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WHAT'S NEW IN INTENSIVE CARE

What's wrong in the control of antimicrobial resistance in critically ill patients from low- and middle-income countries?

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Introduction

Critical care environments are magnets for drug-resistant organisms. Patients are extremely vulnerable to nosocomial infections due to the severity of their clinical condition, the siting of multiple invasive medical devices and their proximity to other infected patients. Use of broad spectrum antibiotics is high in intensive care units (ICUs) compared to other hospital departments, making selection of drug-resistant bacteria more likely. In low- and middle-income countries (LMICs), nosocomial infections are thought to be more common than in high-income countries (HICs) [1], although objective incidence rates are unknown, since routine bacteriological surveillance does not usually occur. In tropical settings, severe malaria is a common cause of sepsis, and antimalarial drug resistance is an increasing problem. Here, we give our perspective on the important threat of antimicrobial drug resistance (AMR) in critical care patients in LMICs, contributing factors and initiatives to address this. For further reading, we refer to the supplement listing additional references.

Antimicrobial drug resistance in severe infections in LMICs

Data from LMICs on the epidemiology of AMR in severe bacterial infections are patchy at best, as illustrated by the recent publications from the World Health Organisation on the global status of AMR [2], and the "Review on Antimicrobial Resistance" commissioned by the UK government [3]. Both reports stress the importance of the global threat posed by AMR, in particular in LMICs, and the grave economic consequences. Proportions of extended-spectrum β-lactamase (ESBL) producing Gram-negative bacteria in healthcare-associated infections (HAI) of >80% in China and around 50% in India have been reported [4]. Methicillin-resistant *Staphylococcus aureus* (MRSA) rates are high in HAI, reported as between 50 and 85% in Sri Lanka, Thailand, and India [5, 6] and causing 84% of *S. aureus*-related device-associated infections in ICUs in LMICs. Fluoroquinolone resistance in *Salmonella typhi* is high in several Asian countries and is on the rise in Africa [7]. Carbapenemase-producing Enterobacteriaceae and *Acinetobacter* spp. are a worrying and increasing problem in LMICs [8]. Prevalence rates between 5 and 8% in HAI of New Delhi metallo-beta-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* have been observed in India. A recent epidemiological study from Thailand showed convincingly that antimicrobial-resistant *Acinetobacter* spp. infections are the most common cause of MDR HAI and contributed to the highest number of deaths attributable to AMR in Thailand in 2010 (79%; 15,168/19,122) [5]. This is likely to occur in many other LMICs.

In falciparum malaria, artemisinin resistance has emerged and is spreading in Southeast Asia, increasingly compounded by partner drug resistance in artemisinin combination therapies [9]. New antimalarials are not expected to come onto the market within this decade. First-line treatment of severe falciparum malaria is with parenteral artesunate, which is now compromised in several Southeast Asian countries.

Problems with antibiotic stewardship and infection prevention and control in LMICs

HAI are an important source for the emergence and spread of MDR infections. The incidence of HAI in

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ICUs in LMIC is estimated to be at least three times higher (47.9 per 1000 patient-days; 95% CI 36.7–59.1) than reported from the USA [10]. Essential prerequisites for infection prevention and control (IPC) practices in ICU settings are human and non-human resources, training and surveillance; all these are scarce in LMICs (Fig. 1). Understaffing is common and lower staff–patient ratios result in increased contacts between staff and multiple patients, making the risks of cross-infection between patients higher. Understaffing also often mandates participation of the patient's family in their care, which may further contribute to the transmission of MDR pathogens. ICUs in LMICs are commonly fully occupied, and isolation or separation of patients with AMR bacterial infection or colonization are rarely implemented.

Hand hygiene measures before and after touching a critically ill patient are of utmost importance for prevention of HAI, and a bundled strategy for improvement has been developed. Implementation of the WHO Guidelines on hand hygiene in health care has been evaluated at eight pilot sites worldwide including in four LMICs (Bangladesh, Costa Rica, Mali, Pakistan), resulting in clearly improved hand hygiene compliance [11]. However, compliance is not necessarily improved by initiatives such as provision of alcohol gels [12]. In LMICs, provision of running water is not always guaranteed, nor is the availability of adequate disinfection, sterilization, waste disposal and environmental cleaning. Multidrug-resistant *Acinetobacter baumannii* survives for prolonged periods in the environment and is a well-recognized cause of nosocomial outbreaks in intensive care units, as has been reported from ICUs in Thailand and Vietnam [5].

Lack of dedicated or single-use sterile equipment and suboptimal use of aseptic techniques around endotracheal intubation and insertion of intravenous and urinary catheters further multiply the potential transmission routes. Guidelines to limit duration of mechanical ventilation or timely removal of lines and catheters are often not implemented.

Antimicrobial stewardship in critical care units in many high-income countries typically involves a daily

Fig. 1 Contributing factors to antimicrobial resistance in low and middle income countries (LMICs). Clockwise from *top left*: **a** Critically ill patients in low-income countries are often looked after in crowded general wards where basic hygiene measures are a challenge. **b** ICUs in poor countries are often very simple in design, and basic provisions like running water are not a given. **c** Instead of an emphasis on hand washing and other simple hygiene measures, emphasis can be on less relevant measures such as wearing reusable overshoes. **d** Support of a microbiological laboratory is rare, particularly in low- and low- to middle-income countries. Local epidemiology of causative micro-organisms and resistance patterns to guide antimicrobial therapy is thus often not known. **e** Availability of individual patient rooms and personal protective equipment is the exception rather than the rule in LMICs. **f** As a result of increasing AMR problems, first-line empirical antibiotic treatment for sepsis in some countries, like India, can be with meropenem and linezolid. Antibiotics often have to be purchased out-of-pocket by the patient's family in the nearby pharmacy, which could lead to incomplete treatment courses for economic reasons; quality assurance of drugs will often be lacking and substandard or falsified antimicrobials are a common problem, well documented for β-lactam antibiotics and antimalarials [17]

review of antibiotic prescriptions and IPC concerns by an intensivist and a Clinical Microbiologist or Infectious Diseases Physician, with additional oversight provided by a pharmacist. This is often not the case in LMICs where lower staffing levels and less sub-specialization hamper this multidisciplinary approach [13]. In malaria, the use of artemisinin monotherapy, instead of combination therapies, is thought to have contributed importantly to the problem of artemisinin-resistant falciparum malaria, in addition to substandard drugs and other inappropriate use of antimalarials.

The lack of laboratory capacity for microbiological diagnosis can lead to overuse of antibiotics, since bacterial sepsis cannot be differentiated reliably from other severe infections. It also impedes appropriate targeting and de-escalation of antimicrobial therapy in patients with genuine bacterial sepsis, and limits the ability to detect and monitor outbreaks of drug-resistant infections.

Way forward

Although lack of access to appropriate antibiotics is an equally important problem in many developing countries, the increasing incidence of AMR is a huge impediment to the treatment of severe infections. In addition, with the high connectivity between countries and continents, spread of highly resistant bacteria is an increasingly observed problem. The potential for severe public health and financial implications are well recognized [3]. Several initiatives are trying to tackle the multitude of problems identified above. To prevent further spread of artemisinin-resistant falciparum malaria in Southeast Asia, malaria elimination programs have been initiated in the affected countries. The International Nosocomial Infection Control Consortium (INICC) is a global academic network working to reduce the number of healthcare-associated infections, particularly in critical care (http://www.inicc.org/). In Vietnam, the VINARES project has introduced ICU microbiological surveillance with a focus on quality management, and stricter treatment guidelines [14]. Use of biomarkers such as procalcitonin for de-escalation of antibiotic therapy in ICU should be evaluated in resource-poor settings [15]. The World Health Organisation (WHO) has launched a "Clean Care is Safer Care" programme [11], and recently compiled recommendations for prevention of HAI in countries with variable economic constraints. (http://apps.who.int/medicinedocs/documents/s16355e/s16355e.pdf). Even in settings with very limited resources, hygiene measures such as simple hand washing with clean water and locally made soap should be implemented. IPC implementation requires education, training, and time investment of healthcare providers at all levels, while strong commitment from policy makers and healthcare facility management is important. Antimicrobial stewardship should be promoted. A setting-adapted pharmacist-driven program across 47 South African hospitals resulted in a large reduction in antibiotic use, and warrants wider implementation [16]. Global ICU registries are needed to capture HAI and their associated mortality. Microbiological capacity at sentinel sites should monitor local resistance patterns, and the aggregated data should be formally reported as recommended by the WHO Global Antimicrobial Resistance Surveillance System (http://www.who.int/drugresistance/surveillance/glass-enrolment/en/). Institutions from high-income countries could help in building microbiological capacity. Investment in intensive care with invasive techniques without considering the prevention of nosocomial infection in LMICs could potentially do more harm than good. Policy makers in LMICs need to evaluate investment in prevention of nosocomial infections against other healthcare investments.

Conclusions

Severe multidrug-resistant bacterial infections are an important and increasing problem in ICUs in LMICs, increasing case fatality. Thorough implementation of setting adjusted IPC practices, better antibiotic stewardship and increased surveillance are essential elements to counter this important threat. Artemisinin resistance in Southeast Asia is spreading westward and compromises the treatment of severe malaria.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-017-4795-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
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