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## Short Communication

## Antimicrobial resistance in urine and skin isolates in Timor-Leste

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## ABSTRACT

**Objectives:** High rates of antimicrobial resistance (AMR) are seen throughout Southeast Asia. However, limited AMR data exist for Timor-Leste, which is situated on the south-eastern portion of the Malay Archipelago. The purpose of this study was to identify AMR in bacteria isolated from urine and skin swabs from patients in Dili, the capital of Timor-Leste.

**Methods:** Urine and skin swabs were collected from symptomatic patients in Timor-Leste and were processed for bacterial culture. Isolates were processed in Australia using a VITEK<sup>®</sup>2 system for bacterial identification and to determine antimicrobial susceptibility according to Clinical and Laboratory Standards Institute (CLSI) guidelines.

**Results:** A total of 154 urine isolates and 57 skin isolates were analysed. Of the Enterobacteriaceae, 35% were resistant to ceftriaxone with an extended-spectrum  $\beta$ -lactamase (ESBL)-producing phenotype. Carbapenem resistance was not observed in any of the Gram-negative isolates. Of the *Staphylococcus aureus* isolates, 11% were of the community-associated methicillin-resistant *S. aureus* (CA-MRSA) phenotype.

**Conclusions:** A moderately high proportion of Gram-negative urine isolates in Timor-Leste demonstrate phenotypic ESBL production, and a relatively low proportion of *S. aureus* isolates were methicillin-resistant. Improved understanding of AMR rates in Timor-Leste can help guide antimicrobial prescribing and inform antimicrobial stewardship strategies.

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## 1. Introduction

Antimicrobial resistance (AMR) poses a major global threat to human health, and high rates of AMR are seen throughout Southeast Asia. The World Health Organization (WHO) has emphasised the importance of ongoing surveillance, but limitations in the capacity for microbiological testing in the region make this challenging [1]. Timor-Leste, which is situated on the south-eastern portion of the Malay Archipelago, is a country with a population of 1.16 million [2] and with poor health outcome indicators [3]. Despite known high rates of AMR in the surrounding region, limited capacity for diagnostic microbiology within

Timor-Leste has resulted in a situation where local AMR patterns are unknown [4,5]. Hospital Nacional Guido Valadares (HNGV) is a 260-bed referral hospital in Dili, the capital of Timor-Leste, that receives a limited microbiology service from the Laboratório Nacional de Saude (LNS), which is co-located. The LNS does not perform blood cultures but has recently developed capacity for urine and wound swab cultures.

Where AMR data are known in surrounding countries, high levels of resistance are found. Among *Escherichia coli* and *Klebsiella* spp. isolates recovered from hospitalised inpatients in 2011 in Indonesia (Timor-Leste's nearest neighbour), extended-spectrum  $\beta$ -lactamase (ESBL) phenotypes were found in 71% and 64%, respectively [6]. The rate of carbapenem-resistant Enterobacteriaceae in an Indonesian intensive care unit in 2011 was 28% [7]. Of 284 *Klebsiella* spp. isolated from hospital-acquired pneumonia cases in Indonesia in 2008, 50% displayed ceftazidime resistance

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[8]. Malaysia and the Philippines similarly have high rates of ESBL phenotypes, ranging from 36–45% and 47–55%, respectively, in hospitalised cohorts [9,10].

Methicillin resistance among *Staphylococcus aureus* within the region is variable [11]. The only study to date performed in Timor-Leste in 2014 found no methicillin-resistant *S. aureus* (MRSA) isolates in 22 community carriers of *S. aureus* [12]. However, many Southeast Asian locations are known to have endemic MRSA, with MRSA comprising between 28–59% of *S. aureus* isolates in Indonesia, Malaysia, Singapore and the Philippines [6,13,14].

Given the lack of consistent microbiology services and the absence of local epidemiological data, antibiotic prescribing in the context of Timor-Leste is challenging. Therapeutic agents are limited to those on the WHO Essential Medicines List. Although empirical antibiotic guidelines for the national hospital in Timor-Leste were developed in 2016, a major limitation is the lack of local antibiograms to ensure adequate coverage in the context of high rates of AMR whilst preserving broad-spectrum antibiotics as much as possible.

A prospective epidemiological study with the aim of describing AMR rates at HNGV was designed. Clinical specimens were obtained from people with urinary tract infection (UTI) or skin and soft-tissue infection (SSTI) in order to target Gram-positive and Gram-negative isolates.

## 2. Methods

### 2.1. Ethical considerations

Ethical approval was obtained from the Cabinet of Quality Control and Ministry of Health for Timor-Leste and the Menzies School of Health and Research (Darwin, NT, Australia).

### 2.2. Study design

A prospective study was conducted between 10 March 2017 and 20 June 2017 at HNGV. Urine and skin samples were collected over the course of this period and were processed at the LNS to establish an AMR profile for commonly encountered Gram-negative and Gram-positive organisms.

Mid-stream urine (MSU) or clean catheter urine specimens were collected from patients aged >5 years with clinical features of UTI in the emergency department and inpatient units of the hospital. Samples that arrived at the laboratory >4 h after collection were excluded, as were urine samples that tested negative for leukocyte esterase on bedside urine dipstick testing.

Swabs of sites of SSTI were collected from patients in the same setting using bacterial rayon transport swabs in Amies medium for all age groups. For inclusion in the SSTI arm of the study, there had to be clinical evidence of a wound with purulent material and either surrounding cellulitis, impetigo, draining sinus or carbuncle. These criteria were in line with the US Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) definition of infection at these sites [15].

### 2.3. Characterisation of bacterial isolates

Urine specimens were plated with 1- $\mu$ L calibrated loops to split HBA/Chromogenic UTI Medium (Thermo Fisher Scientific, Sydney, NSW, Australia) in the LNS. Bacterial skin swabs were plated to Brilliance™ MRSA2 (Thermo Fisher Scientific), colistin, nalidixic acid (CNA) and horse blood agar (HBA) in the LNS. Samples were incubated for 18 h at 35 °C before interpretation. Growth was deemed significant if there was a single colony type of >10<sup>5</sup> CFU/mL. Selected colonies were subcultured to nutrient agar slopes before transfer to Territory Pathology, Royal Darwin Hospital (Darwin, NT, Australia). On arrival, all isolates were re-cultured from nutrient agars to assess for viability. Identification was performed using VITEK®2 Colorimetric Identification Cards on *S. aureus*, *Streptococcus* spp. and *Enterococcus* spp. and all viable Gram-negative isolates. Antimicrobial susceptibility testing was performed using VITEK®2 AST Cards (bioMérieux, Marcy-l'Étoile, France) according to Clinical and Laboratory Standards Institute (CLSI) interpretive criteria for each corresponding organism.

## 3. Results

From 153 bacterial swabs obtained from skin lesions, 57 isolates were initially identified. From 230 urine samples, 154 separate bacterial isolates were initially distinguished.

Of the 57 SSTI isolates, 6 failed subculture after transport; 35 were identified as *S. aureus*, 4 as coagulase-negative staphylococci (CoNS), 3 as *Streptococcus* spp. and 1 as *Bacillus* spp. (Table 1). Eight SSTI samples grew Gram-negative organisms, including *Pseudomonas* spp. (*n* = 3), *Aeromonas* spp. (*n* = 1), *Enterobacter* spp. (*n* = 2) *Morganella* spp. (*n* = 1) and *Proteus* spp. (*n* = 1). VITEK®2 AST for 4 (11%) of the 35 *S. aureus* isolates displayed resistance to ceftaxime, with an oxacillin minimum inhibitory concentration (MIC) of >4  $\mu$ g/mL. All four MRSA isolates were susceptible to clindamycin (MIC < 0.5  $\mu$ g/mL) and trimethoprim/sulfamethoxazole (SXT) (MIC < 2/38  $\mu$ g/mL), consistent with a community-associated MRSA phenotype. The vancomycin MIC range was <1  $\mu$ g/mL for all MRSA isolates.

**Table 1**  
Gram-positive organisms isolated from skin and soft-tissue infections and urinary tract infections in Timor-Leste.

Organism	Total	Susceptibility (%)									
		PEN	AMX	OXA	RIF	FUS	CIP	TET	CLI	SXT	VAN
<i>Enterococcus faecalis</i>	39	–	74	–	–	–	49	–	–	–	97
<i>Staphylococcus aureus</i>	31	2	–	88.6	100	97	100	49	97	86	100
MRSA	4	0	0	0	100	100	100	25	100	100	100
<i>Enterococcus faecium</i>	2	–	0	–	–	–	–	–	–	–	100
<i>Staphylococcus saprophyticus</i>	1	100	–	–	–	–	–	–	100	–	100
<i>Streptococcus agalactiae</i>	1	100	–	–	–	–	–	–	100	–	100
<i>Streptococcus dysgalactiae</i>	1	100	–	–	–	–	–	–	100	–	100
<i>Streptococcus gallolyticus</i>	1	100	–	–	–	–	–	–	–	–	100
<i>Bacillus</i> spp. <sup>a</sup>	1	–	–	–	–	–	–	–	–	–	–
Total	81 <sup>b</sup>										

MRSA, methicillin-resistant *S. aureus*; PEN, penicillin; AMX, amoxicillin; OXA, oxacillin; RIF, rifampicin; FUS, fusidic acid; CIP, ciprofloxacin; TET, tetracycline; CLI, clindamycin; SXT, sulfamethoxazole/trimethoprim; VAN, vancomycin.

<sup>a</sup> Antimicrobial susceptibility testing not performed.

<sup>b</sup> Six isolates failed subculture and four were coagulase-negative staphylococci.

Of the 154 urine isolates, 9 failed to subculture after transport and one was a mixed infection. Organisms isolated included *E. coli* ( $n=49$ ), *Enterococcus* spp. ( $n=41$ ), *Klebsiella pneumoniae* ( $n=18$ ), *Enterobacter* spp. ( $n=10$ ), *Pseudomonas aeruginosa* ( $n=8$ ), *Morganella morganii* ( $n=3$ ), *Acinetobacter baumannii* ( $n=4$ ), *Proteus* spp. ( $n=3$ ), *Aeromonas* spp. ( $n=3$ ) and 1 each of *Staphylococcus saprophyticus*, *Acinetobacter junii*, *Acinetobacter radioresistens*, *Alcaligenes faecalis*, *Citrobacter koseri*, *Pseudomonas fluorescens*, *Providencia stuartii* and *Serratia marcescens*.

Of all Enterobacteriaceae isolates, 65% displayed susceptibility to ceftriaxone (MIC  $\leq 1 \mu\text{g/mL}$ ) and ceftazidime (MIC  $\leq 4 \mu\text{g/mL}$ ). The remaining 35% were phenotypically consistent with ESBL production (Table 2).

Meropenem susceptibility (MIC  $< 0.25 \mu\text{g/mL}$ ) was identified in 91/92 Enterobacteriaceae, with 1 *K. pneumoniae* isolate showing an MIC of  $0.5 \mu\text{g/mL}$  that could be consistent with low-level carbapenemase production.

Whilst all transported samples were initially deemed significant, further identification revealed that five SSTI and five urine isolates were likely contaminants and/or environmental organisms and were not clinically relevant. These isolates included four CoNS, one *Bacillus* spp., two *Acinetobacter* spp. and three oxidase-negative *Pseudomonas* spp. These were not subjected to extensive antimicrobial susceptibility testing.

#### 4. Discussion

Here we describe the first AMR profiles for hospitalised patients in Timor-Leste. Phenotypic Enterobacteriaceae ESBL rates in this study were found to be 35% and the MRSA rate in skin infections was 11%.

Resistance to commonly used Gram-negative agents was particularly prevalent in the 18 *K. pneumoniae* isolates, where ceftriaxone showed a non-susceptibility rate of 56% and the gentamicin and ciprofloxacin resistance rates were 44% and 28%, respectively. Encouragingly, we found little evidence of carbapenemase introduction in this hospital environment, with only one Enterobacteriaceae isolate having a raised meropenem MIC. These high rates of phenotypic ESBL profiles are consistent with similar studies published from the region of Southeast Asia, but the proportion of *S. aureus* isolates that were MRSA was relatively low compared with this same regional data (Fig. 1) [13]. Although these

findings can now guide some empirical antibiotic choices, ongoing surveillance is essential to provide a larger sample size and to monitor changing trends.

AMR readily develops in the context of antibiotic pressure [18]. Antibiotics including amoxicillin, SXT and ciprofloxacin are readily available over the counter in Timor-Leste and it is likely that this has contributed to high rates of Gram-negative resistance to these antibiotics. Conversely, resistance to antibiotics with limited availability in Timor-Leste (including meropenem, amikacin and vancomycin) was rarely identified. Providing appropriate guidance for empirical antibiotic treatment that is likely to be effective, whilst ensuring that broad-spectrum antibiotics such as cephalosporins and carbapenems are not overused leading to further development of resistance, is a delicate balance [19].

Importantly, effective diagnostic microbiology services can contribute to optimal management of these competing priorities by enabling surveillance of AMR and by providing accurate guidance for directed antibiotic therapy in individual cases. Currently, Timor-Leste requires ongoing support for AMR surveillance activities, but plans are in place to further strengthen in-country microbiology services.

With increasing global spread of resistance, recent emphasis has been placed on improved surveillance [4,20]. Despite this, thorough surveillance processes are currently lacking in certain Southeast Asian locations [1,5]. Brief prospective studies such as this one help to fill a void by directing hospital-based treatment guidelines, informing future antimicrobial stewardship and correcting ongoing usage.

This study had several important limitations, some of which relate to the challenges of establishing effective diagnostic microbiology and antimicrobial susceptibility testing in developing countries. There were 15 isolates that failed to subculture following transport and there was collection and storage of a number of samples that were likely contaminants. Difficulties faced with inadequate identification meant likely contaminants and environmental organisms were included in the potentially pathogenic organisms transported (i.e. *Pseudomonas stutzeri/A. junii*). This shows how a lack of standardised identification procedures can lead to misdirection of clinicians if these results are not confirmed.

We acknowledge other limitations, including the fact that this study describes an antimicrobial susceptibility profile at a referral

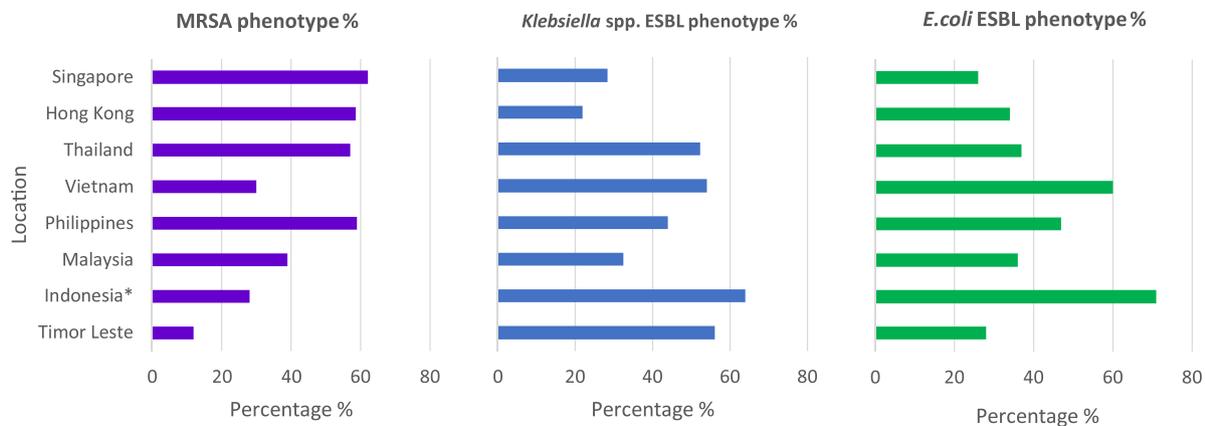
**Table 2**  
Gram-negative organisms isolated from skin and soft-tissue infections and urinary tract infections in Timor-Leste.

Organism	Total	Susceptibility (%)										
		AMX	AMC	CZO	CRO	CAZ	TZP	CIP	AMK	GEN	SXT	MEM
<i>Escherichia coli</i>	49	16	61	51	71	82	83	59	98	88	24	100
<i>Klebsiella pneumoniae</i>	18	–	56	44	44	56	83	72	100	56	33	100
<i>Enterobacter</i> spp.	12	–	–	–	–	75	83	100	100	83	42	100
<i>Pseudomonas aeruginosa</i>	8	–	–	–	–	88	88	88	88	75	–	100
<i>Morganella morganii</i>	4	–	–	–	–	100	100	50	75	50	0	100
<i>Proteus</i> spp.	3	33	66	33	66	66	66	100	66	100	66	100
<i>Acinetobacter baumannii</i>	4	–	–	–	–	50	50	75	50	50	75	100
<i>Acinetobacter</i> spp. <sup>a</sup>	2	–	–	–	–	–	–	–	–	–	–	–
<i>Pseudomonas stutzeri</i>	2	–	–	–	–	100	100	100	100	100	–	100
<i>Pseudomonas fluorescens</i>	1	–	–	–	–	100	100	100	100	100	–	–
<i>Aeromonas</i> spp.	4	–	–	–	–	50	50	0	100	50	50	100
<i>Alcaligenes faecalis</i>	1	100	100	100	100	100	100	100	100	100	–	100
<i>Citrobacter koseri</i>	1	100	100	100	100	100	100	100	100	100	–	100
<i>Providencia stuartii</i>	1	–	–	–	–	0	100	100	100	0	100	100
<i>Serratia marcescens</i>	1	–	–	–	–	0	0	100	100	–	–	100
Total	111 <sup>b</sup>											

AMX, amoxicillin; AMC, amoxicillin/clavulanic acid; CZO, cefazolin; CRO, ceftriaxone; CAZ, ceftazidime; TZP, piperacillin/tazobactam; CIP, ciprofloxacin; AMK, amikacin; GEN, gentamicin; SXT, trimethoprim/sulfamethoxazole; MEM, meropenem.

<sup>a</sup> Antimicrobial susceptibility testing not performed.

<sup>b</sup> Nine isolates failed subculture and there was one mixed infection with organism identification but no further susceptibility testing (*Proteus* + *Pseudomonas* spp.).



**Fig. 1.** Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum  $\beta$ -lactamase (ESBL) resistance phenotype *Klebsiella* spp. and *Escherichia coli* in Southeast Asia, by location. \* Indonesian data available from Mendes et al. [6]; all other non-Timor-Leste data available from SMART Study 2013–2015 [5], 2009–2010 [16], Lai et al. [17], Chen et al. [13] and Chung et al. [8].

hospital site and therefore cannot be extrapolated to the Timor-Leste community generally. In addition, given the complexity of setting up a blood culture service de novo, we were unable to describe any of these invasive isolates. There was also a low number of non-fermenting Gram-negative bacteria and therefore high levels of pan-resistant *P. aeruginosa* and *A. baumannii*, both of which are known to be significant problems in Southeast Asian hospital settings, cannot be excluded [21]. Furthermore, the low number of *S. aureus* isolates with resistance to methicillin is encouraging, however it is limited by small absolute numbers. Lastly, given the study design, no data on *Streptococcus pneumoniae*, *Salmonella*, *Shigella* or *Neisseria gonorrhoeae* antimicrobial susceptibility are provided, all of which are important to guide empirical antibiotic choices for the management of these common infectious diseases.

AMR as a global threat is magnified in locations with limited ability to identify resistance. In this study in Timor-Leste, a developing Southeast Asian nation, we describe hospital-based Enterobacteriaceae ESBL rates and significant resistance to common antibiotics. These susceptibility data, which can be used to inform revision of empirical treatment guidelines, also provide a baseline for ongoing AMR surveillance in Timor-Leste.

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