftazidime was given at a slightly lower dose (100 mg/kg/day) combined with co-trimoxazole. The reported 7-day mortalities amongst the 61 evaluable patients with confirmed melioidosis in that study were lower than in the previous study (47% with conventional treatment compared with 18.5% in the ceftazidime plus co-trimoxazole group overall; 57.7% compared with 25% for septicaemic melioidosis; and 82.3% compared with 30.7% for disseminated septicaemic melioidosis). No significant difference in mortality was found in patients with established septic shock at the time of presentation. It was also reported that no relapses were seen amongst survivors in that study.

Whether the differences between the two studies described above reflected a genuinely better outcome with the combination than with ceftazidime monotherapy, or differences in the severity of illness between patients included in the two studies, was initially unclear. Two studies comparing ceftazidime with and without co-trimoxazole undertaken in Khon Kaen and Ubon Ratchathani were subsequently published as a single paper [14]. The overall in-hospital mortality rates amongst all 449 patients enrolled were not significantly different between those treated with ceftazidime alone (25.1%) and those treated with the combination (26.6%), nor were there differences in death rates amongst the 241 patients with culture-confirmed melioidosis, either overall or occurring ≥48 h after admission. Multiple logistic regression analysis identified that bacteraemia, respiratory failure and renal failure, but not drug regimens, were independently associated with death and treatment failure, even when cases with co-trimoxazole-'resistant' isolates were excluded. On prolonged follow-up, there was also no difference between the two groups in terms of mortality or culture-confirmed recurrence [15]. Thus, there is no evidence to support the routine addition of co-trimoxazole to ceftazidime during the acute phase of treatment for melioidosis, although some have argued that this is warranted in patients with undrained deep-seated infections or when monotherapy fails in places where carbapenems are unavailable or unaffordable [16].

In an effort both to reduce the cost of treatment and to evaluate an agent with a spectrum of activity that might be more appropriate for monotherapy of community-acquired sepsis than ceftazidime alone, amoxicillin/clavulanic acid (co-amoxiclav) (160 mg/kg/day) was compared with ceftazidime (120 mg/kg/day) for treatment of severe melioidosis in Ubon Ratchathani in a large, open, paired randomised controlled trial between 1989 and 1992 [17]. In total, 379 patients were enrolled, of whom 212 proved to have culture-positive melioidosis, with 106 patients in each treatment arm. There were no significant differences in mortality between the two groups (overall 47%). The study design allowed the treating physicians to switch treatment if the clinical response was considered 'unsatisfactory' after ≥72 h, however, and this occurred more frequently in the co-amoxiclav group (16/69) than in the ceftazidime group (4/75). This is clearly a somewhat subjective endpoint, but as a result ceftazidime was considered to remain the treatment of choice, with co-amoxiclav as a second-line option.

The nature of the mixture of amoxicillin and clavulanic acid means that there are complex pharmacokinetic considerations when using it to treat melioidosis. For example, there is in vitro evidence that relatively high concentrations of clavulanic acid must be achieved to potentiate amoxicillin [18], and modelling suggests that the dosing interval for co-amoxiclav in melioidosis should not be >6 h [19]. Since different formulations and ratios of amoxicillin to clavulanic acid are available in different countries, and different regimens have been used by different groups to treat melioidosis, an international consensus statement was published in 2008 to reduce confusion [20]. This recommends the use of amoxicillin/clavulanic acid at a dose of 20/5 mg/kg every 4 h, but only as a second-line agent for acute-phase treatment.

Another β-lactam/β-lactamase inhibitor combination that has good in vitro activity against *B. pseudomallei* [minimum inhibitory concentration required to inhibit 90% of the isolates (MIC_{90}) = 4 mg/L] is cefoperazone/sulbactam [21]. This was evaluated at 25 mg/kg/day in combination with co-trimoxazole (trimethoprim 8 mg/kg/day) in comparison with ceftazidime (100 mg/kg/day) plus co-trimoxazole [22]. In total, 219 patients were enrolled, of whom 102 had culture-confirmed melioidosis. There were no significant differences in mortality between the two groups (18% compared with 14%, respectively) or in fever duration or bacteriological response. This study was, however, relatively underpowered [23]. Furthermore, in a retrospective analysis of 1353 patients with melioidosis who received cephalosporins, the overall mortality rate for those who received cefotaxime or ceftriaxone (71%) was significantly higher than those receiving ceftazidime (41.7%) or co-amoxiclav (53.9%) [24]. Ceftazidime has thus remained the cephalosporin of choice for acute treatment of melioidosis [25]. There is evidence that the total dose, and therefore costs, of ceftazidime may be reduced from 120 mg/kg/day to 96 mg/kg/day if it is given by continuous infusion rather than bolus dosing [26]. To facilitate outpatient treatment with ceftazidime and to optimise pharmacokinetics, clinicians in northern Australia have used a simple elastomeric infusion apparatus to administer ceftazidime [27]. This approach can save significant expenditure on inpatient care if the infrastructure to support outpatient parenteral antibiotic therapy is available, but as yet it has not been widely adopted internationally [28]. In northern Australia there is now a trend towards using increasingly long courses of intravenous (i.v.) antibiotics to treat melioidosis, especially in the presence of deep-seated undrained foci of infection. It has been suggested that this approach may ultimately obviate the need for an eradication phase, although it has not been evaluated in comparative trials. The median duration of the i.v. phase in Darwin is now 4 weeks, and some 27% of patients have had no eradication-phase treatment without developing relapse [29].

The carbapenems are the most active drugs against *B. pseudomallei* in vitro [30]. There are also some theoretical reasons for believing that they may be better therapeutic options than ceftazidime. For example, they exhibit longer post-antibiotic effects [31] and are more rapidly bactericidal [30]. An open, prospective, randomised study was therefore conducted to compare the efficacy of ceftazidime (120 mg/kg/day) with that of imipenem/cilastatin (50 mg/kg/day) for a minimum of 10 days [32]. Unfortunately, the study had to be terminated prematurely due to the withdrawal of pharmaceutical company support, by which time 296 patients