Antimicrobial stewardship and optimizing antimicrobial use in the cancer community

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Infections are common in people with cancer. Broad-spectrum antimicrobial use predisposes cancer patients to unintended negative consequences such as drug-resistant infections. Antimicrobial stewardship programmes promote the responsible use of antimicrobials to help improve patient outcomes and mitigate antimicrobial resistance. Tools are available to support the implementation of integrated antimicrobial stewardship activities at national and health-care facility levels. Select antimicrobial stewardship interventions are supported by evidence for safety and efficacy in cancer patients and could be prioritized.

Effective antimicrobials play a crucial role in preventing and treating infections in people with cancer. Treatment-related agranulocytosis and stem cell transplantation increase the risk, frequency and severity of infection, especially in those with haematologic malignancies and neutropenia *(1)*. Repeated and prolonged contact with health-care settings, breaches in anatomical barriers and surgery also increase the risk of infection in cancer patients. A person with cancer is three times more likely to die from a fatal infection than a person without cancer *(2)*, with approximately half of all deaths in patients with underlying haematological malignancies or solid organ tumours estimated to be infection-related *(3)*.

Broad-spectrum antimicrobials are often prescribed for both prophylaxis and empirical therapy in cancer patients. While this has been shown to reduce morbidity and mortality in patients with chemoradiation-induced neutropenia *(4)*, alterations to the microbiome related to broad-spectrum antimicrobial use is associated with adverse drug reactions, colonization and infection with multidrug-resistant (MDR) organisms and reduced clinical response to some cancer treatment options *(5)*. Antimicrobial therapy prescribed in haematology and oncology patients is not always considered appropriate and concordant with guidelines *(6)*, thereby exposing this vulnerable population to unnecessary unintended negative consequences of antimicrobial use.

In particular, the emergence and increase in drug-resistant infections, largely driven by antimicrobial misuse and overuse, threatens the ability to treat cancer safely and effectively. It is estimated that 27% of pathogens causing post-chemotherapy infections are resistant to standard prophylactic antibiotics in the United States (7). Infections caused by drug-resistant *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter spp.* (ESKAPE), were associated with increased persistence of bacteraemia, metastatic infection and early case-fatality rate in cancer patients *(8)*. Thirty-day survival was significantly lower in patients with haematological diseases undergoing chemotherapy who had MDR Gram-negative bloodstream infections than those who had infections caused by non-MDR organisms *(9)*. The detrimental effects of drug-resistant infections in people with cancer, together with the anticipated rise in both the prevalence and impact of cancer and antimicrobial resistance (AMR), and their interaction, warrants antimicrobial stewardship (AMS) interventions as a critical part of care for people with cancer.

The World Health Organization (WHO) defines AMS as a coherent set of integrated actions which promote the responsible and appropriate use of antimicrobials to help improve patient outcomes across the continuum of care *(10)*. AMS, including the integrated approach to strengthening governance, improving access to and regulation of antimicrobials, raising awareness about AMR, strengthening infection prevention measures and surveillance of AMR and antimicrobial use, is a key strategy to prevent the emergence and spread of AMR *(10)*.

WHO guidance is available to assist in the implementation of

integrated AMS programmes at the national *(10)* and health-care facility levels *(11)*, which can be used by programme managers and policy-makers dealing with cancer as well as oncologists providing clinical care. Assessment tools evaluate AMS preparedness based on essential national and health-care facility core elements and assist in the development of stepwise implementation and monitoring plans *(10)*. The governance and accountability of AMS programmes should be clearly defined and agreed upon, including identification of leadership commitment and oversight, as well as designation of an AMS committee, including with representation from haematology/oncology *(11)*. Due consideration and planning should be given for the human, financial and information technology resources required for AMS activities for cancer patients. Resources could also be leveraged through effectively engaging with relevant stakeholders and partners at all levels.

Tailored local AMS interventions are central to improving antimicrobial prescribing and use and clinical outcomes among cancer patients. Special attention should be given to overprescribing of broad-spectrum antimicrobials, the use of unnecessary combination therapy and inappropriate antimicrobial regimens, particularly antimicrobial treatment with the wrong choice, dose, route or duration *(11)*. There should be a clear linkage of AMS with early diagnosis of infectious diseases by improving microbiology laboratory services. Similarly, infection prevention and control services tailored for cancer patients in health-care facilities and in their communities are crucial. Including cancer patients in the surveillance of health-care-associated infections and AMR is an important step towards mitigating the impact of drug-resistant infections among cancer patients.

The WHO AWaRe classification of antibiotics is a tool designed to support AMS efforts *(12)*. Antibiotics are classified into three groups, Access, Watch and Reserve, based on the impact of different antibiotic agents and classes on AMR and the importance of their appropriate use. At the health-care facility level, the AWaRe classification could be used as a basis for formulary restrictions, to prioritize antibiotics for audit and feedback and for setting targets for antibiotic consumption. The AWaRe classification does not group other antimicrobials, such as antifungals and antivirals, which are often used for prophylaxis and treatment in cancer care regimens, and these should be incorporated into AMS programmes wherever possible.

Barriers exist in implementing AMS interventions in people with cancer because of the high risk of infection and subsequent mortality rates. People with cancer are also often excluded from studies evaluating AMS interventions. Treatment guidelines help prescribers select initial therapy and lead to improved, standardized care for common infectious diseases and form the cornerstone of AMS programmes *(11)*. Guidelines and clinical pathways for empirical treatment of febrile neutropenia and management of sepsis have been shown to improve outcomes, including antimicrobial use *(13,14)* and mortality (*14,15)*. These should be based on national antimicrobial guidelines and informed by local epidemiology of bloodstream and other infections, with regular audit and feedback to ensure compliance.

Prospective audit and feedback, the real-time assessment of antibiotic prescriptions for choice, dose, dosing interval, route and duration, with feedback on ways in which one or more of these areas can be improved, is key to advancing AMS interventions for cancer patients *(11)*. Such interventions could include ceasing glycopeptides in patients with febrile neutropenia who do not have evidence of Gram-positive infection or recommending antimicrobials based on previous colonization with MDR organisms *(16)*. Prospective audit and feedback reduce targeted antimicrobial use in the haematology/oncology setting *(17)*, but more studies are required to determine the impact of this intervention type on patient outcomes.

International guidelines have varying recommendations for de-escalation, the change from an antimicrobial to a narrower-spectrum antimicrobial, and duration of empirical therapy for febrile neutropenia. Early de-escalation or discontinuation of antimicrobials prior to neutrophil recovery in adults with cancer decreases the use of broad-spectrum antibiotics without having adverse clinical impacts *(18)*. Similarly, de-escalation of empirical antibiotic therapy for sepsis in oncology patients did not result in adverse clinical events *(19,20)*, although further studies are needed to determine the safety of doing so in haematology patients.

Antibiotic allergy assessments, which include evaluation of allergy history, graded challenges and de-labelling as appropriate, assist in maximizing the number of antimicrobial agents, including narrower-spectrum agents and those with less propensity for resistance, available for prevention and treatment of infections. In people with cancer, penicillin skin tests and oral drug provocation have been shown to be safe and lead to greater use of penicillin-based antibiotics *(21,22)*.

The safety and efficacy of other AMS interventions require further research in people with cancer. Similarly, much of the existing evidence for the safety and efficacy of antimicrobial stewardship interventions in people with cancer are focused on improving the prescribing and use of antibiotics, and further studies are required to evaluate antifungal and antiviral stewardship activities in this population. Various process and outcome measures can be used to evaluate the impact of AMS activities on antibiotic prescribing and use, as well as clinical and patient outcomes *(11)*, with the need especially urgent

in people with cancer in order to demonstrate the safety and effectiveness of interventions.

The cancer community is a key stakeholder and plays a central role in tackling AMR at all levels. Institutions and health-care professionals providing cancer care, as well as people with cancer and their caregivers, should champion and contribute to the planning, implementation and monitoring of integrated AMS activities. These efforts will optimize the use of antimicrobials and help strengthen the evidence base in the haematology/oncology setting, improve patient outcomes, mitigate AMR and preserve the effectiveness of antimicrobials. ■

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