Microbiome predicts blood infections in pediatric cancer patients

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Bryan Nycz, 3rd-year medical student at the University of Colorado School of Medicine, and scientific mentors show association between microbiome and blood infections. Credit: University of Colorado Cancer Center

Cancer patients receive essential medicines, fluids, blood and nutrients through long, flexible tubes called central venous catheters, or central lines. But every year in the United States, these central lines are associated with an estimated 400,000 blood infections, many of which are fatal, and which cost the healthcare system upwards of $18 billion dollars annually. But what if some or even many of these infections aren't, in fact, introduced by central lines? A study by University of Colorado Cancer Center investigators working at Children's Hospital

Colorado and published in the journal *PLoS ONE* explores another possible cause of cancer-associated blood infections, namely changes in the microbiome, the community of microorganisms that live within the human body. It may be that an imbalanced microbiome along with a leaky gut and not an unhygienic central line is the cause of some bloodstream infections.

"Basically, we wanted to see if the composition of a cancer patient's microbiome could predict who would go on to develop bloodstream and Clostridium difficile infections," says Bryan Nycz, third year medical student at the CU School of Medicine and the paper's first author. Nycz worked with CU investigators Daniel Frank, PhD (a microbiome expert in the CU School of Medicine Division of Infectious Diseases), Samuel Dominguez, MD, PhD (pediatriac infectious disease specialist and medical director of the clinical microbiology laboratory at Children's Hospital Colorado) and Joanne Hilden, MD (director of clinical services for hematologic oncology at Children's Hospital Colorado), among others.

The study took advantage of samples collected during a 2012 outbreak of Clostridium difficile (C. diff). From October through December of that year, stool samples were collected from all pediatric oncology patients admitted to Children's Hospital Colorado, to check for C. diff colonization. Some of these patients subsequently developed C. diff infections and, unfortunately but as expected, some developed blood infections. The fact that stool samples were preserved allowed the current study to explore the link between the composition of patients' microbiomes (via the microorganisms identified in stool) and these two types of infection.

In all, samples and records were available for 42 patients.

First, in this population, the composition of the microbiome differed

based on a patient's type of cancer and type of treatment - in other words (and as expected), the location and type of cancer, along with cancer treatments like chemotherapy and antibiotics, affected the diversity and makeup of patients' microbiomes. Also as researchers expected, the microbiomes of patients who had received bone marrow transplants and subsequent therapies were most affected.

Second, the composition of a patient's microbiome did not necessarily predict which patients would develop C. diff infections. However, Nycz points out that the relatively small sample size may have contributed to not discovering a significant connection between microbiome composition and C. diff infection.

"Although our results did not demonstrate a connection between the microbiome and C. diff infections, our data did hint there might be an association," he says. (An ongoing study hopes to add additional data.)

Third, however, the composition of a patient's microbiome did, in fact, predict whether that patient would develop a blood infection. Specifically, the six patients who developed bloodstream infections had significantly reduced microbiome diversity than patients who remained free of infection. Additionally, when Nycz and his scientific mentors examined the types of bacteria implicated in these infections, three of the six patients who developed bloodstream infections had been infected with types of bacteria that were specifically abundant in their microbiome samples.

"We're proposing 'here's what they have in their bloodstream', and 'here's where the microorganism may have come from' i.e. their gut," Nycz says.

Historically, the widely-accepted term for this type of infection in pediatric oncology patients is "central line associated bloodstream

infection" or CLABSI. However, the current study argues that not all bloodstream infections in this population are introduced via central lines and that CLABSI may thus be an inaccurate term to describe these infections.

"We can't attributew all of these infectiosn to poor central line hygiene," says Nycz. "We should shy away from calling these infections CLABSI and start referring to them more generally as bloodstream infections."

The implication is that appropriate prevention and treatment may depend on the source of infection. If some infections previously called CLABSI are, in fact, due to microbial populations leaking into the bloodstream from the gut ("leaky gut" is especially common in cancer patients), then prevention may depend on maintaining microbiome health, and treatment could include strategies that therapeutically adjust the microbiome. Likewise, patients with altered microbiomes may benefit from closer monitoring for infections.

"It's way too early to suggest that pediatric oncologists make predictions or manipulate patients' microbiomes," says Nycz. "But our results add to a growing body of literature suggesting that the microbiome matters during cancer treatment. In this case, microbiome diversity and composition may help us identify patients at greater risk for blood infections."

As part of the CU School of Medicine Research Track, Nycz will continue studying the link between the microbiome and infection in pediatric cancer patients. The next phase of this ongoing study follows patients for a year after hospital admission to determine how the microbiome changes over time in response to cancer and cancer treatment, and to examine more closely whether changes in the microbiome can predict the development of C. diff and/or bloodstream infections.

More information: Bryan T. Nycz et al, Evaluation of bloodstream infections, Clostridium difficile infections, and gut microbiota in pediatric oncology patients, *PLOS ONE* (2018). DOI: 10.1371/journal.pone.0191232