The impact of antibiotic resistance on cancer treatment, especially in low- and middle-income countries, and the way forward

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The growing antibiotic resistance (ABR) burden is a global public health issue that needs to be addressed urgently, particularly in low- and middle-income countries (LMICs) where health infrastructure is lacking or under-resourced and cancer treatment is already difficult to access, expensive, and requires high out-of-pocket expenditure. This article considers the challenges faced by the cancer community, how antibiotics are used in cancer treatments and the impact of ABR on LMICs, and offers four key areas that need to be addressed by the cancer community in order to make progress against the threat of ABR.

Cancer is the second leading cause of death worldwide, accounting for 10 million deaths in 2020, of which 70% occurred in low- and middle-income countries (LMICs) *(1)*. Compared to the general population of patients, cancer patients are more prone to develop serious infections due both to the illness itself and the cancer treatment they receive *(2)*. Despite efforts to prevent infections, they still remain the second leading cause of death in patients with cancer *(3)*. Neutropenia (i.e., an abnormally low concentration of white blood cells) due to treatment with cytotoxic drugs, altered gut flora, skin disruption, and epithelial surface damage are some of the causes that increase cancer patients' susceptibility to infections *(4)*. Pneumonia and sepsis (a bacterial infection of the blood) are two of the most common reasons for cancer patients to be admitted to intensive care units. In fact, it is estimated that severe sepsis accounts for 8.5% of cancer deaths *(5)*. Bloodstream infections have been the leading complications in cancer patients, making it necessary to use antibiotics routinely in the treatment of these patients. It is evident that the significant burden of infections in cancer patients makes antibiotics indispensable for cancer treatment, both for prevention and treatment of bacterial infections. More specifically, it is estimated that one in every five cancer patients requires antibiotics during their cancer treatment *(6)*. Today, we have a worldwide problem with increasing antibiotic resistance (ABR), where bacteria overcome the action of antibiotics, making them ineffective. This has a devastating impact on cancer treatment, jeopardizing key advances in cancer care and cancer patients' survival. The growing ABR burden is a global public health issue that needs to be addressed urgently *(7)*, particularly in LMICs where health infrastructure is lacking or under-resourced, and cancer treatment is already difficult to access, expensive and requires high out-of-pocket expenditure, thus the costs associated with treating resistant infections would make it altogether inaccessible *(8)*. In most LMICs, the diagnosis of cancer is almost a death sentence due to the lack of access to anticancer drugs and higher costs of treatment alluded to above.

Challenges of cancer care in LMICs

Lung cancer is the leading cause of cancer death worldwide and is the most serious burden in LMICs *(9)*. The reasons for the unacceptably high cancer mortality rates in LMICs are multifactorial, including late-stage diagnosis and treatment, lack of health infrastructure including cancer screening facilities, scarcity of trained cancer care professionals and a higher burden of ABR *(10)*. In fact, more than 90% of high-

income countries (HICs) reported comprehensive cancer treatment services in the public health system, compared to less than 15% of low-income countries in 2019 *(11)*. Other factors critically increasing LMICs cancer-related mortality are a result of rising rates of obesity an increasingly sedentary lifestyle; dietary factors; excessive use of tobacco and alcohol; and persistent infections such as *Helicobacter pylori*, hepatitis B virus and human papillomavirus *(12,13)*. In contrast to HICs, where infection-related cancer mortality is rare, LMICs bear a disproportionate burden of infection-related cancer mortality, including gastric cancer, hepatocellular carcinoma and cervical cancer *(14)*. Disparities in the allocation of resources, established infrastructure, organization and access to medical care will almost certainly result in higher cancer fatality rates in LMICs, where the population is extremely vulnerable, diagnoses are made at later stages of the disease and access to care remains a significant challenge *(15)*. The lack of awareness in the lay and medical communities, delay in seeking medical advice, late-stage presentation, insufficient manpower, and training deficits and poverty are well documented among the challenges of treating cancer in LMICs *(16)*.

Cancer treatment is costly and the high price of cancer medicines has a significant impact on access in LMICs. For example, a standard course of treatment (doxorubicin, docetaxel, cyclophosphamide and trastuzumab) for early-stage human epidermal growth factor receptor 2 positive (HER2+) breast cancer would cost approximately 10 years' average annual wages in India and South Africa.

Large portions of the population in LMICs have limited access to medicines, either due to a lack of availability or because patients must bear the cost of treatment (out-of-pocket) in the absence of government reimbursements, insurance or exclusive access schemes. As a result, they are forced into poverty, or early death *(17)*. The World Health Organization (WHO) identifies four key components of cancer control which include:

- prevention;
- early detection and diagnosis;
- treatment;
- palliative and survivorship care.

Inadequacies in these areas in LMICs impairs the efficacy and sustainability of cancer control programmes in already resource-constrained settings *(18)*. Data from LMICs on the current state of cancer care and infrastructure are limited. Furthermore, the majority of LMICs lack adequate cancer registries, impeding the evolution of an adequate oncology infrastructure *(19)*. The challenges connected with access to cancer care, especially in LMICs, are further exacerbated by the development and spreading of ABR, which decreases (and/or neutralizes) the effectiveness of antibiotics, threatening the survival of people living with cancer.

Use of antibiotics in patients with cancer

Cancer patients are often prescribed with prolonged and varied courses of antibiotic agents either to prevent or treat infection during their treatment. This is because during radiotherapy and cancer chemotherapy, cells that are part of the defence mechanism against infections are adversely affected. These treatments are used to kill harmful cancer cells, but they end up harming other cells that are required for defence against bacterial infections. This means that cancer patients' immune systems are weakened, leaving them prone to infections, including infections caused by resistant pathogens. This is particularly crucial in patients with blood cancer and severe neutropenia *(20)*. For example, patients undergoing haematopoietic stem cell transplantation (HSCT) or induction chemotherapy for acute leukemia are prescribed with antimicrobial prophylaxis, including prophylaxis for invasive fungal infections. These patients suffer from prolonged periods of neutropenia as a side effect of treatment *(21)*. The prolonged use of antibiotics on cancer patients can also lead to lethal bloodstream infections (BSI). *Staphylococcus aureus*, a common Gram-positive bacterium causing bloodstream infections in human beings, is often methicillin-resitant (MRSA). Nonetheless, MRSA is not covered by the recommended initial antibiotic therapy for cancer patients with BSI *(22)*, hence increasing patients' exposure to MRSA infections, and so the associated mortality and economic burden worldwide *(23)*. Similarly, high mortality rates are associated with the Gram-negative carbapenem-resistant *Klebsiella pneumoniae* (CRKP), accounting for about 60% mortality in neutropenic haematological patients *(24)*.

Antibiotics are crucial for patients undergoing chemotherapy, surgery and radiation therapy due to their anti-proliferative, pro-apoptotic and anti-epithelial-mesenchymal-transition (EMT) capabilities (or ability to stop cancerous cells) *(25)*. Antibiotics, such as ciprofloxacin, salinomycin, doxorubicin and mitomycin, are effective against multiple solid cancers *(25,26)*. They are used to treat secondary infections that may be caused by tissue damage, ulcers and compromised wound healing, which allow disease-causing bacteria to infect patients *(27)*.

Impact of ABR on cancer care in LMICs

Cancer patients are at a threefold greater risk of dying from a fatal infection than those who do not have cancer *(28)*. Patients with cancer are treated prophylactically and empirically with antibiotics under neutropenic conditions *(29)*. The widespread and prolonged use of antibiotics to reduce mortality and

morbidity from infections in patients with cancer is likely to contribute to the emergence of antibiotic resistance *(30–32)*. In addition, patients with cancer are vulnerable to health-care-acquired infections as a major source of antibiotic-resistant organisms *(33,34)*. Although comparable data are lacking on a global scale, several hospital microbial surveillance studies in LMICs have shown an increase in antibiotic-resistant microorganisms in cancer patients. In India, for example, about 73% of patients with blood cancers harboured carbapenem-resistant bacteria in their gut *(35)*. In Ethiopia, a study found that bacterial infections in cancer patients accounted for 19.4% of all cases, and multidrug resistance was common *(36)*. Another study in Uganda, where 85% of a certain class of bacteria (Enterobacteriaceae) that cause bloodstream infections in cancer patients were multidrug resistant *(37)*. These findings suggest that key advances in medicines, including newer immunotherapies for cancer patients, may be at risk because of the increasing threat of antibiotic resistance globally. Cases of carbapenem-resistant *Klebsiella pneumoniae* infection following a stem cell transplant were reported in 53.4% of 52 Italian centres in a retrospective study. Even the diagnosis of cancer poses a risk to patients due to resistant pathogens. For example, taking a biopsy to diagnose prostate cancer can be life-threatening because 10% of patients will develop a severe infection. Without effective preventive antibiotic treatment, the risk of infection following a prostatic biopsy is approximately 50% *(38)*.

Infections caused by antibiotic-resistant pathogens, such as vancomycin-resistant *Enterococcus*, FQ-resistant streptococci, and multidrug-resistant Gram-negative bacteria (including extended-spectrum beta-lactamase–producing and carbapenem-resistant (CR) strains) are becoming more common in cancer patients. This is crucial for cancer patients, where delays in proper treatment are associated with significantly increased mortality *(39)*. The problem of antimicrobial overuse extends beyond antibiotic resistance and includes fungal and viral resistance as well as *Clostridium difficile* infections *(40)*. In LMICs, although diagnostic capacity for HIV, TB and malaria has been integrated into the respective control programmes for these disease groups, anecdotal evidence suggests that diagnostic microbiology is not consistently available in the management of cancer patients to either identify sources of infection or the infecting microbes *(41)*. Similarly, cancer medicines and second-line antibiotics used to treat resistant pathogens are very costly and frequently not available in LMICs. There is a lack of knowledge and awareness about the impact of ABR on cancer patient outcomes within the cancer community. Moreover, the World Health Organization recently stated that the threat of ABR is booming at an alarming rate. The joint epidemics of cancer and ABR can contribute significantly to the impact on persistent health inequities in LMICs.

Addressing ABR for better cancer care in LMICs

Although data are still scarce, it is evident that ABR poses an increasing challenge to cancer treatment. This information is critical for quantifying ABR's contribution to preventable deaths among cancer patients, as well as raising awareness, supporting advocacy and guiding policy actions to combat ABR on a national scale.

- **Implement an (inter)national surveillance system:** Cancer organizations and infectious disease societies can work together with national cancer registries to guide data collection on variables relevant to antibiotic resistance and work with health-care professionals and hospitals to develop rigorous policies and data collection mechanisms for antibiotic surveillance and stewardship *(42)*. Accurate reporting of deaths by ABR in cancer patients will allow for: 1) a better overview of the ABR magnitude; 2) implement timely interventions; and 3) restrict the spread of resistant infections to other cancer patients.
- **Ensure access to effective medical countermeasures:** The availability, affordability and sustained access to quality-assured medicines and microbial diagnostics is another important area of focus in LMICs for combatting ABR in patients with cancer *(43)*. To provide successful cancer treatment, people living with cancer need effective antibiotics. Hence, it is important to focus on research and development for discovering and introducing new medicines and diagnostics, as few new classes of antibiotics have been discovered since the 1980s.

  Patients have shared experiences of feeling they had received a death sentence when they received a cancer diagnosis, as they realized they could not afford the costly treatments. Most could not pay the high cost of diagnostics and treatments, and stockouts often disrupted their treatment regimens and schedules.
- **Strengthen infection, prevention and control (IPC):** Robust clinical guidelines, patient advice, sustainable water, sanitation and hygiene (WASH) infrastructure and improved IPC measures are also required for better management of ABR in cancer patients. Similarly, courses and training for health practitioners will be a big step towards containing the development and spread of ABR.
- **Raise awareness and seek joint action:** At present, there is a lack of knowledge and awareness in the cancer community about the link between ABR and cancer, and the impact of ABR on cancer care outcomes. It is crucial to highlight the need to raise awareness about the relationship between these two global health threats

among the oncology health workforce, programme managers, patient groups, cancer advocates and other stakeholders working in the field of cancer. To overcome the challenge that ABR poses to cancer patients and caregivers worldwide, the cancer community and relevant stakeholders must join forces with other global health actors, including stakeholders in communicable diseases, to bring together best practices and resources. ■

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