Linking sepsis aetiology, antimicrobial use, and antimicrobial resistance in Malawi to inform pragmatic sepsis trials in sub-Saharan Africa

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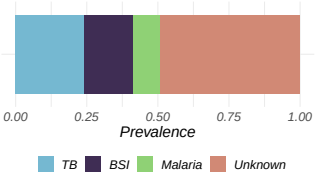
Background: Sepsis in sub-Saharan Africa

Pooled cause of sepsis

Sub−Saharan Africa



SOURCE: Lewis et al 2019
Crit Care 11;23(1)
10.1186/s13054−019−2501−y

- Sepsis is caused by a diverse range of pathogens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Mortality after Fluid Bolus in African Children with Severe Infection

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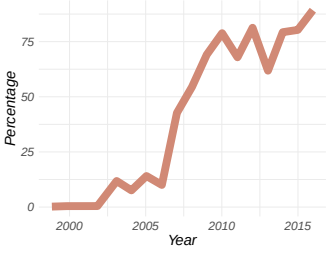
- Optimum treatments are unknown

3GC resistance, *K. pneumoniae*

Blantyre, Malawi



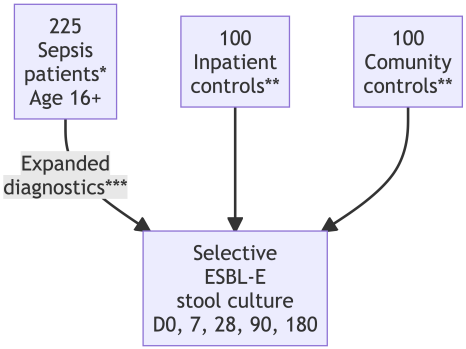
SOURCE: Musicha et al 2017
Lancet ID 17;10

- Antimicrobial resistance is an increasing threat to treatment

Talk outline: Modelling to inform pragmatic sepsis trials

- Methods: the DASSIM study (**D**eveloping an **A**ntimicrobial **S**trategy for **S**epsis **I**n **M**alawi)
- Sepsis aetiology in Queen Elizabeth Central Hospital, Blantyre, Malawi
- Modelling determinants of sepsis outcome
- Colonisation with extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E) in sepsis survivors
- Modelling determinants of ESBL-E colonisation
- Bringing aetiology and AMR together to inform putative interventions

Methods: The DASSIM study



* Defined by fever plus one of GCS < 15, SBP < 90mmHg, SpO2 $<90\%$, RR > 30

** Age/sex matched, no antimicrobial exposure 4 weeks

*** Blood culture, mycobacterial blood culture, urinary LAM, sputum Xpert, acute and convalescent sera for dengue, chikungunya, leptospira, spotted fever group and epidemic typhus group rickettsioses.

Sepsis aetiology

Table 1: Baseline characteristics

Variable	Value
Age (years)	36 (28-44)
Male sex n/N (%)	114/225 (51%)
Living with HIV, n/N (%)	143/213 (67%)
CD4 count (cells/microL)	156 (51-298)
Receiving ART, n/N (%)	117/143 (82%)
Temperature (C)	38.5 (37.9-39.0)
Heart rate (beats/min)	121 (102-132)
Respiratory rate (breaths/min)	34 (32-38)
Systolic blood pressure (mmHg)	99 (85-119)
Oxygen saturation (%)	96 (94-98)
Glasgow coma score $<$ 15 n/N (%)	21/225 (9%)
Unable to stand unaided n/N (%)	63/225 (28%)
Length of time unwell for (days)	7 (3-14)
Lactate (mmol/L)	3.4 (2.3-5.2)

Note:
Median (IQR) unless stated
ART = Antiretroviral therapy

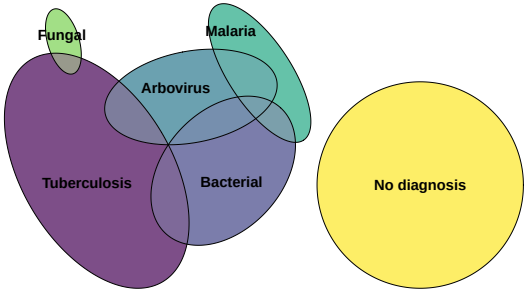


Figure 1: 34% of the cohort diagnosed with tuberculosis

TB treatment is associated with survival

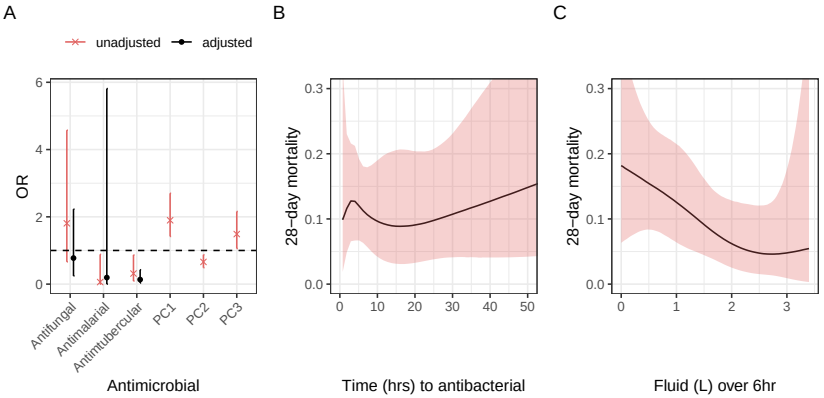


Figure 2: Modelled determinants of sepsis mortality using Bayesian logistic regression; aOR of death with TB treatment vs no treatment 0.17 (95% CrI 0.05-0.49)

ESBL carriage in sepsis survivors

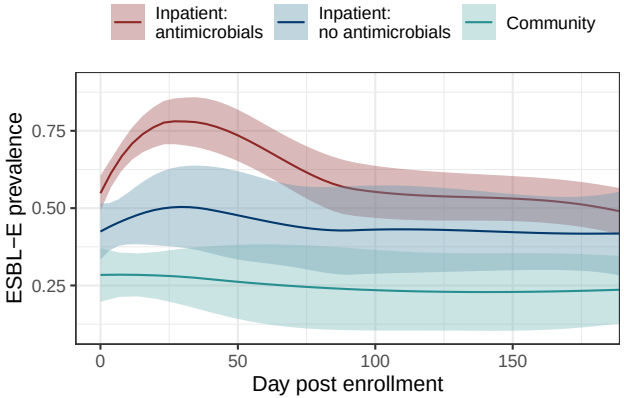


Figure 3: ESBL prevalence in sepsis survivors and matched controls; 83% of participants with confirmed aetiology received ceftriaxone - it would be expected to be active in 24%

Antimicrobial exposure drives ESBL-E carriage

Table 2: Parameter estimates (95% CrI) from multistate model

Variable	Value
Effect of Antibacterials	
Hazard ratio ESBL-E Loss	0.16 (0.05-0.58)
Hazard ratio ESBL-E Gain	0.57 (0.16-2.25)
Half life of effect (days)	43.67 (15.42-97.66)
Effect of Hospitalisation	
Hazard ratio ESBL-E Loss	10.01 (1.24-52.34)
Hazard ratio ESBL-E Gain	27.82 (3.60-143.18)
Mean time in state	
Colonised (days)	9.65 (4.22-25.07)
Uncolonised (days)	5.76 (2.54-14.30)

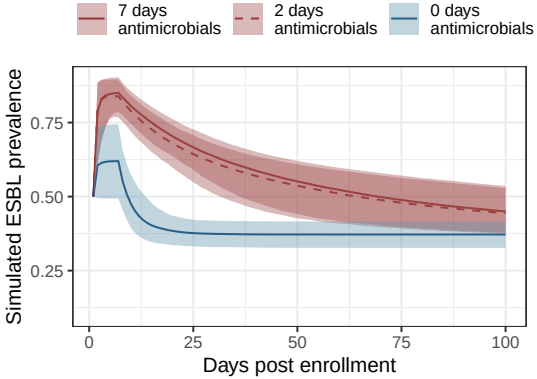


Figure 4: Simulating different antimicrobial exposures from the multistate model

Conclusions

- Sepsis in Blantyre is caused by a variety of pathogens, which differ from high-income settings
- HIV-associated TB dominates
- TB therapy was associated with survival
- High prevalence of ESBL-E colonisation, driven by antibacterial exposure
- Truncating courses of antibacterials may have a limited effect on ESBL carriage

The future ... ?

- Pragmatic trials in sepsis/severe febrile illness in sSA
  - Role of empiric antitubercular chemotherapy?
  - Role of rapid diagnostic tests?
  - Supportive care: fluids, pressors, oxygen?
- AMR endpoints in clinical trials of sepsis
  - What to measure?
  - When?

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References

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Colonization dynamics of extended-spectrum beta-lactamase-producing Enterobacterales in the gut of Malawian adults. Lewis et al. Nature Microbiology 7, 1593–1604 (2022). https://doi.org/10.1038/s41564-022-01216-7

Slides and code at https://github.com/joelewis101