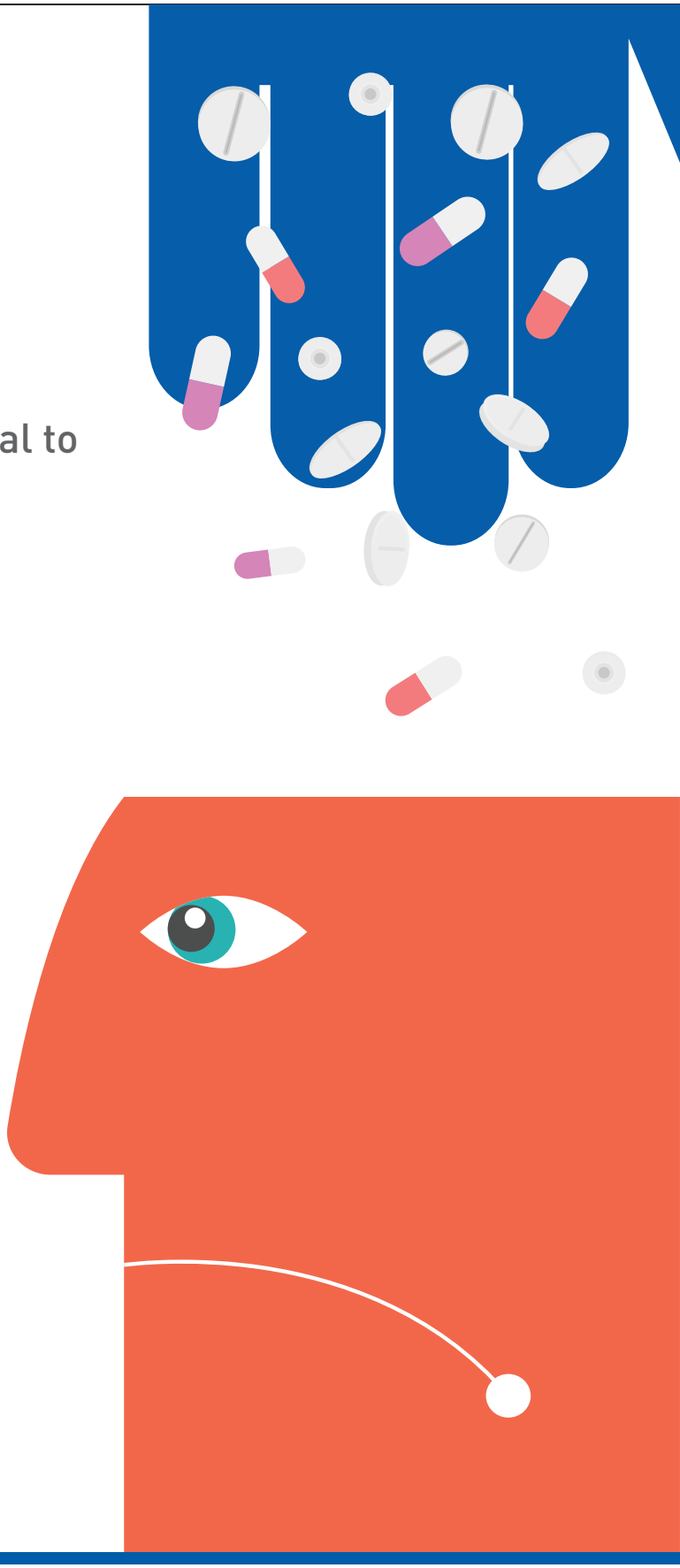
Canary in a Coal Mine

Stewardship programs are essential to preserve our last antibiotics



The patient had been in hospital for three months suffering from a chronic infection in an open wound on his back. Many years earlier, he'd had spinal surgery to resect a tumour. He had been on antibiotics for more than 10 years to control the infection. To close the chronically draining wound, correct loosened hardware and stabilize his spine, he had more surgery. The procedure went well, but afterward, three cultures from the affected area identified a colony of multi-drug resistant Pseudomonas aeruginosa.

After starting on antibiotics, the patient's wound appeared to be healing, but after the stitches had been removed, the wound opened, revealing exposed bone and hardware. Antibiotics were continued, and he had more surgery to reclose the wound, but it reopened again. Lab results showed that the abscess was brewing the same nasty bacteria as before, but it had become resistant to the first antibiotic.

Doctors tried a stronger antibiotic, amikacin, which is ototoxic and nephrotoxic, and then colistin, which is also nephrotoxic and neurotoxic, but the patient experienced significant side effects to both drugs and the infection persisted. Were they out of options?

Since the discovery of penicillin in 1928, antibiotics have provided cures for infectious diseases, prevented many postoperative infections and saved many lives. But globally, we are running out of options. Antibiotic drug development has slowed to a crawl, and at the same time, more bacteria are becoming superbugs, developing multiple resistances that can evade our last available treatments.

In February 2017, the World Health Organization published a list of antibiotic-resistant priority pathogens that pose the greatest risk to human health. The most critical group includes superbugs that are known to be particular threats in hospitals, nursing home and among patients requiring care with ventilators and blood catheters. That group includes carbapenem-resistant *Pseudomonas aeruginosa*[1], a Gram-negative aerobic bacterium that can develop multiple-drug resistance by employing several tricks to evade destruction, such as producing pumps to remove antibiotics that enter its cells[2]. It can be found in soil, water in hot tubs, and can thrive on moist medical

equipment, such as catheters and endotracheal tubes, since it produces a slimy covering to protect itself.

In terms of health risk from superbugs, Canada ranks in the middle of the pack globally, according to Dr. Cheryl Main. She is a medical microbiologist and Infectious Disease doctor with the Hamilton Regional Laboratory Medicine Program (HRLMP) and associate professor of pathology and molecular medicine at McMaster University in Hamilton, Ontario. Main says, "I've seen patients where we're down to our last few drugs in terms of treatment options. Those cases are few and far between, but the fact that we're seeing them at all is scary. There have been times where I've held my breath. And some of the drugs that we use to treat really resistant bugs have quite nasty side effects. I've had patients who survived their infection but suffered renal failure that required dialysis." The HRMLP is one of the largest integrated lab medicine programs in Canada. It is a joint venture of Hamilton Health Sciences and St. Joseph's Healthcare Hamilton and is affiliated with the McMaster University Academic Program in Laboratory Medicine. The HRMLP processes samples for 18 hospitals in southwestern Ontario.

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Canada's ranking traces to improved infection controls and antibiotic stewardship programs that are reducing the need for antibiotics and helping to preserve the ones we have left. Infection control measures are critical since some superbugs not only mutate, they can also swap plasmids, small rings of DNA with other bugs, passing on antibiotic resistance powers. Main says in Canada for example, we see fewer cases and are faster to isolate emergency room (ER) patients with methicillin-resistant Staphylococcus aureus (MRSA). In some parts of the United States, they don't tend to bother isolating as often, since a large majority of ER patients have the bug.

Strong stewardship means swift identification of the pathogen, establishing susceptibility and then ensuring patients are treated with the right agent for the right length of time. "At our hospital sites, the infectious disease doctor reviews every ICU patient's treatment plan," says Main. "They assess which antibiotics they're on and why, and work with the care team to recommend ways to narrow the therapy to something that's not as broad in spectrum, or to shorten or stop treatment."

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Education initiatives make a difference to guide customized therapy choices and ensure clinicians follow good stewardship practices. The Antimicrobial Stewardship Program at Hamilton Health Sciences produces an Antibiogram, an evidence-based tool that provides a snapshot view of the percentages of isolates which are known to be susceptible to antibiotics listed. It is accessible to staff through the hospital intranet.

To address the issue that asymptomatic bacteriuria (ABU) is commonly treated with antibiotics in clinical practice but should only be treated in cases of pregnancy or patients undergoing urologic procedures, Main and colleagues conducted a study. They compared rates of inappropriately treated positive urine cultures at one hospital where medical residents received a multifaceted educational intervention to rates at another hospital which did not receive education as the control group. During the baseline period, 160 of 341 (46.9%) positive urine cultures were obtained from asymptomatic patients at both hospitals and 94 of 160 (58.8%) were treated inappropriately with antibiotics. After educational intervention, rates at the test hospital dropped considerably, with only 2 of 24 (8%) instances of inappropriate antibiotic treatment compared to 14 of 29 (52%) at the control site[3].

In another study, Main and her colleagues demonstrated that creating an automated infectious disease consultation for Staphylococcus aureus led to a significant decrease in time to involvement and better adherence to infectious diseases guidelines[4].

One of Main's education programs was called Swabs Don't Do the Job. "When surgeons were draining brain abscesses, for example, a lot of swabs were sent to the labs. But swabs pick up only a very small amount of fluid, about 150 microlitres, and we didn't see growth in cultures. With this program, we encouraged all physicians and particularly surgeons to send actual tissue or fluids instead of swabs, so we would have a better chance of

HELPFUL RESOURCES

Choosing Wisely is a campaign organized by the Canadian Medical Association and the University of Toronto to help clinicians and patients discuss unnecessary tests and treatments, including the inappropriate use of antibiotics.
Learn more at **www.choosingwiselycanada.org**.

Symptom-Free Pee: Let It Be. The Association of Medical Microbiology and Infectious Disease Canada launched an awareness campaign in November 2016 to coincide with the WHO's Antibiotic Awareness Week. The campaign urges clinicians to reduce unnecessary use of antibiotics to treat asymptomatic bacteriuria.
Read more at **www.ammi.ca**.

WHO Antibiotics Awareness Week will take place from November 13-19, 2017. Learn more about raising global awareness and access education materials at **www.who.int/campaigns/world-antibiotic-awareness-week/en** and follow #AntibioticResistance on Twitter.

WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL
1. Acinetobacter baumannii, carbapenem-resistant
2. Pseudomonas aeruginosa, carbapenem-resistant
3. Enterobacteriaceae, carbapenem-resistant, ESBL-producing

Priority 2: HIGH
1. Enterococcus faecium, vancomycin-resistant
2. Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
3. Helicobacter pylori, clarithromycin-resistant
4. Campylobacter spp., fluoroquinolone-resistant
5. Salmonellae, fluoroquinolone-resistant
6. Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM
1. Streptococcus pneumoniae, penicillin-non-susceptible
2. Haemophilus influenzae, ampicillin-resistant
3. Shigella spp., fluoroquinolone-resistant

identifying what exactly was growing in wounds rather than what was just sitting on surface infection sites," says Main.

Lab technologists play critical roles in front-line antibiotic stewardship programs in hospitals across Canada. Beyond processing samples under increasing time pressures, lab technologists use their knowledge and experience when reporting test results. "Doctors tend to prescribe as soon as they see the name of a bug, but we don't want to jump to the strongest antibiotic first. Otherwise, we lose them for the future. We need to establish susceptibility and use the right drug. We review all cases with the microbiologist during daily rounds and they discuss options for good stewardship with physicians," says Ali Jissam MLT, a senior lab technologist at HRLMP.

Lab technologists also get involved with problem-solving critical cases, such as the patient with a superbug-colonized open wound on his back. To find a solution, microbiology lab technologists arranged for a promising new drug to be tested at the Public Health Lab and the National Microbiology Laboratory in Winnipeg. The drug, ceftolozane-tazobactam, is an antibacterial agent consisting of a cephalosporin and a beta-lactamase inhibitor. It was approved by Health Canada in 2015 for treating specific infections that are proven or strongly suspected to be caused by susceptible bacteria, including complicated Pseudomonas aeruginosa[5].

Jissam is modest about the role of the technologist on the team of front-line professionals managing antibiotic stewardship programs. "Physicians and nurses obtaining the best specimens is the most important step. But the next most important things are lab technologists determining

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> *– Ali Jissam MLT, a senior lab technologist at HRLMP*

susceptibility on the bench and working with the team to help ensure appropriate use and guard the antibiotics we have left."

For the back wound patient, the care team members hope that the new agent, the last line of defense available, will defeat his specific, multiple-resistant superbug infection once and for all. Until it does, he is a canary in a coal mine, warning us that we will soon be out of time to win battles against infections if we are not careful to use what we have left judiciously. ■

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