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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

How Should We Manage Antimicrobial Resistance in Resource-Limited Settings?

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Abstract

Patients living in low- and middle-income countries (LMICs) shoulder the greatest burden of infections caused by antimicrobial-resistant pathogens. Speedy access to appropriate broad-spectrum antimicrobials significantly improves health outcomes and reduces transmission of antimicrobial-resistant pathogens, but persons living in LMICs have compromised access to these antimicrobials. This article considers how inequities in microbiology diagnostics, antimicrobial access, and antimicrobial affordability influence outcomes for patients infected with antimicrobial-resistant pathogens who live in resource-limited settings.

Case

"What are your final antibiotic recommendations?" asked the medical officer.

The three of us considered the question as we stood in an inpatient oncology ward in Kampala, Uganda. Our 20-year-old patient was critically ill: hypotensive, febrile, and obtunded. Three weeks ago, she had received her first dose of chemotherapy to treat her newly diagnosed acute myelogenous leukemia. She was now experiencing a common chemotherapy-related side effect, neutropenic fever. This oncologic emergency required rapid initiation of appropriate antibiotics. Each hour of delay increased her risk of death.

Our discussion continued down an all-too-familiar path. "Which intravenous antibiotics does the hospital pharmacy currently stock?" we asked.

"Ceftriaxone and levofloxacin," the medical officer responded. "But she's been receiving ceftriaxone for the past 3 days without improvement and was taking levofloxacin prophylaxis when her fever started."

"Have you been able to obtain blood cultures?" we queried.

"No," replied the medical officer. "She couldn't afford them. Her family is trying to gather the money, but they haven't been able to yet. Do you know if there are any active research studies that supply blood cultures?"

"Yes," we replied. "There is one research study that supplies blood cultures and is enrolling participants. We can contact the study coordinator to see if our patient qualifies."

Even without culture results to guide us, our patient's clinical picture was consistent with a bacterial bloodstream infection. At our hospital, there was a 75% chance that this infection was caused by multidrug resistant gram-negative bacteria. According to the medical officer, the 2 first-line antibiotics for treating neutropenic fever—meropenem and chloramphenicol—were out of stock at the free on-site pharmacy. Our patient's family would need to secure funding, travel to an off-site pharmacy, and buy antibiotics. Without the appropriate antibiotics, her chance of dying was over 80%.[1]

"Ideally, we would start her on meropenem since it won't worsen her ongoing bone marrow suppression," we reminded the medical officer. "Can her family afford this?"

The medical officer glanced at our patient's family members, now clustered around us. "The family has few resources. If they can't afford blood cultures, they won't be able to afford meropenem. They can afford 3 days of chloramphenicol. Since she will need at least 7 days of antibiotic therapy, this should give enough time for the meropenem to be restocked in our pharmacy."

The medical officer handed the chloramphenicol prescription to the patient's family member, instructed them to travel as quickly as possible to the nearest private pharmacy, and return to the ward so it could be administered to our patient.

Commentary

As an infectious diseases physician and a medical microbiologist who provide care at a cancer institute in Uganda, we recognize this case as representative of one of our typical patient consults. It highlights many of the challenges faced by patients, families, and health care professionals who manage infections in settings where there are high rates of antimicrobial resistance (AMR) but limited resources and little access to broad-spectrum antimicrobials. AMR occurs when an infectious microorganism (eg, bacteria, fungus, virus) develops resistance to an antimicrobial agent, rendering that antimicrobial useless. As a result, if a patient develops an infection from a resistant organism, the number of antimicrobials that can successfully treat that pathogen decreases. In 2021, the World Health Organization listed combatting AMR as 1 of the top 10 public health issues.[2] Recent headlines tell us that "Antimicrobial resistance will be worse than COVID"[3] and that the "superbugs" are here to stay.[4] But what does this mean for 85% of the global population who live in low- and middle-income countries (LMICs), bear the majority of the burden of AMR, and lack the resources to appropriately treat these infections?

Recent studies show that approximately 20% of global deaths are related to sepsis, a dysregulated inflammatory response in the setting of an infection. Sepsis-related mortality rates are highest in LMICs[5]; the rates of death attributable to AMR are also highest in some LMICs.[6] For patients with infections, survival depends upon the ability of clinicians to rapidly select, procure, and administer the appropriate antimicrobials and patients' own ability to complete the full course of treatment. Inability to complete these steps increases patient mortality and contributes to AMR. For those living in resource-limited settings, the disproportionate number of AMR-related deaths are deeply rooted

in inequities: inequities in microbiologic diagnostic access, inequities in antimicrobial access, and inequities in antimicrobial affordability.

Diagnostic Inequity

In resource-limited settings, access to microbiology laboratories is often limited. Microbiology laboratories are costly—they require skilled personnel and consistent access to laboratory supplies.[7] For this reason, they are often located in large urban centers. However, as our story illustrates, even patients with access to a microbiology laboratory may not be able to afford diagnostic testing. In Uganda, where the poverty rate is high,[8] a blood culture costs 60 000 to 75 000 Uganda shillings (15 to 20 USD), or 6 to 8 days' wages. Given patients' lack of access to diagnostic testing, clinicians rely heavily on clinical practice guidelines to direct empiric antimicrobial therapy. However, most infection management guidelines were developed in the United States and Europe, where there is widespread access to microbiology diagnostics and infection surveillance networks. Since AMR is less prevalent in these settings and the microbiology of infections differs regionally,[6] international guidelines do not adequately account for the patterns of resistance and the specific pathogens that occur in many LMICs. For example, we and our colleagues found that more than 50% of the bacteria isolated from Ugandan patients with neutropenic fever were resistant to the first-line antibiotics recommended in the US-based neutropenic fever guidelines.[9,10] As a result, the 30-day mortality rate for patients with neutropenic fever was 46% to 54%,[10,11] which contrasts starkly with the 2.6% to 21.4% mortality rate—depending on the number of comorbidities—for patients being treated in the United States.[12]

As highlighted by our case, research studies may be one of the few avenues through which patients have access to affordable laboratory diagnostics. Only after we began research studies of AMR among Ugandan patients with cancer were we able to update the US-based neutropenic fever guidelines to reflect local patterns of resistance and feel confident about which antibiotics to give patients. Development of local guidelines is predicated upon increased access to microbiology laboratories. Clinicians and researchers play a critical role in advocating for increased global and local investment in laboratory infrastructure.[13] Without supporting and strengthening local microbiology laboratories, the burden of deaths due to AMR will continue to increase for those living in LMICs.

Antimicrobial Access Inequity

Of course, selecting the appropriate antimicrobial is only one piece of the puzzle. Patients must also be able to procure the antimicrobial. In some ways, our patient was fortunate. Since she was receiving care in the capital city of Kampala, there were 3 private pharmacies within walking distance that routinely stock meropenem. Patients in rural Uganda may travel many kilometers to procure meropenem. This barrier results in further antibiotic treatment delay, thus increasing patient mortality.

Countrywide antibiotic access is also a concern. In our studies with colleagues, 10% to 25% of identified bacteria were resistant to all the locally available antibiotics (M. Lubwama, et al, unpublished data, 2017-2021). Recently developed antibiotics that most effectively combat resistant gram-negative bacteria (eg, ceftazidime-avibactam, ceftolozane-tazobactam) are not available for purchase in Uganda. Antimicrobials are typically developed in high-income countries (HICs) and, given the high cost of drug development, new antimicrobials are often first marketed and sold in HICs.[14] For a patient living in a place like Uganda, it may take 10 years before a newly developed

antimicrobial is available.[15] Thus, countries with the highest rates of AMR have the least access to antimicrobials most likely to treat these infections. These structural injustices perpetuate and worsen inequities in patient outcomes. Recent efforts have been made to improve the development and rapid dissemination of new antimicrobial agents in LMICs, including government investment in developing new antimicrobials; industry-sponsored funding of the AMR Action Fund; technology transfer to manufacturing sites in South America, Africa, and the Middle East; routine use of best-practice plans to address global access issues for newly developed antimicrobials; and implementation of standardized forecasting processes to ensure uninterrupted antibiotic supplies in LMICs.[14] These mechanisms must be strengthened to ensure access to antimicrobials for those who need them most.

Antibiotic Affordability

Our case poignantly illustrates the ways in which a patient's finances affect their treatment in resource-limited settings. Our patient was unable to afford meropenem, the best available antibiotic to treat her infection. While she could afford chloramphenicol, she could only purchase half of the recommended treatment regimen. For many of our patients, the process of obtaining funds leads to significant antibiotic treatment delays.

Recently, we and our colleagues conducted a survey[16] and focus groups of health care workers to assess barriers to antibiotic delivery at our institute. The health care workers described more than 20 ways in which patients obtain funds (ie, "mobilize money") to purchase antibiotics. These included asking friends and family, selling animals or land, being sponsored by religious institutions, and asking for money on the street (E. A. Gulleen, et al, unpublished data, 2022). They pointed out that mobilizing money can take hours or even days. For those with severe infections, a 1-hour delay in antibiotic initiation is associated with increased mortality.[17] Thus, the speed at which a family can mobilize money can be the difference between life and death.

As we reviewed the ways patients mobilize money, one physician commented, "Of course some people try to mobilize money, but just can't."

"What do you do when a patient can't mobilize money?" we asked.

The doctor held up her hands in a gesture of defeat. "You just use an antibiotic that is available at the free on-site pharmacy, since there's a small chance that it still might work."

This conversation highlights the moral dilemmas faced by clinicians who manage infections in settings where there are high rates of AMR and access to antimicrobials is a challenge. The clinician has a moral obligation to provide the best possible care for the patient within the allotted resources. In our focus groups, the clinicians told us of many ways they personally help patients mobilize money. These included paying for medications for the patients, contacting local donors, calling friends at private pharmacies, and working with local leadership to increase funding for antimicrobials at the on-site pharmacy (E. A. Gulleen, et al, unpublished data, 2022). The clinicians emphasized that these actions helped them cope with the moral injury that comes with providing care in a broken system in which the tools are often inadequate.

Implications for the Future

With the growing burden of AMR falling squarely on the shoulders of those living in LMICs, what is the solution? We have highlighted how inequities in microbiology diagnostic access, antimicrobial access, and antimicrobial affordability contribute to worse outcomes for patients in LMICs who develop infections with antibiotic-resistant organisms. The COVID-19 pandemic revealed how infections can rapidly traverse the globe. Likewise, antibiotic-resistant pathogens can rapidly disseminate. Thus, there is an urgent need to combat AMR on a global scale. However, we cannot combat AMR unless we address the inequities that drive differences in infection-related outcomes for those living in LMICs.

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Editor's Note

The case to which this commentary is a response was developed by the editorial staff. The 2 studies whose findings from unpublished data are summarized in this article were reviewed by Fred Hutchinson Cancer Center Institutional Review Board (FHIRB0008433, 2017; FHIRB0010736, 2022) and the Ugandan Cancer Institute Research and Ethics Committee (SBS 390, 2018; 15-2020, 2022).

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Conflict of Interest Disclosure

Authors disclosed no conflicts of interest.

The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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