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Oral eradication therapy for melioidosis: Important but not without risks

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ABSTRACT

Objectives: The purpose of this study was to quantify the adverse effects from oral eradication therapy for melioidosis, which is usually with high dose trimethoprim-sulfamethoxazole for 3–6 months.
Methods: This retrospective cohort study reviewed side effects from oral eradication therapy in patients presenting with first episode culture-confirmed melioidosis in the tropical north of Australia's Northern Territory between 1st October 2012 and 1st January 2017.
Results: 234 patients presented for the first time with culture-confirmed melioidosis. Of these, 16 (6.8%) died during the intensive phase treatment and 6 (2.6%) did not have complete treatment at Royal Darwin Hospital. Of the remaining 212 patients, 203 (95.8%) were initially prescribed trimethoprim-sulfamethoxazole as oral eradication therapy, 6 (2.8%) were prescribed doxycycline and 3 (1.4%) had no eradication therapy. Of the 203 prescribed trimethoprim-sulfamethoxazole, 61 (30.0%) experienced adverse effects, which necessitated a cessation, a change in antibiotic or reduction in dose.
Conclusions: In patients treated for melioidosis in northern Australia there are high rates of adverse effects from oral trimethoprim-sulfamethoxazole, frequently necessitating a change in therapy or a reduction in dose. Given the side effects and low rates of oral therapy completion in our region we emphasise the importance of the prior often prolonged intensive phase intravenous therapy and using weight based trimethoprim-sulfamethoxazole dosing for eradication therapy.

Introduction

Melioidosis results from infection with the Gram-negative bacterium *Burkholderia pseudomallei* and has diverse clinical presentations including pneumonia, localised cutaneous lesion, bacteremia without evident focus, osteomyelitis, septic arthritis and severe sepsis with multiple organ abscesses (Wiersinga et al., 2012; Wiersinga et al., 2018). It is endemic in Southeast Asia and northern Australia, with increasing recognition in many other tropical and sub-tropical locations (Limmathurotsakul et al., 2016).

Therapy is divided into an intravenous intensive phase and an oral eradication phase (Dance, 2014; Lipsitz et al., 2012). International guidelines recommend at least 10–14 days intravenous therapy with either ceftazidime or a carbapenem, followed by a minimum of 12 weeks of oral trimethoprim-sulfamethoxazole (Lipsitz et al., 2012). Amoxicillin-clavulanic acid and doxycycline are considered second line agents (Lipsitz et al., 2012). There are low rates of adherence to oral eradication therapy in our region, which has led to the progressive lengthening of the duration of intravenous intensive phase therapy (Pitman et al., 2015). Duration of intravenous therapy recommended in northern Australia is determined by the site and severity of melioidosis, based on the antibiotic duration determining focus as previously defined (Pitman et al., 2015). For instance, intravenous therapy is recommended for four weeks for complicated pneumonia and deep-seated abscess, at least six weeks for osteomyelitis and eight weeks for neurological melioidosis and arterial infection (Pitman et al., 2015). This therapy is often given via a Peripheral Inserted Central Catheter (PICC) with an elastomeric infusor device, which has been shown to be safe and effective in an out of hospital program (Huffam et al., 2004). The duration of oral eradication therapy is typically three months, but this is extended to six months in neurological, arterial and bone melioidosis (Pitman et al., 2015). The rationale for oral eradication therapy is to prevent relapse of melioidosis (Currie, 2015; Dance, 2014).

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The northern Australian guideline has been shown to be associated with low rates of relapse, despite frequent poor adherence to oral eradication therapy, and this low relapse rate has been attributed to the longer duration of intravenous therapy (Pitman et al., 2015; Sarovich et al., 2014). It is therefore possible that some patients in our region could have their oral eradication therapy shortened or even avoided (Pitman et al., 2015). However, the risks of oral eradication therapy are not known so the potential benefits of such reduction are not quantified. The purpose of this study was to determine the incidence of side effects from oral eradication therapy in our patient cohort.

Materials and methods

Study design

This retrospective cohort study reviewed side effects from oral eradication therapy in patients presenting with first episode culture-confirmed melioidosis in the tropical north of Australia's Northern Territory between 1st October 2012 and 1st January 2017. The medical records and outpatient letters of all patients enrolled in the Darwin Prospective Melioidosis Study (Currie et al., 2000; Currie et al., 2010) between 1st October 2012 and 1st January 2017 were retrospectively reviewed. Additional parameters such as site of infection, age, sex and risk factors were taken from data collected for the Darwin Prospective Melioidosis study (Currie et al., 2000; Currie et al., 2010). Duration of intravenous antibiotics, duration of hospital stay, duration of Hospital in the Home admission, recrudescence and relapse rates were also collected retrospectively with follow up until October 31st 2018.

Definitions

An adverse effect was defined as a side effect, which was documented in the medical record or outpatient letter, was attributed to the oral therapy, and necessitated either a change or cessation of therapy, or a reduction in dose. Adverse effects were divided into categories which included drug rash with eosinophilia and systemic symptoms (DRESS), acute kidney injury, bone marrow suppression (which could include anaemia, leucopenia, thrombocytopenia or pancytopenia), gastrointestinal (which could include nausea, vomiting, abdominal pain or liver function derangement), rash or other. The presence of these side effects was determined by the medical documentation only and laboratory parameters were not additionally analysed.

Recrudescence was defined as the development of clinical illness during the oral eradication phase with concurrent new culture of *B. pseudomallei* in a clinical specimen. Recurrence was defined as the development of clinical illness after the oral eradication phase with new culture of *B. pseudomallei* in a clinical specimen. Recurrence was considered either relapse, in which the *B. pseudomallei* isolated was of the same genotype as that from the original infection, or new infection, in which the new *B. pseudomallei* was a different genotype from that of the original infection.

Ethical issues

The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC 02/38).

Results

Baseline characteristics

There were 234 patients presenting for the first time with culture-confirmed melioidosis between 1st October 2012 and 1st January 2017. Of these, 16 (6.8%) died during the intensive phase treatment and 6 (2.6%) did not have complete treatment at Royal Darwin Hospital. Baseline characteristics of the remaining 212 patients are given in Table 1.

Table 1
Baseline characteristics of 212 included patients.

Characteristic	Number (%) except where indicated
Male	125 (59.0)
Age (median)	51 years (iqr 39–60)
Any risk factor	193 (91.0)
- Diabetes	105 (49.5)
- Hazardous alcohol use	98 (46.2)
- Chronic renal disease	31 (14.6)
- Chronic lung disease	61 (28.8)
- Malignancy	20 (9.4)
- Immunosuppressive therapy	21 (9.9)
- Rheumatic heart disease or congestive cardiac failure	20 (9.4)
- Kava use	4 (1.9)
- Other	12 (5.7)
Antibiotic duration determining focus	
- Skin	28 (13.2)
- Bacteremia no focus	13 (6.1)
- Pneumonia	97 (45.8)
- Deep-seated collection	53 (25.0)
- Osteomyelitis	18 (8.5)
- Central nervous system infection	2 (1.0)
- Arterial infection	1 (0.5)
Duration of intravenous antibiotics post last culture positive drain	28 days (iqr 15–32)
ICU admission	46 (21.7)
Duration of hospital admission (median)	18 days (iqr 8–36)
Hospital in the Home admission	154 (72.6)
Duration of Hospital in the Home admission (median)	20 days (iqr 13–26)
Self discharge	23 (10.8)

Table 2
Predominant Side Effects from trimethoprim-sulfamethoxazole and outcomes.

Predominant side effects from trimethoprim-sulfamethoxazole	Number (% of side effect)	Number antibiotic changed (% of side effect)	Number dose reduced or ceased (% of side effect)
All side effects	61 (100)	47 (77.0)	14 (23)
Drug rash with eosinophilia and systemic symptoms (DRESS)	2 (3.3)	2 (100)	0
Acute kidney injury	22 (36.1)	14 (63.6)	8 (36.4)
Bone marrow suppression	13 (21.3)	10 (76.9)	3 (23.1)
Rash	14 (23.0)	12 (85.7)	2 (14.3)
Gastrointestinal[b]	7 (11.5)	6 (85.7)	1 (14.3)
Other[a]	3 (4.9)	3(100)	0

[a] Includes 1 eosinophilia, 1 headache, and 1 hyperkalaemia.
[b] Includes 2 with nausea, 3 with nausea and vomiting, 2 with liver function derangement.

Recrudescence and relapse

Of the 212 patients, 203 (95.8%) were commenced on trimethoprim-sulfamethoxazole and 6 (2.8%) on doxycycline, while 3 (1.4%) had no oral eradication therapy. The intended duration of oral therapy was 3 months in 188 (88.7%) patients and 6 months or greater in 21 (9.9%) patients. 7 (3.3%) patients died during oral eradication therapy, all from causes unrelated to melioidosis. Six (2.8%) patients had recrudescence of melioidosis, and 9 (4.2%) had recurrence, of which genotyping of paired *B. pseudomallei* strains showed 7 were relapses, 1 was a new infection, and in 1 patient paired isolates were not available for genotyping.

Adverse effects from oral eradication therapy

No patient who was prescribed doxycycline as initial oral eradication therapy experienced an adverse effect necessitating a dose reduction or change in agent. The dose of trimethoprim-sulfamethoxazole recommended in our guideline is as recommended in international guidelines and this is higher than standard use dosage; child 6 + 30 mg/kg up to 240 + 1200 mg; adult 40–60 kg, 240 + 1200 mg; >60 kg, 320 + 1600 mg orally, twice daily; with addition of folate, child 0.1 mg/kg up to 5 mg adult dose, daily (Currie, 2015). Of the 203 who were commenced on trimethoprim-sulfamethoxazole, 61 (30.0%) experienced a side effect necessitating a dose reduction or change in agent. Of these, 45 (73.8%) were changed to doxycycline, 2 (3.3%) to amoxicillin-clavulanic acid, while 11 (18.0%) had trimethoprim-sulfamethoxazole dose reduced and 3 (4.9%) had trimethoprim-sulfamethoxazole ceased with no replacement. An additional two patients were changed from trimethoprim-sulfamethoxazole to doxycycline for reasons other than an adverse effect.

The predominant reason for cessation, dose reduction or change in agent is given in Table 2. Twelve patients experienced multiple side effects and in these patients the predominant reason was determined by the severity, with the following order: drug rash with eosinophilia and systemic symptoms (DRESS), acute kidney injury, bone marrow suppression, rash, gastrointestinal side effect and other. In the 22 patients whose predominant reason was acute kidney injury, one patient also developed bone marrow suppression, one patient also rash, one patient also rash and fever, one patient also vomiting, and one patient also nausea, vomiting, liver function derangement and fever. In the 13 patients whose predominant reason was bone marrow suppression, two patients also developed fever, and one patient also liver function derangement. In the 14 patients whose predominant reason was rash, one patient also developed liver function derangement and fever, one patient also liver function derangement and eosinophilia, one patient also nausea and one patient also hyperkalaemia. There were no deaths attributed to oral eradication therapy.

Of the 52 patients who were unable to complete the prescribed course of trimethoprim – sulfamethoxazole due to an adverse effect or had their antibiotic changed for another reason, there were 4 (7.7%, 95%CI 2.1–18.5) episodes of recrudescence and 1 episode of relapse (1.9%, 95%CI 0.05–10.2). There was no recrudescence or recurrence in the 11 who had trimethoprim-sulfamethoxazole dose reduced. Of the 140 remaining patients who were commenced on trimethoprim-sulfamethoxazole and did not experience an adverse effect, there were 2 patients with recrudescence (1.4%, 95%CI 0.2–5.1), which included 1 patient who experienced recrudescence 3 times, 5 relapses (3.6%, 95%CI 1.2–8.1), 1 reinfection and 1 recurrence in which whether relapse or reinfection was not able to be determined.

Discussion

Patients in northern Australia who are treated for melioidosis experience high rates of side effects to oral trimethoprim-sulfamethoxazole, which often results in a change of therapy, a reduction in dose, or cessation of therapy. Trimethoprim-sulfamethoxazole monotherapy has been internationally considered the first line agent for oral eradication therapy since the randomised controlled trial in Thailand found recurrence rate with trimethoprim-sulfamethoxazole alone was non-inferior to trimethoprim-sulfamethoxazole in combination with doxycycline and was associated with fewer side effects (Chetchotisakd et al., 2014). The discontinuation rate due to an adverse event from the planned 20 weeks of trimethoprim-sulfamethoxazole was 12% in the Thai study (Chetchotisakd et al., 2014). In our study, 3/203 (1.5%) patients had trimethoprim – sulfamethoxazole ceased completely and 47/203 (23.2%) had their antibiotic changed due to an adverse event. The higher rates seen in our population group may in part reflect more frequent monitoring of complete blood count, renal and liver function, which typically occurs at least monthly in our setting rather than the 4, 12, and 20 week follow up in Thailand (Chetchotisakd et al., 2014). In addition there has historically been a tendency for higher doses of trimethoprim – sulfamethoxazole in Australia, although more recently the dosing regimen has been aligned globally (Lipsitz et al., 2012). Nevertheless, from our clinical experience, most adults with melioidosis in our region are commenced on the maximum dose of 320 + 1600 mg and the substantial rates of side effects to oral trimethoprim-sulfamethoxazole seen in this study most likely reflect this high dosing used for melioidosis.

It is interesting to note that the majority of our patients who experienced a side effect were changed to an alternative agent, most commonly doxycycline and in a few incidences, amoxicillin-clavulanic acid. A study from Thailand showed that doxycycline alone was inferior to conventional treatment with chloramphenicol, trimethoprim-sulfamethoxazole, and doxycycline (Chaowagul et al., 1999). Amoxicillin – clavulanic acid has been similarly shown to be inferior (Rajchanuvong et al., 1995). Despite an earlier study

from Darwin also showing higher relapse with doxycycline (Jenney et al., 2001), there was a low rate of recrudescence and relapse rate in the current study despite 53/212 (25.0%) of patients taking doxycycline at some stage during the oral eradication phase. We examined each case of relapse and recrudescence and found recrudescence was associated with osteomyelitis, and relapse was associated with the presence of unrecognized foci or incomplete eradication therapy when there were extensive internal collections. This likely reflects an inadequacy of source control rather than a failure of the oral antibiotic itself. We postulate that in recent years we may not be seeing the clinical failure with doxycycline and the concomitant acquired doxycycline resistance that occurred in a past era (Jenney et al., 2001) because of the reduction in bacterial burden from the prolonged intravenous therapy now used and the first line preference for trimethoprim-sulfamethoxazole, even if it subsequently requires a change to doxycycline. Unlike in prior times, with our current regimen few patients are exposed to doxycycline when their bacterial burden is high. Our guideline recommends doxycycline as the preferred second line agent as in our clinical experience patients have often been unable to tolerate the high doses of amoxicillin-clavulanic acid recommended for the treatment of melioidosis (Cheng et al., 2008).

A limitation of this study is its retrospective nature and the definitions used for adverse effects. An adverse effect was defined as a side effect documented in the medical record or outpatient letter, which was attributed to the oral therapy and necessitated either a change or cessation of therapy, or a reduction in dose. There is a possibility that some side effects may have been omitted in the medical documentation, while attribution of side effects to trimethoprim-sulfamethoxazole may have been incorrect in some cases. Additionally, we did not seek actual completion rate of oral eradication therapy in this study and we were unable to quantify the adherence of individual patients. We also did not audit the dosing prescribed by clinicians in our population.

In conclusion, despite often poor adherence to oral eradication therapy, there was a high rate of adverse effects from trimethoprim-sulfamethoxazole in patients treated for melioidosis in northern Australia. Dose reduction or a change to doxycycline therapy was common, but in our setting where prolonged intravenous therapy is possible, treatment was still successful in the vast majority of patients. Given the side effects and low rates of oral therapy completion in our region we emphasise the importance of prolonged intensive phase intravenous therapy and a trimethoprim-sulfamethoxazole dose based on weight. Further studies are required to identify if there are subsets of patients who may benefit from a reduction in oral therapy duration or even omission of the eradication therapy phase. Ideally randomised comparative studies with analysis of costs and outcomes can help optimise therapy regimens for melioidosis of differing severity and in different geographical circumstances.

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Transparency declarations

No conflicts of interest to declare. BJC conceptualized the study. RPS acquired the data. LW provided assistance with data consolidation, and statistical analysis. RPS and BJC drafted the manuscript. All authors have read and approve the final manuscript.

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