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CLINICAL RESEARCH

Trimethoprim + Sulfamethoxazole Reduces Rates of Melioidosis in High-Risk Hemodialysis Patients

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Introduction: Melioidosis causes sepsis and death in the Top End of Northern Australia during the monsoonal wet season. Dialysis-dependent adults suffer higher melioidosis rates compared to low rates among renal transplant patients who routinely receive trimethoprim+sulfamethoxazole prophylaxis.

Methods: We performed a prospective interventional study to determine the efficacy and safety of daily trimethoprim+sulfamethoxazole prophylaxis in hemodialysis patients during the wet season, from 1 November 2014 to 30 April 2015. Hemodialysis (for ≥ 3 months) patients ≥ 18 years of age were offered treatment. A total of 269 patients on hemodialysis were eligible. Eight of the 269 patients (3%) were excluded from the analysis for being on melioidosis treatment. In all, 169 of 261 patients (64.8%) received the prophylaxis, and 92 of 261 patients (35.2%) did not, because of allergy history (n = 10), remoteness and logistical reasons (n = 60), poor dialysis attendance (n = 11), and refusal (n = 11). We monitored for clinical side effects 3 times weekly and neutropenia, thrombocytopenia, and liver function monthly throughout treatment and for 2 months posttreatment.

Results: In all, 169 of 261 patients (64.8%) received the prophylaxis. There was no age (years) difference by group (prophylaxis vs. nonprophylaxis, 54.7 [11.3] vs. 54.3 [11.2] [$P = 0.751$]). Sixteen of 261 patients (6%) had melioidosis. The event frequency was 0% (0/169, prophylaxis, vs. 17.4% [16/92, nonprophylaxis], $P < 0.001$). Higher thrombocytopenia and neutropenia rates were noted in the prophylaxis group. These did not warrant treatment stoppage. There was no difference in liver function. Three patients (1.8%) withdrew from the treatment because of side effects.

Discussion: Daily dosing was effective and safe. Posthemodialysis dosing in the subsequent seasons was effective and safer. We recommend this approach in melioidosis-prevalent regions.

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Melioidosis causes severe sepsis and death in the Top End of Northern Australia during the monsoonal wet season.[1] The wet season (melioidosis season) is defined to capture the seasonal presentation in the tropical wet season (November to April),[2] with average monthly rainfalls of 100 to 500 mm in the 6 months (Figures 1 and Supplementary Figure S1) and high humidity of > 80%.[3] Melioidosis is caused by the saprophytic Gram-negative bacterium and Tier 1 select agent *Burkholderia pseudomallei,* which naturally occur in tropical soil and water.[4] *Burkholderia pseudomallei* is widespread in Northern Australia and Southeast Asia and is increasingly recognized as being endemic in other tropical regions globally.[1,4–6] The Darwin Prospective Melioidosis Study (DPMS) is a long-running, large, prospective observational study started in October 1989 that aims to understand the clinical and microbiological aspects of melioidosis in the Top End of the Northern Territory (NT), and to use this information to lessen the burden of the disease through earlier diagnosis and improved treatment. The

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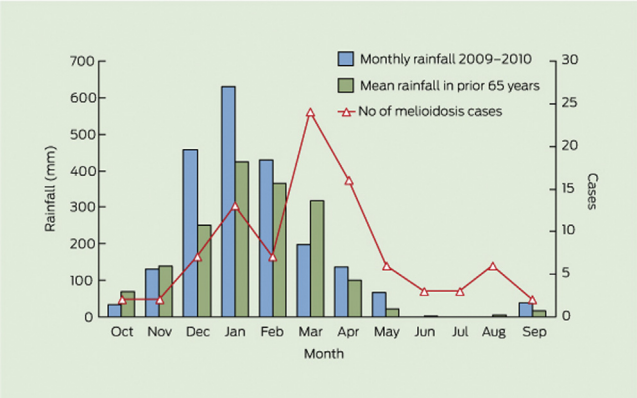

Figure 1. Correlation between cases of melioidosis managed at Royal Darwin Hospital in 2009–2010 and rainfall at Darwin airport. Reproduced with permission from Parameswaran U, Baird RW, Ward LM, et al. Melioidosis at Royal Darwin Hospital in the big 2009–2010 wet season: comparison with the preceding 20 years. *Med J Aust.* 2012;196:345–348. Copyright © 2012 The Medical Journal of Australia.

study has documented all cases of melioidosis in the Top End of the NT since 1 October 1989,[7,8] with around 85% of cases occurring during the tropical wet season (November to April)[2] (Figure 1).

Chronic kidney disease (CKD) is an independent risk factor for melioidosis, and CKD is associated with a higher mortality rate whenever melioidosis occurs.[9,10] Other factors associated with high risk for melioidosis include diabetes mellitus, hazardous alcohol use, chronic lung disease, rheumatic heart disease and cardiac failure, and immune-suppressive medications, most notably the use of corticosteroids. Age and indigenous ethnicity are also independent predictors for melioidosis. These factors are also common among adult patients dependent on dialysis in this region.[11] In our region, we have previously reported staggering higher incidence rates of melioidosis among adults dependent on dialysis than among those without dialysis-dependent CKD (988.8/100,000 vs. 24.0/100,000 patient-years), equating to a crude relative risk for melioidosis among adults dependent on dialysis of 38.4 (95% confidence interval [CI] = 25.7–57.5).[11]

As observed in some previous wet seasons, during the 2011 to 2012 wet season, we observed a higher frequency of melioidosis among the dialysis cohort.[12] Rates of melioidosis are lower among our renal transplant cohort. Our routine practice to specifically mitigate wet season–associated melioidosis for the renal transplant and immunosuppressed cohort includes consideration of trimethoprim+sulfamethoxazole (TMP+SMX) prophylaxis treatment, at a dose higher than usually used for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.[13] Pharmacodynamic and pharmacokinetic studies of TMP+SMX for the treatment of melioidosis indicate that high doses of oral TMP+SMX are required for eradication after an initial intensive treatment with intravenous ceftazidime or meropenem.[10,14–18] There are no published data on the prophylactic use of TMP+SMX (or any other antibiotics) to reduce melioidosis in high-risk groups, although TMP+SMX has been used as postexposure prophylaxis for *Burkholderia pseudomallei* infection among laboratory staff.[19] Therefore, following the increase in both the number of melioidosis cases observed in the 2011 to 2012 wet season, and the concomitant increase in the size of the prevalent dialysis patient cohort, we undertook a prospective open-label intervention by implementing a prophylaxis guideline for hemodialysis patients in the Top End of the Northern Territory over the wet season (1 November 2014 to 30 April 2015), using oral trimethoprim+sulfamethoxazole (TMP+SMX), 160/800 mg daily.

The aim of this study was to determine the efficacy and safety of prophylaxis with daily TMP+SMX for melioidosis in hemodialysis patients from the Top End of Northern Australia during the wet season from 1 November 2014 to 30 April 2015.

MATERIALS AND METHODS

Study Design

The study was a prospective, open-label, interventional study carried out as part of the larger Darwin Prospective Melioidosis Study, which documents all cases of melioidosis and treatment in the Top End of the Northern Territory.[20]

Study Population

All patients ≥ 18 years of age who had been on maintenance hemodialysis for ≥ 3 months were offered the prophylactic treatment. All eligible hemodialysis patients throughout the Top End received daily TMP+SMX, excluding persons with known hypersensitivity to trimethoprim and/or sulfamethoxazole, lipoamides, or any other ingredients in the formulations of the tablets, severe hepatic failure, marked liver parenchymal damage or jaundice, or serious hematological disorders (thrombocytopenia < 80,000 platelets/μl, leukopoenia < 3.5 × 10^9/l (neutrophil count < 2.7 × 10^9), and porphyria, and any other contraindications to TMP+SMX. Those who declined the treatment were also excluded from the prophylaxis treatment. The cohort could therefore be described categorically as those who received the intervention and a control group of those who were ineligible for the intervention (or TMP+SMX-group [prophylaxis] vs. nonprophylaxis group).

All patients received the usual wet season advice on melioidosis prevention.[14]

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