

Developing an Antimicrobial Strategy for Sepsis in Malawi

-

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

August 2019

Contents

Preface	9
1 Introduction	11
1.1 Chapter Overview	13
1.2 Sepsis in sub-Saharan Africa	13
1.3 ESBL-E in sub-Saharan Africa	13
1.4 Conclusions	13
1.5 Thesis overview	13
1.6 Appendix	13
1.7 References	13
2 Methods	15
2.1 Chapter Overview	17
2.2 Study site	17
2.3 Clinical Study	17
2.4 Diagnostic Laboratory Procedures	17
2.5 Molecular methods	17
2.6 Bioinformatics	17
2.7 Statistical Analysis	17
2.8 Study Team	17
2.9 Data Collection and Storage	17
2.10 Ethical Approval, Consent and Participant Remuneration	17
3 <i>Mycobacterium tuberculosis</i> BSI: an IPD meta analysis	19
4 Sepsis in Blantyre, Malawi	21
4.1 Chapter overview	21
4.2 Methods	21
4.3 Study population	21
4.4 Aetiology	21
4.5 Treatment	21
4.6 Outcome	21
5 Early response to resuscitation in sepsis	23
6 Gut mucosal carriage of ESBL-E in Blantyre, Malawi	25
7 Genomics of ESBL <i>E. coli</i>	27
References	29

List of Tables

List of Figures

Preface

Placeholder

Chapter 1

Introduction

Placeholder

1.1 Chapter Overview

1.2 Sepsis in sub-Saharan Africa

1.2.1 Search strategy

1.2.2 Defining sepsis

1.2.3 Applicability of sepsis-3 definitions in sub-Saharan Africa

1.2.4 Sepsis epidemiology in sub-Saharan Africa

1.2.4.1 Incidence

1.2.4.2 Risk factors: the sepsis population in sub-Saharan Africa

1.2.4.3 Outcomes

1.2.5 Sepsis aetiology in sub-Saharan Africa

1.2.5.1 Bacterial zoonoses, Rickettsioses and arboviruses

1.2.5.2 HIV opportunistic infections: PCP, histoplasmosis and cryptococcal disease

1.2.6 Sepsis management

1.2.6.1 Early goal directed therapy

1.2.6.2 Evidence to guide antimicrobial therapy in sSA

1.2.6.3 Evidence to guide intravenous fluid therapy in sub-Saharan Africa

1.3 ESBL-E in sub-Saharan Africa

1.3.1 Search strategy

1.3.2 Introduction: definition and classification of ESBL-E

1.3.3 Global molecular epidemiology of ESBL-E: an overview

1.3.3.1 1980s-1990s: First identification of ESBL in nosocomial pathogens

1.3.3.2 1990s-2010s: Emergence and globalisation of CTX-M

1.3.3.3 Epidemiology of gut mucosal carriage of ESBL-E: the first step towards invasive infection

1.3.3.4 Molecular mechanisms underlying success of CTX-M: mobile genetic elements and high-risk clones

1.3.4 Epidemiology of ESBL-E in sub-Saharan Africa

1.3.4.1 Invasive ESBL-E infection

1.3.4.2 Gut mucosal carriage of ESBL-E in sub-Saharan Africa

Chapter 2

Methods

Placeholder

2.1 Chapter Overview

2.2 Study site

2.2.1 Malawi

2.2.2 Queen Elizabeth Central Hospital

2.2.3 Participating Laboratories

2.2.3.1 Malawi-Liverpool-Wellcome Clinical Research Programme

2.2.3.2 Malawi College of Medicine Tuberculosis Laboratory

2.2.3.3 Wellcome Trust Sanger Institute

2.3 Clinical Study

2.3.1 Entry Criteria

2.3.2 Study Visits and Patient Sampling

2.3.2.1 Enrollment assessment and first six hours

2.3.2.2 Subsequent visits

2.3.2.3 Blood, urine, and stool, sputum and CSF collection

2.3.2.4 Imaging: chest x-ray and ultrasound scanning

2.3.3 Outcomes and sample size calculations

2.4 Diagnostic Laboratory Procedures

2.4.1 Point of care diagnostics

2.4.2 Laboratory diagnostics

2.4.2.1 Haematology and biochemistry

2.4.2.2 Aerobic blood and CSF culture

2.4.2.3 Mycobacterial blood culture

2.4.2.4 Sputum Xpert

2.4.2.5 Urinary LAM

2.4.2.6 Selective stool culture for ESBL-E

2.4.2.7 Acute and convalescent serologies

2.5 Molecular methods

Chapter 3

Mycobacterium tuberculosis BSI: an IPD meta analysis

Chapter 4

Sepsis in Blantyre, Malawi

Placeholder

4.1 Chapter overview

4.2 Methods

4.3 Study population

4.4 Aetiology

4.5 Treatment

4.6 Outcome

Chapter 5

Early response to resuscitation in sepsis

Chapter 6

Gut mucosal carriage of ESBL-E in Blantyre, Malawi

Chapter 7

Genomics of ESBL *E. coli*

Blah blah blah

References