International Journal of Infectious Diseases 134 (2023) 168–171

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Preventing empirical antibiotic treatment failure in migrant populations: screening by infection risk, not ethnic background

Steven L. Taylor[1,2,*], Lito E. Papanicolas[1,2], Erin Flynn[1,3], Mark A. Boyd[4], Steve L. Wesselingh[1], Geraint B. Rogers[1,2]

[1] South Australian Health and Medical Research Institute, Adelaide, Australia
[2] College of Medicine and Public Health, Flinders University, Adelaide, Australia
[3] National Centre for Epidemiology & Population Health, The Australian National University, Canberra, Australia
[4] Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia

ARTICLE INFO

Article history:
Received 13 February 2023
Revised 14 May 2023
Accepted 14 June 2023

Keywords:
Antibiotic resistance
Extended-spectrum beta-lactamases
Bacteremia
Sepsis
Microbiome
Resistome

ABSTRACT

Multidrug-resistant organisms (MDROs) are a major international health threat. In many low and middle-income countries poorly regulated antibiotic use, limited surveillance, and inadequate sanitation give rise to high rates of antibiotic resistance. A resulting reliance on last-line antibiotic options further contributes to the emergence of MDROs. The potential for these pathogens to spread across international borders is a matter of considerable concern. However, this problem is commonly framed as primarily a threat to the health security of countries where resistance is not yet endemic. In fact, it is little acknowledged that those at greatest risk from antibiotic treatment failure are individuals who move from regions of high MDRO prevalence to settings where standard empirical treatment options remain largely effective. In this perspective, we highlight the poor treatment outcomes for disseminated bacterial infections in individuals who have moved from settings in which MDROs are common to those where MDROs are currently less common. We discuss MDRO screening strategies that could avoid stigmatizing vulnerable populations by focusing on future risk of disseminated infection, rather than past risk of acquisition. In practical terms, this means screening individuals before childbirth, immunosuppressive treatments, major surgery, or other events associated with disseminated infection risk, rather than prioritizing screening for individuals from regions with high carriage rates. We argue that such measures would reduce antibiotic treatment failure and improve outcomes while protecting migrant populations from the divisive consequences of targeted screening programs.

Introduction

Decline in the effectiveness of antibiotics due to the spread of acquired antibiotic resistance (AMR) threatens our ability to treat common infections and to undertake essential surgical procedures safely [1]. Multidrug-resistant organisms (MDROs) that emerge where antibiotic stewardship is ineffective can move rapidly across international borders [2], with major consequences for global population health [3]. The increasing mobility of populations makes responding effectively to a constantly shifting AMR landscape a considerable challenge for health systems around the world.

Antibiotic prescription practices and guidelines are informed by local patterns of antibiotic sensitivity. As a result, last-line antibiotics are more commonly given as empirical therapy in regions where MDROs are more prevalent. In contrast, where MDROs currently remain relatively rare, such as in Northern Europe, Australia, and New Zealand [3], last-line antibiotics are more commonly held in reserve [4]. We argue that such variance in local policies may poorly serve individuals migrating from regions where MDROs are common. These individuals are at higher risk of antibiotic treatment failure when receiving empiric therapy tailored to low carriage regions. The ability to identify AMR carriage in those at increased risk of disseminated bacterial infection would provide important opportunities for targeted changes in empirical antibiotic therapy in such settings.

The critical importance of effective empirical antibiotic therapy

Multidrug resistance can be acquired in pathogens that commonly cause life-threatening infections, such as extended-spectrum beta-lactamases, as well as other, less common

* Corresponding author: Tel: +61(0)8 8204 5711.
E-mail address: steven.taylor@sahmri.com (S.L. Taylor).

https://doi.org/10.1016/j.ijid.2023.06.014

pathogens, such as the multidrug-resistant yeast, *Candida auris* [5]. In the case of extended-spectrum beta-lactamases, carriage is now endemic in many global regions [6], with infection resulting in the failure of commonly used first-line treatments, such as ceftriaxone [2]. The rapid global spread of carbapenemase-producing Enterobacterales (CPE) is of even greater concern [7]. CPE genes are often co-carried with multiple other antibiotic-resistance genes, resulting in bacterial strains that are phenotypically resistant to most available antibiotics including carbapenems. This results in high rates of treatment failure and increased mortality, with a sepsis mortality rate of 60-70% in immunosuppressed patients [8]. Importantly, these pathogens can be carried asymptomatically for years [9], only to emerge to cause infection following immunosuppression, disruption of mucosal barriers caused by surgery, chemotherapy or radiotherapy, or enteric infection.

Disseminated bacterial or invasive fungal infections are commonly fatal in the absence of prompt and effective therapy. In fact, a large retrospective cohort study of adult patients with septic shock determined that every hour delay in initiation of active empirical therapy following the onset resulted in an increased chance of mortality of 8% [10]. In such circumstances, a patient who has spent time in regions with substantially different AMR carriage patterns is considerably more likely to experience failure of empirical treatment based on local pathology data.

Populations at increased risk of antibiotic treatment failure

Global rates of AMR carriage differ by region [3]. For example, the metallo-beta-lactamase, New Delhi metallo-β-lactamase (NDM), which confers carbapenem resistance in Gram-negative bacteria, is most prevalent in South Asia, particularly the Indian sub-continent [11]. Residence, or even short trips to these regions, particularly if this includes access to health care (including medical tourism) are risks factor for carriage of concerning MDROs such as NDM [12]. Carbapenemases are also endemic in high-income countries in Southern Europe, however, the epidemiology is different with carbapenem-resistant *Klebsiella pneumoniae* (KPC) being the predominant resistance mechanism [13]. Although both these acquired resistance mechanisms result in reduced carbapenem efficacy, an infection caused by CPE-carrying NDM requires different treatment from those carrying KPC. As such, even in countries with high levels of AMR, the empirical treatment approach tailored to local resistance determinants may not be appropriate for recent migrants or overseas travelers.

High AMR carriage rates have similarly been documented among asylum seekers and refugees from conflict zones, including Iraq, Afghanistan, Syrian territories, and Sub-Saharan Africa [14]. Notably, AMR carriage in asylum seekers in the Netherlands showed no particular decline more than a year after arrival [14]. Many different factors contribute to these high carriage rates, including limited control of access to antibiotics, disruption of sanitation and medical infrastructure, antibiotic prophylaxis in field hospitals, cramped accommodation, and poor quality of services available to those fleeing conflict zones [15]. Recently, the close relationship between conflict and AMR dissemination has been further illustrated, with the isolation of carbapenem- and fluoroquinolone-resistant *Acinetobacter baumannii* from war-injured patients from Ukraine in German Bundeswehr Hospitals [16].

The movement of MDROs from regions of high endemicity (e.g., Middle East and North Africa) to those of relatively low prevalence (e.g., Australia), is often framed principally as a threat to the health security of the receiving country. This perception is inaccurate and misleading. Rather, the threat of MDROs is primarily to the carriers themselves. For example, in a systematic meta-analysis of AMR carriage and infection in migrants to Europe, there was no evidence of substantial onward transmission to host populations [17]. Reframing the challenge faced by local healthcare systems, first, as a duty to ensure equitable health outcomes for all populations within a country, and second, as an opportunity to contribute to achieving wider health equity and stronger global health security, would be both progressive and appropriate.

Current challenges in identifying multidrug-resistant organism acquisition

Given the increased risk of empirical treatment failure associated with MDRO carriage, it is recommended that physicians inquire about recent overseas travel and medical treatment as a means to better understand the relative risk of MDRO infection. However, how frequently such history is sought or considered is unclear. The guidance from the European Centre for Disease Prevention and Control for CPE control, for example, notes the importance of such information but does not include such questions in CPE assessment flow charts [18]. In addition, defining what should be considered a history of increased risk exposure is challenging, given that MDROs can be carried asymptomatically for months or even years [14]. Therefore, while knowing a patient's exposure to environments with high MDRO prevalence can be a useful marker of carriage risk, how such information is collected and utilized is the subject of increasing discussion. With the stigma surrounding such questions, or worse, assumptions being made based on ethnic background, it is difficult to utilize such information reliably to assess risk of MDRO carriage.

Screening by risk of infection, rather than risk of carriage

In regions where MDROs are endemic, regular screening of all patients is considered necessary. Italy, for example, has high endemicity of CPE [19] and highlights the need for regular screening of all hospitalized patients. Such an approach, while potentially effective, requires considerable resources. However, like screening all hospitalized patients, screening people who have an increased risk of disseminated infection, rather than an increased risk of MDRO carriage, also has the potential to protect the most vulnerable groups. Events such as major surgery, organ and stem cell transplant, or childbirth, are predictable periods of greatly increased infection risk. Unlike disseminated infections that develop without warning, such as community-acquired sepsis, these periods provide an opportunity to screen for MDRO carriage before an infection develops. Taking the example of perinatal sepsis, women in many settings are offered screening for group B streptococcus (GBS) at 35-37 weeks gestation. Potentially, such screening could be expanded to include Gram-negative pathogens, including those with antibiotic resistance.

While GBS detection resulted in intrapartum prophylaxis being offered, identification of maternal MDRO carriage could simply inform the choice of empirical antibiotics *should* peripartum sepsis develop to provide adequate coverage. The ability to reduce the risk of treatment failure in this way would both improve maternal and infant outcomes and reduce total antibiotic usage. Such a screening approach could be widely applicable. Detection of MDRO carriage by rectal swab ahead of pancreatic surgery, for example, has been shown to be associated with a significantly greater risk of septic complication caused by the same organism [20].

While clinical events such as childbirth are associated with an increased risk of systemic infection, it is the carriage of MDROs that results in an increased likelihood of empiric antibiotic treatment failure. The clinical event, however, provides a rationale for MDRO screening that is distinct from an individual's carriage risk, as associated with, for example, their migrant status. In this way, the screening of individuals ahead of an event or procedure that carries a high sepsis risk differs fundamentally from programs

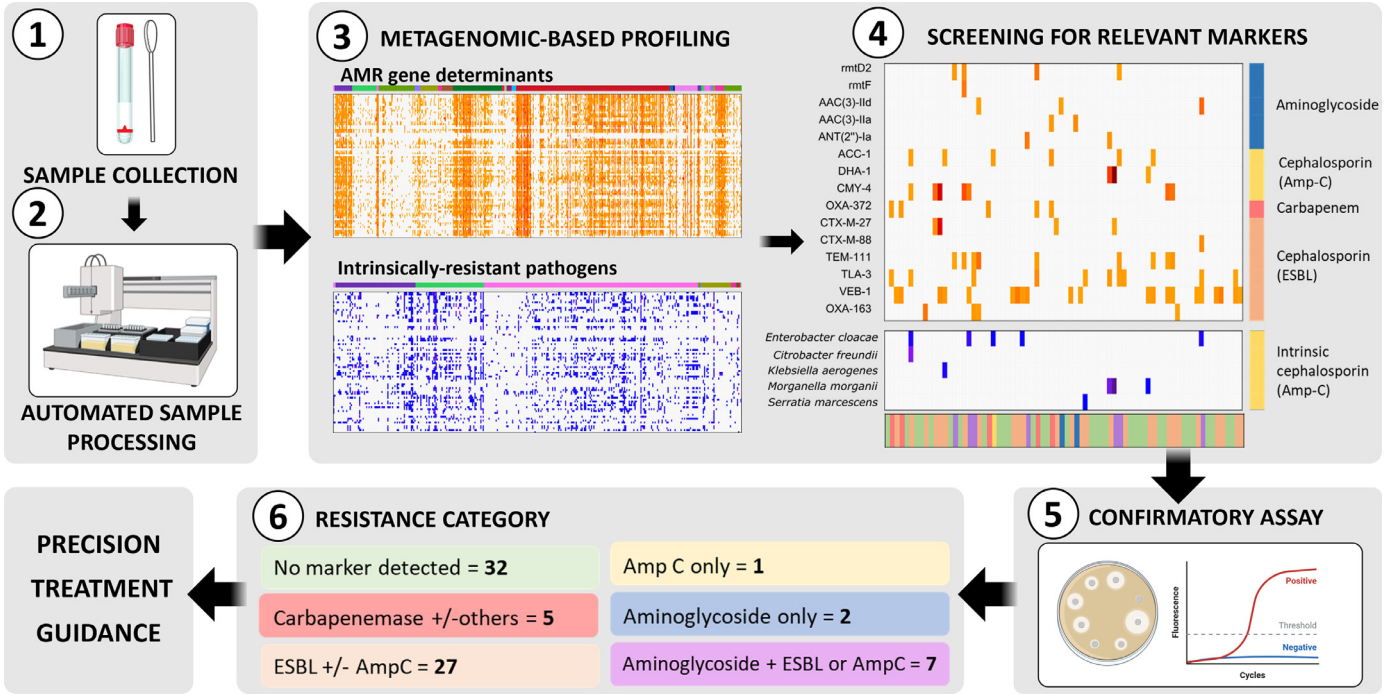

Figure 1. A metagenomic approach to support comprehensive screening for pathogens that cause antibiotic treatment failure. An example analytical scheme where (1) A swab is collected from the patient before undergoing a high-risk procedure (e.g., chemotherapy). (2) Microbial DNA is extracted using high-throughput sample processing, similar to that used for Group B Strep screening. (3) Shotgun metagenomic sequencing is performed to allow AMR gene determinants and microbial composition to be determined. (4) AMR and pathogen screening is filtered to include only clinically relevant markers that may alter empiric antibiotic selection in the event of infection. In this example, filtering includes markers relevant to the treatment decisions in maternal and neonatal sepsis. (5) A secondary confirmation assay is performed. Either culture-based or a secondary molecular assay. (6) Resistance category defined through metagenomics and confirmed through a secondary test can then be attached to the clinical records for a patient along with guidance on appropriate changes to empirical antibiotic therapy in the case of disseminated infection.
AMR, antimicrobial resistance; AmpC, AmpC beta-lactamases; ESBL, extended-spectrum beta-lactamases.

where migrant populations are screened for MDRO carriage *en masse*. While the latter has the potential to be divisive and stigmatizing, the former focuses on the health of the individual, irrespective of origin or status.

Emerging diagnostics enable comprehensive screening

MDRO screening programs must provide rapid, reliable, consistent information, in a manner that is readily accessible and clinically useful. Current approaches to screening typically target specific AMR genes or pathogens, either through culture-based or molecular assays. Expanding such schemes to include a wide range of emerging threats would require prohibitive levels of additional capacity.

In contrast, metagenomic sequencing approaches enable the resistome (the totality of resistance genes) including resistance within bacteria, fungi, and protozoa, within a clinical sample to be defined in a single reaction. By aligning resistome data with specific antimicrobial combinations that would provide effective coverage based on AMR genes present, appropriate empirical therapy could be initiated immediately should disseminated infection develop (Figure 1). Attaching information on confirmed MDRO carriage in an individual's clinical notes, along with guidance on appropriate changes to empirical antibiotic therapy in the case of disseminated infection, could reduce instances of treatment failure and poor clinical outcomes.

The COVID-19 pandemic has demonstrated the value to public health systems of molecular diagnostics deployed at considerable scale. The growing sophistication and decreasing cost of metagenomics add to their potential as a basis for routine MDRO screening. Indeed, using such approaches to improve antibiotic treatment outcomes would align with the efforts by the World Health Organization to expand molecular methods for AMR diagnostics to enhance the Global Antimicrobial Resistance Surveillance System (GLASS) initiative [21].

Conclusion

Our failure to respond adequately to the challenge of AMR contributes to disparities in health outcomes that are clinically devastating and largely preventable. Screening for MDROs is necessary for surveillance and selecting appropriate antimicrobial therapy, however, must be performed in a manner that is effective and equitable. We support targeting screening to situations where there are predictable periods of increased infection risk, such as childbirth, immunosuppressive treatment, and major surgery, rather than likelihood of carriage. Such a system both protects those most vulnerable and is a move toward improved health equity, particularly for members of migrant and refugee communities.

Declarations of competing interest

The authors have no competing interests to declare.

Funding

S.L.T. is supported by a National Health and Medical Research Council (NHMRC) Investigator Grant (GNT2008625). G.B.R. is supported by a Matthew Flinders Professorial Fellowship.

Ethical approval

No ethical approval was required.

Authors' contributions

S.L.T., L.E.P., E.F., M.A.B., S.L.W., and G.B.R. all conceived, wrote, edited, and approved the final version of this perspective.

References

[1] Goff DA, Kullar R, Goldstein EJC, Gilchrist M, Nathwani D, Cheng AC, et al. A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. *Lancet Infect Dis* 2017;**17**:e56–63. doi:10.1016/S1473-3099(16)30386-3.

[2] Baker S, Thomson N, Weill FX, Holt KE. Genomic insights into the emergence and spread of antimicrobial-resistant bacterial pathogens. *Science* 2018;**360**:733–8. doi:10.1126/science.aar3777.

[3] Antimicrobial Resistance CollaboratorsGlobal burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022;**399**:629–55. doi:10.1016/S0140-6736(21)02724-0.

[4] Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs, https://www.cdc.gov/antibiotic-use/core-elements/hospital.html; 2019 [accessed 19 February 2023].

[5] Chow NA, Muñoz JF, Gade L, Berkow EL, Li X, Welsh RM, et al. Tracing the evolutionary history and global expansion of Candida auris using population genomic analyses. *mBio* 2020;**11**:e03364 –19. doi:10.1128/mBio.03364-19.

[6] Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum beta-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev* 2013;**26**:744–58. doi:10.1128/CMR.00023-13.

[7] Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. *J Infect Dis* 2017;**215**:S28–36. doi:10.1093/infdis/jiw282.

[8] Micozzi A, Gentile G, Santilli S, Minotti C, Capria S, Moleti ML, et al. Reduced mortality from KPC-K.pneumoniae bloodstream infection in high-risk patients with hematological malignancies colonized by KPC-K.pneumoniae. *BMC Infect Dis* 2021;**21**:1079. doi:10.1186/s12879-021-06747-8.

[9] van Duijkeren E, Wielders CCH, Dierikx CM, van Hoek AH, Hengeveld P, Veenman C, et al. Long-term carriage of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in the general population in the Netherlands. *Clin Infect Dis* 2018;**66**:1368–76. doi:10.1093/cid/cix1015.

[10] Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**:1589–96. doi:10.1097/01.CCM.0000217961.75225.E9.

[11] Khan AU, Maryam L, Zarrilli R. Structure, Genetics and Worldwide Spread of New Delhi metallo-β-lactamase (NDM): a threat to public health. *BMC Microbiol* 2017;**17**:101. doi:10.1186/s12866-017-1012-8.

[12] Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010;**10**:597–602. doi:10.1016/S1473-3099(10)70143-2.

[13] European Centre for Disease Prevention and Control *Rapid risk assessment: carbapenem-resistant Enterobacteriaceae - first update 4*. Stockholm: European Center for Disease Prevention and Control; 2018.

[14] Ravensbergen SJ, Louka C, Ott A, Rossen JW, Cornish D, Pournaras S, et al. Proportion of asylum seekers carrying multi-drug resistant microorganisms is persistently increased after arrival in the Netherlands. *Antimicrob Resist Infect Control* 2019;**8**:6. doi:10.1186/s13756-018-0455-5.

[15] Elisabeth M, Maneesh PS, Katarina SF, Slobodan Z, Michael S. Antimicrobial resistance & migrants in Sweden: poor living conditions enforced by migration control policies as a risk factor for optimal public health management. *Front Public Health* 2021;**9**:642983. doi:10.3389/fpubh.2021.642983.

[16] Higgins PG, Hagen RM, Podbielski A, Frickmann H, Warnke P. Molecular epidemiology of carbapenem-resistant Acinetobacter baumannii isolated from war-injured patients from the Eastern Ukraine. *Antibiotics (Basel)* 2020;**9**:579. doi:10.3390/antibiotics9090579.

[17] Nellums LB, Thompson H, Holmes A, Castro-Sánchez E, Otter JA, Norredam M, et al. Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis. *Lancet Infect Dis* 2018;**18**:796–811. doi:10.1016/S1473-3099(18)30219-6.

[18] Magiorakos AP, Burns K, Rodríguez Baño J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. *Antimicrob Resist Infect Control* 2017;**6**:113. doi:10.1186/s13756-017-0259-z.

[19] Ambretti S, Bassetti M, Clerici P, Petrosillo N, Tumietto F, Viale P, et al. Screening for carriage of carbapenem-resistant Enterobacteriaceae in settings of high endemicity: a position paper from an Italian working group on CRE infections. *Antimicrob Resist Infect Control* 2019;**8**:136. doi:10.1186/s13756-019-0591-6.

[20] Frigerio I, Cosola D, Regi P, Giardino A, Girelli R, Scopelliti F, et al. Screening for multi drug resistant intestinal contamination in pancreatic surgery. *HPB (Oxf)* 2018;**20**:S174. doi:10.1016/j.hpb.2018.06.005.

[21] World Health Organization *Global Antimicrobial Resistance Surveillance System (GLASS): molecular methods for antimicrobial resistance (AMR) diagnostics to enhance the Global antimicrobial Resistance Surveillance System. CC BY-NC-SA 3.0 IGO*. Geneva: World Health Organization; 2019.