Developing an Antimicrobial Strategy for Sepsis in Malawi

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Thesis submitted in accordance with the requirements of the Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy by Joseph Michael Lewis

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Preface

Placeholder

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Introduction

Placeholder

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Placeholder

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Chapter 3

Mycobacterium tuberculosis BSI: an IPD meta analysis

Chapter 4

Sepsis in Blantyre, Malawi

4.1 Chapter overview

4.2 Methods

blah blah

4.3 Results

4.3.1 Study population

Figure 4.1 shows flow through the study. 225 patients were recruited in 20 months between 19th February 2017 and 2nd October 2018. In total, 4 patients (2%) were lost to follow up over the 180-day study period; 5 patients (2%) withdrew; and 7 patients (3%) transferred out of the study area before 180 days. Four of the five patients who withdrew gave a reason for their wish to withdraw, all that they no longer wished the inconvenience of being involved in the study. 15/225 (7%) patients had their final study visit before 180 days, and so were not included in the 180-day outcome analysis.

4.3.2 Symptoms and health-seeking behaviour

Table 4.1 shows the baseline characteristics of the recruited participants. They were young (median [IQR] age 36 [28-44]) and predominantly HIV-infected. Of those who were HIV-infected, the majority (117/143 [82%]) were on ART, almost exclusively the Malawian first-line

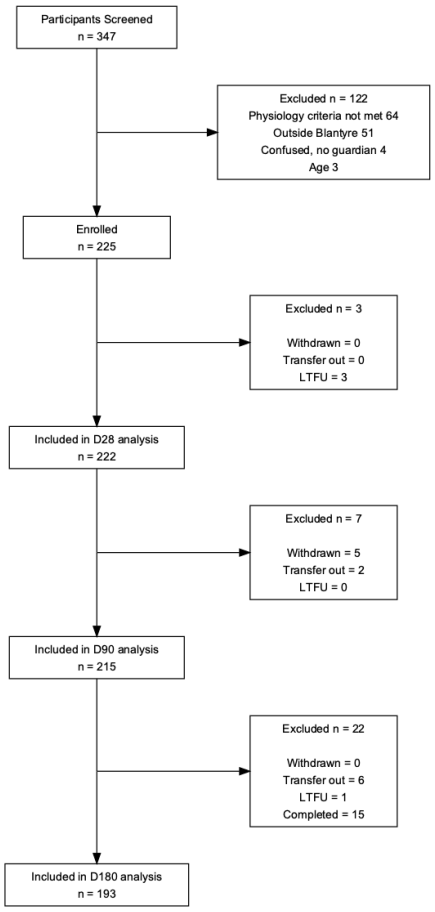

Figure 4.1: Study recruitment and follow up.

regimen of efavirenz, lamivudine and tenofovir. Figure 4.2 shows the presenting symptoms of the participants. Almost all (221/225 [98%] of participants) experienced subjective fever. Participants had been unwell for some time, a median (IQR) of 7 (3-14) days; 32/225 (14%) of participants had been unwell for more than 4 weeks. 18/225 (8%) of participants had been admitted to hospital within the last 4 weeks. Over half (123/225 [55%]) of participants had sought care for their current ilness (Table 4.2), most commonly (101/123 [82%] of participants) at a government health centre, a median (IQR) or 2 (1-6) days previously. 60/225 (27%) of all participants had recieved an antimicrobial for their current illness: 7/60 (12%) of all prehospital antimicrobials were antimalarials, the remainder anitbacterial, most commonly co-trimoxazole or ciprofloxacin. Prehopsital intravenous or intramuscular antimirobials were administered in 16/60 (27%) participants recieving antimicrobials: ceftriaxone (n=6), benzylpenicillin (n=4), gentamicin (n=3) and artesunate (n=3).

Table 4.1: Participant Characteristics

Variable	Value
Demographics	
Age (years)	36 (28-44)
Male sex	114/225 (51%)
HIV/TB status	
HIV Reactive	143/225 (64%)
HIV Non Reactive	70/225 (31%)
HIV Unknown	12/225 (5%)
Ever treated for TB	37/225 (16%)
Of those, current TB treatment	10/37 (27%)
ART status*	
Current ART	117/143 (82%)
Months on ART	29 (4-73)
ART regimen: EFV/3TC/TDF	110/117 (94%)
ART regimen: other	7/117 (6%)
Current CPT†	98/141 (70%)
Tobacco/alcohol use	
Never tobacco	196/225 (87%)
Ex tobacco	17/225 (8%)
Current tobacco	12/225 (5%)
Current alcohol	51/225 (23%)
Education	
Primary incomplete or complete	97/225 (43%)
Secondary school complete	48/225 (21%)
Some secondary education	47/225 (21%)
College or higher	17/225 (8%)
No formal schooling	16/225 (7%)
Employment	
Unemployed	82/225 (36%)
Currently employed	65/225 (29%)
Self-employed	56/225 (25%)
Student	21/225 (9%)
Retired	1/225 (0%)
Toilet facilities	
Pit latrine with slab +/- foot rest	104/225 (46%)
Hanging toilet/latrine	59/225 (26%)
Pit latrine with slab and cover +/- foot rest	45/225 (20%)
Flush Toliet (any type)	14/225 (6%)
No toilet	2/225 (1%)
Composting toilet	1/225 (0%)
Main water source	
Piped outside dwelling	69/225 (31%)

Table 4.1: Participant Characteristics *(continued)*

Variable	Value
Tube well/borehole	64/225 (28%)
Public tap/standpipe	51/225 (23%)
Piped into dwelling	30/225 (13%)
Unprotected well/spring	5/225 (2%)
Surface water (including rainwater collection)	4/225 (2%)
Tube well with powered pump	2/225 (1%)
Electricty	
Electricity available in house	119/225 (53%)
Main cooking fuel	
Charcoal	161/225 (72%)
Wood	61/225 (27%)
Electricity	3/225 (1%)
Animals at home?	
Any animal	71/225 (32%)
Poultry	46/71 (65%)
Dogs	18/71 (25%)
Goats	12/71 (17%)
Other	11/71 (15%)

Note:

ART = Antiretroviral therapy, CPT = Co-trimoxazole preventative therapy, EFV: Efavirenz, 3TC: Lamivudine, TDF: Tenofovir. Numeric values are median (IQR)) unless otherwise stated.

* ART status includes HIV reactive only as denominator

† Missing CPT data for two participants.

4.3.3 Admission physiology and laboratory investigations

Figure to show crossover

4.3.4 Aetiology

4.3.5 Treatment

Table: Time to antimicrobials Time to fluid Amount of fluid

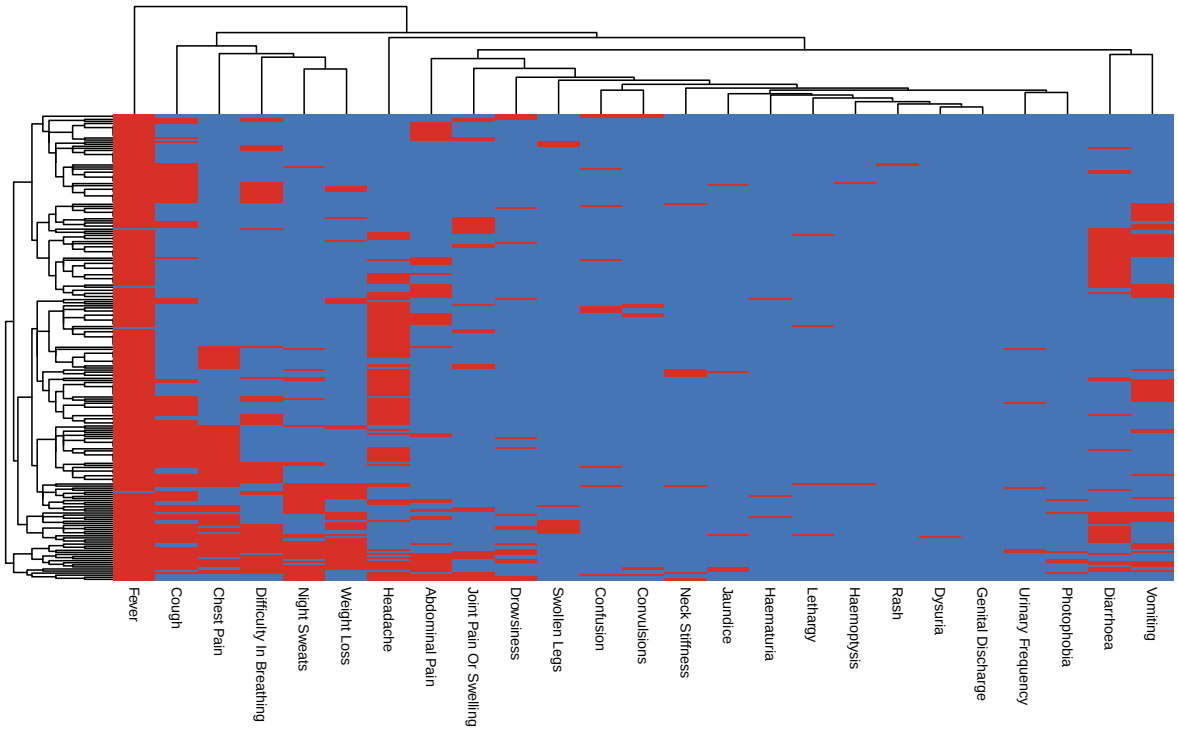

Figure 4.2: Symptoms of recruited participants. A: Row and column clustered heatmap of participant symptoms. Each row represents a patient. Red = presence, blue = absence. B: Frequency of occurence of symptoms

4.3.6 Outcome

Table - 28 and 90 day mortality

Figure - KM survival curve

Logistic regression - determinants of 28 day mortality

Morbidity -

Table 4.2: Prehospital heathcare seeking and antimicrobial exposure

Variable	Value
Pre-hospital healthcare seeking	
Sought care prior to attendance at hospital	123/225 (55%)
At health centre	101/123 (82%)
At hospital	16/123 (13%)
At private doctor	8/123 (7%)
Somewhere else	1/123 (1%)
Days prior to today that participant sought care	2 (1-6)
Prehospital antimicrobial exposure	
Recieved any antimicrobial prior to attendance at hospital	60/225 (27%)
Co-trimoxazole	12/60 (20%)
Ciprofloxacin	10/60 (17%)
Amoxicillin	9/60 (15%)
Ceftriaxone	6/60 (10%)
Metronidazole	5/60 (8%)
Benzylpenicillin	4/60 (7%)
Artesunate	3/60 (5%)
Gentamicin	3/60 (5%)
Erythromycin	2/60 (3%)
LA	2/60 (3%)
SP	2/60 (3%)
Azithromycin	1/60 (2%)
Flucloxacillin	1/60 (2%)
Days prior to today that antimicrobials started	2 (1-5)
Method of transport to hospital	
Minibus	78/225 (35%)
Taxi	65/225 (29%)
Private car/truck	42/225 (19%)
Ambulance	37/225 (16%)
Other	2/225 (1%)
Walk	1/225 (0%)
Cost (MWK) of transport to hospital	1000 (275-3000)

Note:
LA = Lumefantrine-artemether, SP = Sulfamethoxazole-pyrimethamine, MWK = Malawian Kwacha. Numeric values are median (IQR)) unless otherwise stated.

Table 4.3: Admission physiology, haematology and biochemistry

Variable	Value
Admission physiology	
Temperature (°C)	38.5 (37.9-39.0)
Heart rate (min^{-1}))	121 (101-132)
Systolic blood pressure (mmHg)	99 (85-119)
Diatsolic blood pressure (mmHg)	66 (57-76)
Respiratory rate (min^{-1})	34 (32-38)
Oxygen saturation (%)	96 (95-98)
GCS	
15	204/225 (91%)
11-14	16/225 (7%)
< 11	5/225 (2%)
Admission CD4 count	
CD4 count* (μL^{-1})	98 (31-236)
Admission haematology	
Haemoglobin ($x10^9$ g dL^{-1})	10.8 (8.2-13.2)
White cell count ($x10^9$ L^{-1})	6.5 (4.4-11.4)
Neutrophil count ($x10^9$ L^{-1})	4.0 (2.1-7.5)
Platelet count count ($x10^9$ L^{-1})	218 (146-297)
Admission biochemistry	
Potassium (mmol L^{-1})	4.0 (3.6-4.4)
Bicarbonate (mmol L^{-1})	19 (17-22)
Chloride (mmol L^{-1})	101 (97-104)
Urea (mmol L^{-1})	4.8 (3.5-8.0)
Creatinine (mmol L^{-1})	76 (59-103)

Note:
GCS = Glasgow coma scale. Numeric values are median (IQR)) unless otherwise stated.
* CD4 count includes only HIV-infected participants.

Chapter 5

Early response to resusitation in sepsis

Chapter 6

Gut mucosal carriage of ESBL-E in Blantyre, Malawi

Chapter 7

Whole genome sequencing of ESBL *E. coli* carriage isolates

Placeholder

7.1 Chapter overview

7.2 Methods

7.2.1 Bioinformatic pipeline

7.2.2 Global *E. coli* collection

7.2.3 Statistical analysis

7.3 Results

7.3.1 Samples and quality control

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7.3.4.1 β-lactam resistance

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7.3.4.4 Chloramphenicol, co-trimoxazole, tetracycline and other resistance determinants

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7.4 Discussion

References