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Short Report: Consensus Guidelines for Dosing of Amoxicillin-Clavulanate in Melioidosis

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Abstract

Melioidosis is an infectious disease endemic to northern Australia and Southeast Asia. In response to clinical confusion regarding the appropriate dose of amoxicillin-clavulanate, we have developed guidelines for the appropriate dosing of this second-line agent. For eradication therapy for melioidosis, we recommend 20/5 mg/kg orally, three times daily.

INTRODUCTION

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, endemic to northern Australia and Southeast Asia. *B. pseudomallei* is regarded as a potential bioweapon and imported cases of melioidosis are not infrequently reported in travelers returning from endemic areas. As researchers and clinicians treating substantial numbers of patients with melioidosis in Australia and Thailand, we have been made aware of confusion regarding dosing of amoxicillin-clavulanate used in the management of melioidosis. This is particularly true in light of conflicting pharmacokinetic data and a range of combination formulations containing ratios of amoxicillin:clavulanate (A:C) of between 2:1 and 16:1.

METHODS

We became aware of misquoted dosing recommendations in our own recent reviews of melioidosis,^{1,2} other guidelines that have not provided dosing recommendations³ or

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These Guidelines were developed as a consensus amongst a group of clinicians with extensive experience of treating melioidosis in the endemic regions of Thailand and Australia.

provided incorrect dosing recommendations,⁴ and multiple recent case reports where an incorrect dose of amoxicillin-clavulanate was administered for melioidosis.^{5,6} A correspondence was conducted among researchers and clinicians who are active in clinical research and who treat or have treated significant numbers of patients with melioidosis in the endemic areas. Dosing recommendations were reached by consensus and were based on the available pharmacokinetic evidence, clinical trials, and clinical experience with this agent.

RESULTS

First-line treatment recommendations suggest an intravenous intensive course of ceftazidime or a carbapenem followed by a prolonged oral eradication course of cotrimoxazole (commonly used in Australia) or cotrimoxazole with doxycycline (commonly used in Thailand).⁷ However, amoxicillin-clavulanate is still used as a second-line agent in eradication treatment of melioidosis, particularly for patients with sulfonamide allergy, those who are intolerant of cotrimoxazole (particularly with neutropenia or gastrointestinal intolerance), in pregnant patients (where cotrimoxazole is relatively contraindicated) and in children (where doxycycline is contraindicated).

For intravenous intensive phase therapy, amoxicillin-clavulanate at a dose of 20/5 mg/kg 4-hourly is an alternative to ceftazidime or carbapenems for less severe cases where this agent is available.^{8,9} However intravenous amoxicillin-clavulanate is associated with higher rates of treatment failure,⁸ and there are few indications for this agent if first-line agents are available.

For eradication treatment of melioidosis, we recommend that oral amoxicillin-clavulanate (coamoxiclav) should be used at a dose of 20/5 mg/kg three times a day. For adult patients < 60 kg, a dose of 1000/250 mg three times daily is suggested. In regions where coamoxiclav is only available in fixed 2:1 combinations, we use 500 mg/250 mg three times daily with additional amoxicillin (500 mg three times daily). For patients > 60 kg, we use a maximum dose of 1500/375 mg three times daily. We do not recommend twice daily regimens or formulations containing A:C ratios of > 4:1 (such as “Duo Forte” or “XR” formulations) because of inadequate clavulanate.¹⁰ Oral eradication treatment should be continued for 12–20 weeks.

CONCLUSION

These recommendations are based on our extensive clinical experience with this agent, but there is also substantial evidence suggesting that coamoxiclav is associated with higher relapse rates when compared with cotrimoxazole-based regimens for oral eradication-phase treatment.^{11,12} These studies also reinforce the need to monitor patients carefully for gastrointestinal intolerance to ensure compliance. Checkerboard susceptibility testing suggests that clavulanate is key to the antimicrobial action of the combination, leading to the suggestion that more frequent oral dosing (6- or 4-hourly) may provide more optimal serum concentrations.¹⁰ However, the efficacy and tolerability of such regimens are as yet unknown. Ongoing research is examining the efficacy of simpler primary eradication regimens such as cotrimoxazole alone. Work is required in defining the optimal PK/PD relationships for antibiotics used to manage melioidosis.

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