Cancer Association of South Africa (CANSA)

Fact Sheet
on
Antibiotic Resistance and Cancer Treatment

Introduction

According to Frieden (2013) antibiotic resistance is one of the most serious health threats currently faced by the world. Infections from resistant bacteria are now too common, and some pathogens have even become resistant to multiple types or classes of antibiotics (antimicrobials used to treat bacterial infections).

[Picture Credit: Antibiotics I]

The loss of effective antibiotics will undermine the ability to fight infectious diseases and manage the infectious complications common in vulnerable patients undergoing chemotherapy for cancer, dialysis for renal failure, and surgery, especially organ transplantation, for which the ability to treat secondary infections is crucial.

Frieden (*ibid*) concludes: "When first-line and then second-line antibiotic treatment options are limited by resistance or are unavailable, healthcare providers are forced to use antibiotics that may be more toxic to patients and frequently more expensive and less effective. Even when alternative treatments exist, research has shown that patients with resistant infections are often much more likely to die, and survivors have significantly longer hospital stays, delayed recuperation, and long-term disability.

"Efforts to prevent such threats build on the foundation of proven public health strategies: immunisation, infection control, protecting the food supply, antibiotic stewardship, and reducing person-to-person spread through screening, treatment and education."

World Cancer Day, 2020.

"On February 4th, it is World Cancer Day. We all know someone who has suffered from cancer: a family member, a friend, colleague or neighbor. Maybe yourself? Less well-known is how fundamental effective antibiotics are during the course of cancer treatment. Cancer patients rely on antibiotics for prevention and treatment of infections. This is one of the most common complications of their illness. Antibiotic resistance may thus have detrimental effects on cancer treatment outcomes and must be addressed - if we shall be able to safely continue utilizing the advances of modern medicine."

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Imai, H., Saijo, K., Komine, K., Yoshida, Y., Sasaki, K., Suzuki, A., Ouchi, K., Takahashi, M., Takahashi, S., Shirota, H., Takahashi, M. & Ishioka, C. 2020.

Background: Oxaliplatin and irinotecan are generally used to treat advanced colorectal cancer (CRC) patients. Antibiotics improve the cytotoxicity of oxaliplatin but not irinotecan in a colon cancer cell line *in vitro*. This study retrospectively assessed whether antibiotics improve the treatment efficacy of oxaliplatin- but not irinotecan-based therapy in advanced CRC patients. *Patients and Methods*. The medical records of 220 advanced CRC patients who underwent oxaliplatin- or irinotecan-based therapy were retrospectively reviewed. The oxaliplatin and irinotecan groups were further divided into antibiotic-treated (group 1) and antibiotic-untreated (group 2) subgroups.

Results: In oxaliplatin groups 1 and 2, the response rate (RR) was 58.2% and 30.2%, while the disease control rate (DCR) was 92.5% and 64.2%, respectively; the median progression-free survival (PFS) was 10.5 months (95% confidence interval (CI) = 7.5-12.2) and 7.0 months (95% CI = 17.0-26.0), respectively, and the median overall survival (OS) was 23.8 months (95% CI = 5.1-9.1) and 17.4 months (95% CI = 13.1-24.9), respectively. In irinotecan groups 1 and 2, the RR was 17.8% and 20.0%, while the DCR was 75.6% and 69.1%, respectively; the median PFS was 8.2 months (95% CI = 6.2-12.7) and 7.9 months (95% CI = 12.0-23.0), respectively, and the median OS was 16.8 months (95% CI = 5.9-10.6) and 13.1 months (95% CI = 10.4-23.7), respectively.

Conclusion: To improve the treatment efficacy of oxaliplatin-based therapy in advanced CRC patients, adding antibiotics is a potential therapeutic option.

Kreftforeningen, PB 4 Sentrum, 0101 Oslo. 2020. What are the consequences of antibiotic resistance for cancer patients? https://kreftforeningen.no/antimicrobial-resistance/the-consequences-for-cancer-patients/

“Bacterial infection is one of the most common complications among cancer patients. A weakened immune system and infections can prove life-threatening for patients with serious diseases. After surgery, many patients require antibiotics to treat infected wounds. Radiation therapy and chemotherapy kill cancer cells, but also cells that are part of our defence mechanism against infections. This means that patients who receive radiation or chemotherapy often develop infections that require treatment with antibiotics. Transplantations and immunotherapy are also impossible to perform without antibiotics. It is estimated that 1 in 5 cancer patients need antibiotics during their cancer treatment. In Norway, the Oslo University Hospital reports that 20 percent of their cancer patients under treatment receive antibiotics. Some cancer types, such as acute leukemia and bone marrow cancer (multiple myeloma) for example, cannot be treated without antibiotics. Antibiotic resistant bacteria will set cancer treatment back for decades, while the incidence of cancer cases will continue to rise in the years to come. For the patients, this may mean higher mortality, more difficult and more expensive treatment, and many side and late effects. Many treatment options will disappear entirely. Antibiotic resistance will also have major consequences for the patients’ interactions with healthcare personnel and family members whereby protective “yellow coats”, isolation and confinement rooms will be required.”

Monserrat-Martinez, A., Gambin, Y. & Sierecki, I. 2019.

“Since their discovery in the early 20th century, antibiotics have been used as the primary weapon against bacterial infections. Due to their prophylactic effect, they are also used as part of the cocktail of drugs given to treat complex diseases such as cancer or during surgery, in order to prevent infection. This has resulted in a decrease of mortality from infectious diseases and an increase in life expectancy in the last 100 years. However, as a consequence of administering antibiotics broadly to the population and sometimes misusing them, antibiotic-resistant bacteria have appeared. The emergence of resistant strains is a global health threat to humanity. Highly-resistant bacteria

like *Staphylococcus aureus* (methicillin-resistant) or *Enterococcus faecium* (vancomycin-resistant) have led to complications in intensive care units, increasing medical costs and putting patient lives at risk. The appearance of these resistant strains together with the difficulty in finding new antimicrobials has alarmed the scientific community. Most of the strategies currently employed to develop new antibiotics point towards novel approaches for drug design based on prodrugs or rational design of new molecules. However, targeting crucial bacterial processes by these means will keep creating evolutionary pressure towards drug resistance. In this review, we discuss antibiotic resistance and new options for antibiotic discovery, focusing in particular on new alternatives aiming to disarm the bacteria or empower the host to avoid disease onset."

Key Facts Around Antibiotic Resistance

The World Health Organization released the following key facts around antibiotic resistance during November 2017:

- Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines.
- Bacteria, not humans or animals, become antibiotic-resistant. These bacteria may infect humans and animals, and the infections they cause are harder to treat than those caused by non-resistant bacteria.
- Antibiotic resistance leads to higher medical costs, prolonged hospital stays, and increased mortality.
- The world urgently needs to change the way it prescribes and uses antibiotics. Even if new medicines are developed, without behaviour change, antibiotic resistance will remain a major threat. Behaviour changes must also include actions to reduce the spread of infections through vaccination, hand washing, practising safer sex, and good food hygiene.

(World Health Organization, 2017).

[Picture Credit: Drug Resistance]

Dr. Honar Cherif, Ass. Professor and Head of the Department of Hematology, Uppsala University Hospital, Sweden. 2020.

"Patients treated for cancer are at high risk for serious infections that increase suffering and delay essential cancer treatment. Effective antibiotic treatment is therefore lifesaving. Antibiotic resistance threatens modern cancer care and may have devastating consequences for already vulnerable patients."

Papanicolas, L.E., Gordon, D.L., Wesselingh, S.L. & Rogers, G.B. 2018.

"The global spread of antibiotic-resistant pathogens threatens to increase the mortality of cancer patients significantly. We propose that chemotherapy contributes to the emergence of antibiotic-resistant bacteria within the gut and, in combination with antibiotics, drives pathogen overgrowth and translocation into the bloodstream. In our model, these processes are mediated by

the effects of chemotherapy on bacterial mutagenesis and horizontal gene transfer, the disruption of commensal gut microbiology, and alterations to host physiology. Clinically, this model manifests as a cycle of recurrent sepsis, with each episode involving ever more resistant organisms and requiring increasingly broad-spectrum antimicrobial therapy. Therapies that restore the gut microbiota following chemotherapy or antibiotics could provide a means to break this cycle of infection and treatment failure."

Contributions Which Individuals and Health Professionals can Make

According to the World Health Organization (*ibid*), individuals and health professionals can make the following contributions:

"Individuals

To prevent and control the spread of antibiotic resistance, individuals can:

- Only use antibiotics when prescribed by a certified health professional.
- Never demand antibiotics if your health worker says you don't need them.
- Always follow your health worker's advice when using antibiotics.
- Never share or use leftover antibiotics.
- Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, practising safer sex, and keeping vaccinations up to date.
- Prepare food hygienically, following the WHO Five Keys to Safer Food (keep clean, separate raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention in healthy animals.

"Health professionals

To prevent and control the spread of antibiotic resistance, health professionals can:

- Prevent infections by ensuring your hands, instruments, and environment are clean.
- Only prescribe and dispense antibiotics when they are needed, according to current guidelines.
- Report antibiotic-resistant infections to surveillance teams.
- Talk to your patients about how to take antibiotics correctly, antibiotic resistance and the dangers of misuse.
- Talk to your patients about preventing infections (for example, vaccination, hand washing, safer sex, and covering nose and mouth when sneezing)."

(World Health Organization, 2017).

De Silva, N., Jackson, J. & Steer. 2018.

AIMS: To document patient characteristics, infection types, patterns of antibiotic resistance and outcomes in all patients with cancer requiring inpatient management for suspected infection at a regional Australian cancer centre.

METHODS: We studied patients ≥18 years of age who were admitted under the oncology unit at Albury Wodonga Health during a 12-month period and who had a microbiological test performed for suspected infection during their admission. Data were extracted retrospectively from electronic records and analysed through descriptive statistics.

RESULTS: We identified 275 episodes of suspected infection occurring in 208 patients (M/F: 61%/39%). Median age was 68 years, solid tumour 76%, haematological malignancy 24%. A positive

culture was obtained in 28% of cases: Gram-positive 48.5% and Gram-negative 51.5%. Drug resistant Pseudomonas aeruginosa was seen in 38% (5/13) of pseudomonas isolates, three times the rate seen in general hospital admissions. Extended spectrum beta lactamase was seen in 22% of Gram-negative isolates. Empiric IV antibiotic choice was guideline concordant in 61% of neutropenic fever (NF) (NF) presentations. Only 17% of NF presentations received antibiotics within the recommended hour of emergency department triage. The inpatient mortality rate was 3%. Fifty-seven percent of NF presentations satisfied Multinational Association of Supportive Care in Cancer risk index criteria for outpatient management.
CONCLUSIONS: This is the first study of this type in patients with cancer at an Australian regional cancer centre. The study highlighted key areas for improvement in antibiotic prescription and control of antibiotic resistance at our institution.

Antibiotic Resistance: the Facts
"Antimicrobial resistance (AMR), including antibiotic resistance, adversely affects cancer treatment and could undermine key advances being made in cancer care. The growing cancer burden, in combination with the increasing threat of AMR, is a global public health issue that needs to be addressed urgently. It affects everyone, everywhere." (UICC, 2020.)

"A major menace looms. In 2017, many more people could begin dying from common bacterial infections. As resistance to antibiotics booms, diseases from gonorrhoea to urinary tract infections are becoming untreatable – a situation that looks set to get worse as the world reaches a new tipping point." (McKenzie, 2017).

"The world is about to reach the point where more antibiotics will be consumed by farm animals worldwide than by humans. This will mean more resistant bacteria, which could be a big threat. The livestock industry has long played down any risk to human health caused by using antibiotics in farming, but the danger is now accepted, according to the UN Food and Agriculture Organization (FAO).

The UN General Assembly has called for countries to encourage the best use of antibiotics. But it hasn't yet called for specific measures, such as banning their use to assist livestock growth – rather than fight infections – which can promote resistance."
(*ibid*).

Technology Networks. 2020. Antibiotic Resistance Calls Future of Cancer Treatment Into Question.
" 'The effectiveness of cancer treatments threatened by rising antibiotic resistance' reveals that four in 10 (41%) UK oncologists have seen a rise in drug-resistant infections in the past 12 months and that 95% of them are worried about the impact of "superbugs" on their patients. Almost half (46%) of cancer doctors polled say they believe drug-resistant infections could make chemotherapy unviable. Every day, cancer patients rely on antibiotics for prevention and treatment of infections. This is one of the most common complications of their treatment. Cancer is typically treated with a range of surgical and non-surgical interventions and many of these treatments leave a patient with a weakened immune system and more vulnerable to infection. This is where the risk of multidrug-resistant bacteria rears its head. Revealingly, the oncologists reported that on average 23% of all their patients contract a bacterial infection during treatment. The research goes on to show that a third of all cancer patients require surgery as part of their treatment, 5% of whom will contract a potentially life-threatening resistant infection."

Meunier, A., Nerich, V., Fagnoni-Legat, C., Richard, M., Mazel, D., Adotevi, O., Bertrand, X. & Hocquet, D. 2019.

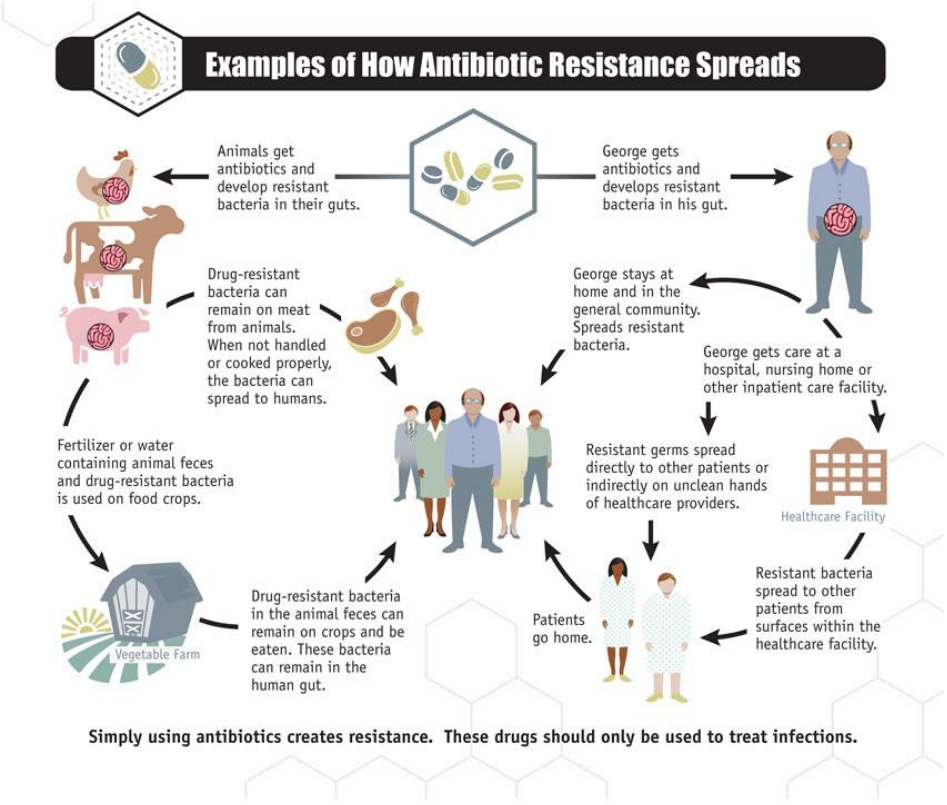
BACKGROUND: Infections with antibiotic-resistant pathogens in cancer patients are a leading cause of mortality. Cancer patients are treated with compounds that can damage bacterial DNA, potentially triggering the SOS response, which in turn enhances the bacterial mutation rate. Antibiotic resistance readily occurs after mutation of bacterial core genes. Thus, we tested whether cancer chemotherapy drugs enhance the emergence of resistant mutants in commensal bacteria.

METHODS: Induction of the SOS response was tested after the incubation of Escherichia coli biosensors with 39 chemotherapeutic drugs at therapeutic concentrations. The mutation frequency was assessed after induction with the SOS-inducing chemotherapeutic drugs. We then tested the ability of the three most highly inducing drugs to drive the emergence of resistant mutants of major bacterial pathogens to first-line antibiotics.

RESULTS: Ten chemotherapeutic drugs activated the SOS response. Among them, eight accelerated the evolution of the major commensal E. coli, mostly through activation of the SOS response, with dacarbazine, azacitidine and streptozotocin enhancing the mutation rate 21.3-fold ($P < 0.001$), 101.7-fold ($P = 0.01$) and 1158.7-fold ($P = 0.02$), respectively. These three compounds also spurred the emergence of imipenem-resistant Pseudomonas aeruginosa (up to 6.21-fold; $P = 0.05$), ciprofloxacin-resistant Staphylococcus aureus (up to 57.72-fold; $P = 0.016$) and cefotaxime-resistant Enterobacteria cloacae (up to 4.57-fold; $P = 0.018$).

CONCLUSIONS: Our results suggest that chemotherapy could accelerate evolution of the microbiota and drive the emergence of antibiotic-resistant mutants from bacterial commensals in patients. This reveals an additional level of complexity of the interactions between cancer, chemotherapy and the gut microbiota.

[Picture Credit: How Antibiotic Resistance Spreads]



Very Few Antimicrobial and Antibiotic Drugs Being Developed

"The period from 1950 to 1960 was truly the golden age of antibiotic discovery, as one-half of the drugs commonly used today were discovered in this period. Unfortunately, the increasing use of antibiotics for human and nontherapeutic animal use (growth promotion) led all too soon to the development of resistant bacterial pathogens. Recognizing the correlation between antibiotic use and resistance development, much of subsequent antibiotic research has been devoted to the discovery and design of new compounds effective against the successive generations of resistant pathogens. It is interesting to note that microbial geneticists in the 1950s thought that the development of antibiotic-resistant strains concomitant with antibiotic use would be an unlikely and rare event at most!" (Davies, 2006).

Davies (2006) concludes: "Antibiotic resistance has occurred in our lifetimes. Within two to three years after the introduction of a new antibiotic treatment, resistance usually develops (although there have been a few notable exceptions – penicillin resistance in streptococci, for example). Nonetheless, antibiotics are an irreplaceable component in the control and treatment of infectious diseases; we cannot do without them."

[Picture Credit: Antibiotics II]

Antibiotic Resistance and Treatment of Cancer Patients

Bacterial infection is one of the most frequent complications in cancer patients and haematopoietic stem cell transplant recipients. The emergence of antimicrobial resistance has become a significant problem worldwide, and cancer patients are among those that may be seriously affected. Antibiotics are the main line of defence when one's immune system is overwhelmed by bacteria. Bacterial infections can affect anyone, but the old, the young, the sick, and cancer patients are particularly vulnerable.
(Gudiol & Carratalà, 2014).

Cancer treatments increase the risk of getting an infection, so antibiotics are an essential part of treating cancer patients. Many cancer patients need antibiotics during all stages of their treatment.

Surgery	**Radiotherapy**	**Chemotherapy**
Usually used to remove tumours. At least 5% of patients develop an infection. Infections can cause pain, longer hospital stays, and longer recovery time. Infections can make cancer treatments less successful.	Used to kill cancer cells, but can damage nearby healthy cells. Cells in hair, skin, and mouth and gut linings are most affected by this. Loss of these protecting cells increase the risk of getting an infection for which an antibiotic would be needed.	Used to stop the growth of cancer cells. Weakens the immune system and increases the risk of getting an infection. Infections can get worse quickly and cause severe illness. Infections can delay further chemotherapy sessions and make cancer treatment less successful
Antibiotics are crucial for controlling these infections and improving survival rates.		

Antibiotic resistance poses a threat to everyone, but cancer patients are at particular risk. Cancer is typically treated with surgery, radiation, chemotherapy, and/or transplantation of bone marrow or

blood stem cells. Each of these treatment techniques leaves a patient more vulnerable to infection than is a healthy adult of similar age.

According to the South African National Cancer Registry (2013), one in nine women and one in six men have a lifetime (0-74) risk of developing a cancer.

Antibiotic-Resistant Gram-Negative Bacterial Infections in Patients With Cancer

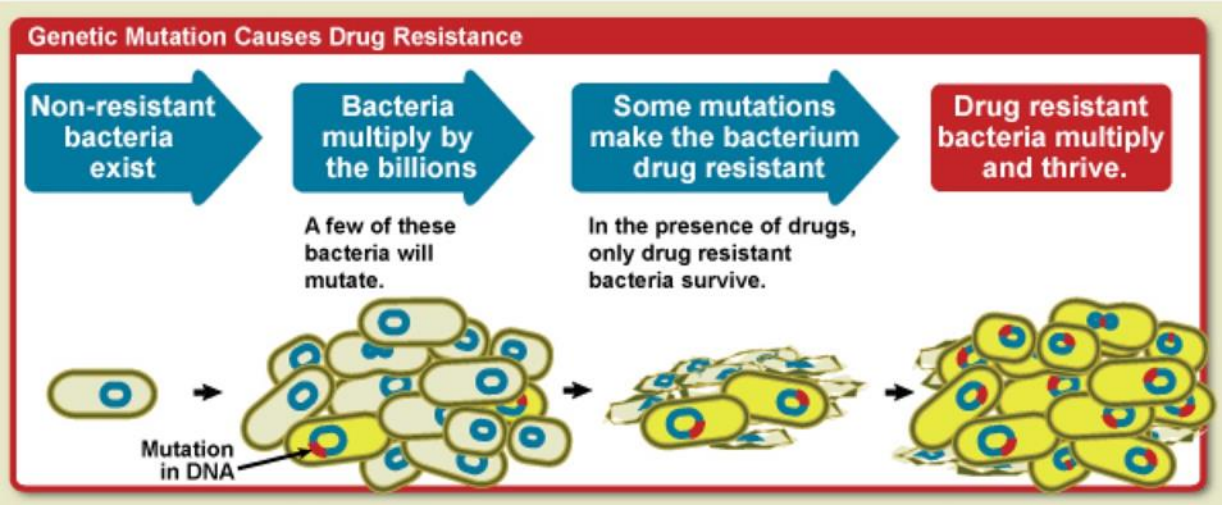
According to Perez, et al., 2016, a dramatic evolution has occurred in the significance of infections caused by gram-negative bacteria. Decades of progress in the care of patients with cancer, concomitant to the development of safe and effective antimicrobials, are being undermined. Patients with cancer, particularly those with haematologic malignancies, remain exquisitely vulnerable to infection with gram-negative bacteria as a result of neutropenia, lymphocyte dysfunction, mucositis, and the use of invasive devices.

[Picture Credit: Seek Qualified Advice]

You Can, I Can

There is not something which everyone **CAN** do
There is actually something that everyone **MUST** do

And that is:
Do not ask, and do not expect, antibiotics for colds, sore throats, or flu
Colds, sore throats, and flu are caused by viruses and antibiotics do not work
Only take antibiotics prescribed by a doctor
Use antibiotics EXACTLY as prescribed on the container
Always complete the full course of antibiotics
Never give or share antibiotics with others
The good news is that by doing something very simple
everyone can do something very good -
everyone can, in a very concrete way help cancer patients,
now and into the future
(ANON)



[Picture Credit: Genetic Mutation Causes Drug Resistance]

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