Can Antibiotic Treatment Time For *Mycobacterium ulcerans* Infection Be Reduced?

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Background & Aims

Mycobacterium ulcerans disease, known as the Buruli ulcer, is a necrotising infection of the skin and subcutaneous tissue[1]. Significant toxicities are commonly associated with the currently recommended eight-week antibiotic treatment regimens, with up to 22% of patients experiencing an antibiotic complication severe enough to warrant cessation of at least one antibiotic[2]. We aimed to investigate the antibiotic duration required to achieve sterilisation of *M. ulcerans* disease lesions and the influence of patient characteristics on this outcome.

Methods

Prospective observational *M. ulcerans* case data was examined from patients treated with antibiotics prior to surgery and post-excisional culture assessment at Barwon Health, Victoria, from 25/5/1998 to 30/6/2019. Unsuccessful lesion sterilisation was measured by a positive *M. ulcerans* culture. A chi-square test of goodness-of-fit examined the association between antibiotic duration before surgery and culture positive outcome. To assess influence of baseline characteristics on culture outcome, a multivariate Cox regression analysis was performed.

Results

Ninety-two patients were included with a median age of 60 years (IQR 28-74.5) and 51 (55.4%) were male. Rifampicin-based regimens were predominantly used in combination with clarithromycin (47.8%) and ciprofloxacin (46.7%). Median duration of antibiotic treatment before surgery was 23 days (IQR 8.0-45.5) (Table 1).

The proportion of patients with a positive *M. ulcerans* culture following 1-2 weeks of antibiotics was 51.6%, after 2-4 weeks was 27.3%, and there were no culture positive results after 2.7 weeks of antibiotics. A significant association existed between antibiotic duration before surgery and culture positive outcome ($p<0.001$) (Figure 1A & B). The patient baseline variable 'age' ($p=0.06$) and immune suppression ($p=0.07$) showed weak evidence of an influence on culture positivity (Table 2).

Table 1: Baseline Characteristics

Treatment Cohort (n=92)		
	n (%)	Mean ± SD (Range)
Gender		
• Male	51 (55.43)	
• Female	41 (44.57)	
Age (years)		51.8±26.4 (2-91) Median = 60 (IQR 28-74.5)
• 0-19	19 (20.7)	
• 20-59	26 (28.3)	
• ≥ 60	47 (51.1)	
WHO Category of Lesions		
• 1	54 (58.7)	
• 2	16 (17.39)	
• 3	22 (23.91)	
Lesion Type		
• Nodule	4 (4.4)	
• Oedematous	24 (26.1)	
• Plaque	4 (4.4)	
• Ulcer	60 (65.2)	
Antibiotic duration (days)		29.4±24.2 (1-89)
Lesion Site		
• Upper limb	29 (31.5%)	
• Lower limb	61 (66.3%)	
• Head/Trunk	2 (2.2%)	
Number of antibiotics		
• 2	79 (85.9%)	
• 3+	13 (14.1%)	
Weight (kg)		
• 0-90	21 (22.8%)	
• ≥ 90	8 (8.7%)	
• Missing	63 (68.5%)	
Antibiotic regimen		
• RCla	44 (47.8%)	
• RCp	43 (46.7%)	
• Other	5 (5.4%)	

Table 2: Cox regression model with adjusted and unadjusted associations between identified variables and rates of positive *M. ulcerans* culture.

Variable	Failures (%)	Follow-up (days)	Rate per 100-person days (95% CI)	Crude hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Gender							
Female	10 (24.4)	1115	9.0 (4.83,16.67)	1	0.97	1	0.86
Male	12 (23.5)	1587	7.6 (4.5,14.1)	1.0 (0.4,2.3)		0.9 (0.4,2.2)	
Age (years)							
0-15	1 (7.1)	603	1.7 (0.2-11.8)	1	0.14	1	0.07
16-64	9(23.1)	995	9.0 (4.7,17.4)	4.1 (0.5,32.6)		4.3 (0.5,34.5)	
≥65	12(30.8)	1104	10.9 (6.2,19.1)	5.1 (0.7,39.3)		6.6 (0.8,50.8)	
Immune suppression							
No	21 (26.3)	2351	8.9 (5.8,13.7)	1	0.16	-	0.06
Yes	1 (8.3)	351	2.8 (0.4,20.2)	0.3 (0.0,2.3)		0.2 (0,1.6)	
Diabetes							
No	22 (27.2)	2271	9.7 (6.4,14.7)	-	-	-	-
Yes	0 (0.0)	238	0	-		-	
Antibiotic regimen							
RCla	9(20.5)	1517	5.9 (3.1,11.4)	1	0.48	-	-
RCp	12 (27.9)	1026	11.7 (6.6,20.6)	1.7 (0.7,4.0)		-	
other	1 (20.0)	159	6.3 (0.9,44.6)	1.0 (0.1,7.7)		-	
Weight (kg)							
0-90	4 (19.1)	707	5.7 (2.1,15.1)	1	0.71	-	-
≥ 90	2 (25.0)	251	8.0 (2.0,31.9)	1.3 (0.2,7.3)		-	-
Missing	16 (25.4)	1744	9.2 (5.6,15.0)	1.6 (0.5,4.7)		-	-
Duration of symptoms							
0-42	15 (27.8)	1593	9.4 (5.7,15.6)	1	0.50	-	-
≥42	6 (16.7)	1030	5.8 (2.6,12.0)	0.6 (0.2,1.6)		-	-

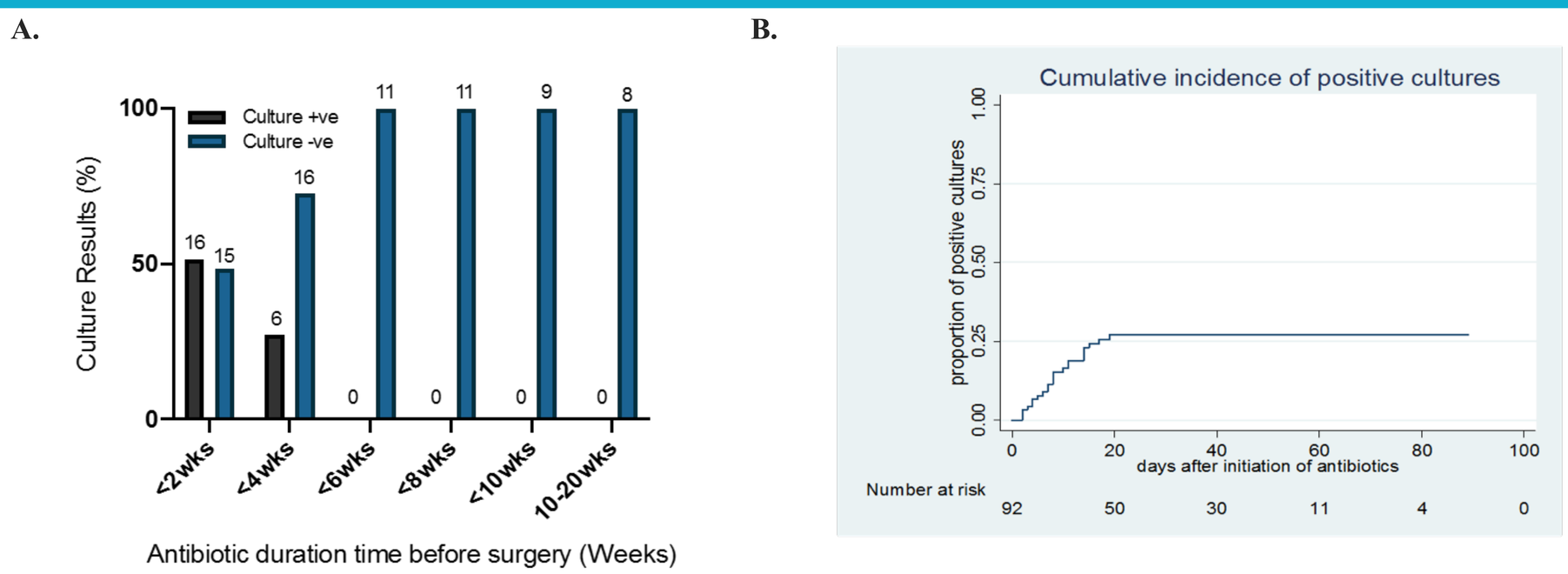

Figure 1: Relationship between antibiotic duration before surgery (weeks) & culture outcome. A. The excised *M. ulcerans* lesions were cultured and the outcome (+ve/-ve) was evaluated in response to the duration of antibiotic treatment before surgery. Positive cultures were not evident after 2.7 weeks ($p<0.0001$, Chi-squared test). B. A Kaplan-Meier curve showing the cumulative incidence of positive *M. ulcerans* cultures according to days of antibiotic treatment.

Conclusions

- For this Australian cohort is appears that a significant proportion of *M. ulcerans* disease lesions can be sterilised in less than three weeks of antibiotic therapy.
- This provides the potential to significantly reduce toxicities and cost experienced by patients by reducing the duration of antibiotic treatment.

References

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