Decolonization and Pathogen Reduction Approaches to Prevent Antimicrobial Resistance and Healthcare-Associated Infections

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[D. Peter Drotman] This podcast series is brought to you by *Emerging Infectious Diseases*, often referred to simply as EID. I'm Dr. D. Peter Drotman, Editor-in-Chief. EID is an open access, high impact, peer reviewed scientific journal published monthly by CDC. EID publishes articles on new and reemerging infectious diseases that occur anywhere around the world so as to improve the understanding of factors involved in disease emergence, control, and prevention.

[Candice Hoffmann] Hi, I'm Candice Hoffmann. In this episode of the EID podcast, we're discussing one of the world's most urgent public health problems, antimicrobial resistance, also known as AMR.

[Mike Mangalea] My name is Mihnea Mangalea, or my friends and colleagues might know me as Mike. I am a bioinformatician at CDC in the Division of Healthcare Quality and Promotion. I also consider myself a microbial ecologist in that I'm interested in understanding communities of microbes by analyzing their sequence, their genetic material, and kind of characterizing them and figuring out who they are, what they're doing, and what they might be carrying that is important for health care.

[Candice Hoffmann] That was Dr. Mike Mangalea, the first author of a perspective piece in the June 2024 issue of *Emerging Infectious Diseases.* The article is titled, "Decolonization and Pathogen Reduction Approaches to Prevent Antimicrobial Resistance and Healthcare-Associated Infections."

[Mike Mangalea] The authors on this perspective piece are all part of this microbial ecology working group where we try to understand big problems in healthcare, such as AMR, for example, from the perspective of microbes and their interactions with each other and within their different communities and how we can use our understanding of microbial ecology to develop new solutions to these big problems.

[Candice Hoffmann] And AMR is a big problem. In the United States, more than 2.8 million antimicrobial-resistant infections occur each year. It is a leading cause of death globally, with nearly 5 million deaths associated with bacterial AMR in 2019.

[Mike Mangalea] AMR or antimicrobial resistance occurs in microbes that develop the ability to resist drugs used for treatment that were originally effective.

And when we're talking about AMR, these microbes are bacteria and fungi, and the drugs that would be used to treat them are antibiotics and antifungals. So, AMR is a natural phenomenon. It's part of the natural ecology of microbes. And that's because they've been competing with each other for hundreds of millions of years to occupy every niche on the planet. And so, they compete for resources and nutrients and just to survive, basically. And actually, most early antibiotics came from microbial natural products that were effective at competing with one another. For example, the most important medical discovery invention of the 20th century, penicillin, came from the penicillium mold, which is a fungus. And the person who discovered penicillin, Alexander

Fleming, actually predicted the threat of AMR, which emerged shortly after the first antibiotics were released over 70 years ago.

[Mike Mangalea] Nowadays, AMR is spread across the globe due to the interconnectivity of our modern world. And actually, most of us have relatively low level of AMR within our microbiomes, within the community of organisms living in, on, and around us. And this is called colonization.

[Candice Hoffmann] Colonization is when a germ or microbe is found on or in the body but does not cause symptoms or disease. When a person is colonized, and it leads to infection, it often happens like this:

[Mike Mangalea] And I can give you a kind of a real-world example, or a fictional story, of how colonization with an AMR microbe might lead to infection. And that would go something like this (and this is a plug for our microbial ecology website at cdc.gov and a little blurb on pathogen reduction we have there):

So, a fictional patient called Lucy is colonized with an AMR microbe (we'll call that a pathogen), and that is either part of her microbiome or it has recently been acquired in the healthcare setting in the hospital where she is receiving healthcare. And one of the aspects of colonization is that it may not present with symptom of infection, and we call this asymptomatic colonization. So, the healthcare provider is not aware of this colonization. And so, as Lucy is receiving healthcare and potentially receiving IV antibiotics for infection prevention following an invasive procedure or surgery, that antibiotic used in the hospital might wipe out both beneficial microbes and the pathogens intended for it to kill. And so, the original AMR pathogen survives that she was originally colonized with and that out-competes the current landscape and it leads to a dominance. And then, that is when this pathogen can start to cause infection in Lucy and can lead to either a local or a more serious infection requiring further treatment. And then this can be shed in the environment in the healthcare facility or be transmitted to another person. And this leads to a cascade of potential AMR infections.

[Candice Hoffmann] The article we're discussing in this episode focuses on decolonization and pathogen reduction approaches to prevent AMR and healthcare-associated infections. Let's hear some examples of pathogen reduction strategies and how they work.

[Mike Mangalea] Pathogen reduction is actually central to some forms of currently recommended and practiced antibiotic prophylaxis, like before and during surgeries, specifically for preventing surgical site infections. And a couple of examples of this are using anti-staphylococcal agents, which are more targeted towards killing and reducing *Staphylococcus aureus* for preventing orthopedic and cardiothoracic infections after surgeries.

Another example of pathogen reduction as a form of prophylaxis is combined oral antimicrobial prophylaxis prior to invasive or bowel surgeries, elective colorectal surgeries.

And there are actually topical treatments—going back to my first example of anti-staphylococcal agents—topical treatments that are used to reduce pathogens or decolonize skin areas with these antimicrobials. And that could be a nasal ointment of the nose with mupiricin, which is an antibiotic that is used to decolonize and reduce pathogens such as *Staphylococcus aureus* in the nose, and chlorhexidine gluconate bathing for more broad bathing of the body to reduce healthcare-associated infection and prevent them.

[Candice Hoffmann] Chlorhexidine gluconate is an antiseptic skin cleanser. If you've had surgery or a medical procedure where it was recommended, you might know it by the brand name Hibiclens.

[Mike Mangalea] The clinical effectiveness of both chlorhexidine gluconate bathing and mupirocin have shown to be extremely effective and beneficial for reducing *Staphylococcus aureus* infections. And this kind of forms the basis for pathogen reduction in other body sites.

The reason that it's so effective against *Staphylococcus aureus* in that most *Staph aureus* infections actually arise from previous colonization. So, about a third of us have *Staphylococcus aureus* colonization already in our nose or nasal area. And so, this kind of decolonization or reduction of the burden of this organism is really effective and important for preventing *Staph aureus* infections, including and especially methicillin-resistant *Staph aureus*, which can be decolonized and reduced as well with chlorhexidine gluconate and mupirocin.

And in the paper, we talk about some large-scale clinical trials that have shown the effectiveness of these approaches, and these approaches are also beneficial for prevention of other healthcare-associated infections. And a beneficial aspect of something like chlorhexidine gluconate bathing is that it can actually spare some of the beneficial microbes on the skin and allow for recovery of the normal skin microbiota to replenish after this treatment. So again, the successes of both chlorhexidine bathing and mupirocin really form the basis for pathogen reduction at other body sites.

[Mike Mangalea] So, both pathogen reduction and decolonization can be implemented in periods of increased risk for a patient, increased for both infection risk and transmission risk, such as in healthcare facilities or before periods of high risk, such as surgeries or other invasive procedures.

[Candice Hoffmann] The article also discusses ways to leverage the human microbiome in pathogen reduction.

[Mike Mangalea] What we aimed to show in our paper is that the importance of an intact human microbiome and how the disruption of this important microbial ecosystem in, on, and around us, for example, like the intestinal microbiome community, which is this large, diverse, and complex ecosystem of microbes. Disruption of this intact human microbiome can open the door for pathogens to colonize or already colonized pathogens to dominate this landscape and can lead to active infections. And these infections may be implicated by AMR or have specific determinants that would make them more difficult to treat. And really, the impact of the human microbiome is that it provides something that we call colonization resistance. And this is a pivotal function of the healthy microbiome in that the resident microbes within us can actively or collectively protect us against colonization with potential AMR pathogens at the basic level just by taking up space and using up resources and nutrients that those pathogens might. And so, in healthcare, the loss of colonization resistance can occur in people, for example, receiving broad spectrum antibiotics, which pose a high risk for adverse-associated or antibiotic-associated adverse events and secondary infections like *Clostridioides difficile* infection.

And we really aim to show that antibiotic-mediated dysbiosis of the human microbiome has a large epidemiological and human health impact. And this often results in colonization with AMR pathogens that play an outsized role.

[Candice Hoffmann] Dysbiosis is when something disrupts the microbiome in someone's body.

[Mike Mangalea] So, you can think of it as like an injury to the ecosystem or an insult to this collective community of microbes by wiping out or reducing beneficial microbes that make up important contributions to our overall health. And then in terms of colonization resistance, simply removing them and allowing something that is not beneficial to take its place is a problem that could lead to colonization with an AMR pathogen and eventual infection with that pathogen. And so, we show that reducing the quantity of pathogens in a patient can reduce the risk of infection as well as transmission. And we also highlight some preferred attributes for pathogen reduction approaches moving forward.

[Mike Mangalea] Moving forward, we believe that application of antimicrobial stewardship is important to reduce both the occurrence and spread of AMR. And that's because right now the only available treatment for AMR infections are antibiotics themselves. And so going back to antimicrobial stewardship, this involves getting the right dose of the right drug for the right duration in the right patient. And collectively, this would aim to improve the appropriate use of antibiotics and reducing unnecessary use.

[Candice Hoffmann] The article includes a figure that outlines preferred attributes of decolonization and pathogen reduction approaches to prevent AMR and healthcare-associated infections.

[Mike Mangalea] Pathogen reduction is still, we believe, an essential area for further development. And this is going to take developing a combination of different types of pathogen-reducing agents.

And in our perspective, we illustrate this. And the only figure in the paper is an outline of the Parthenon with each pillar describing a preferred attribute or an ideal attribute of what these agents might possess that would make them beneficial for pathogen reduction and decolonization.

So, the first one of that is limiting the spectrum of treatment to narrowly cover the target organism. So, as opposed to something that is a broad-spectrum antimicrobial that would eliminate multiple families of bacteria, if we could limit the spectrum of treatment to narrowly cover only one organism.

The second pillar of pathogen-reducing agents that we outlined in the paper is to limit the distribution of the treatment to a single or selected body site. And this goes back to application of the nasal ointment for pathogen reduction of *Staphylococcus aureus*.

Another important aspect would be to use different mechanisms of action to avoid cross-resistance or resistance from multiple different drugs in the same organism. So, if a patient has to undergo long-term antibiotic treatment for whatever reason, if it would be possible, to use drugs that have different mechanisms of action to avoid cross resistance. And then using potent agents for the right amount of time is another important aspect. And this goes back to antimicrobial stewardship and the right drug, the right dose, and the right duration, and the right patient.

Something that I haven't mentioned yet is using stable or reproducible agents like bacteriophage, for example, which are the natural predators of bacteria. Bacteriophage actually means “bacteria eater” in Greek. And these can actually infect and replicate inside bacteria, inside target bacteria, and actually reproduce over time and go on to infect more of that target bacteria. And so that is another one of our pillars of pathogen reduction.

And lastly, and kind of ties into the whole theme of the perspective piece, is sparing the human microbiome. So, strategies that can keep or restore beneficial microbes is an aspect that we would consider a favorable attribute or preferred attribute of pathogen-reducing agents.

[Candice Hoffmann] As the authors mention in this article, pathogen reduction is an essential area for further research or investigation. Dr. Mangalea discussed some promising strategies, some of which are already in use, and some that are under development.

[Mike Mangalea] We believe that pathogen-reducing agents will incorporate both live biotherapeutic products, which could be something like a probiotic. And we have at least one example in our paper that shows a preclinical study that ingestion of a probiotic bacillus species actually greatly reduced the number of *Staphylococcus aureus* bacteria within people. For example, that could be one promising approach in terms of using a probiotic for pathogen reduction. For restoring healthy microbiomes and replacing those communities that may be containing AMR pathogens, that could also be accomplished through fecal microbiota products. So, products derived from healthy fecal donors that can be given to patients to replace those pathogenic microbes and restore those healthy microbes.

And I should mention that both replacing healthy microbiome communities with fecal microbiota products or phage therapy, for example, these are alternative treatment options that are still under development, but in some cases can be as effective as antibiotics.

[Mike Mangalea] Phage therapy has been developed in countries that have historically had more limited access to antibiotics and have been forced to pursue it more, as opposed to other countries where antibiotics have been the top line of defense against microbes for a really long time, like in our country. However, in other places, bacteriophage therapy has been developed and pursued more. And this is still an active area of development. And it's actually seeing resurgence in some places where antimicrobial resistance has made it so the original drugs are not as effective anymore.

[Candice Hoffmann] You can learn more about other promising current and future approaches to pathogen reduction in the article.

Dr. Mangalea is a microbial ecologist and bioinformatician in CDC’s Division of Healthcare Quality Promotion in the National Center for Emerging and Zoonotic Infectious Diseases.

[Mike Mangalea] CDC's role in protecting people from AMR infections is really a multifaceted approach. To start, CDC leads the US public health response with core public health actions of response and surveillance. The CDC supports outbreak investigations with a boots-on-the-ground approach to control and stop spread of outbreaks of infectious microbes with the goal of

preventing more of those infections and stopping outbreaks. CDC works with partners across academia, other governmental agencies, pharmaceutical companies to establish and strengthen infection prevention and control measures. CDC also raises awareness of AMR threats. An example of this is the AR lab network, which is a detection network that has tested thousands, maybe up to over hundreds of thousands of bacterial isolates for resistance determinants and analysis of their genomes using whole genome sequencing, for example, to characterize and profile these isolates for the specific genes that are causing antimicrobial resistance.

And lastly, data analysis to characterize and track the rates of AMR infections from specific pathogens. So, I actually work as a part of a team of bioinformaticians that analyzes bacterial isolates and communities of bacteria to profile and characterize their resistance determinants, among other things.

[Candice Hoffmann] We asked what advice Dr. Mangalea would have for researchers who want to learn more about AMR and pathogen reduction.

[Mike Mangalea] Researchers that want to learn more about this topic, I would say the CDC has really great resources that cover the range of AMR topics, such as how AMR spreads, how AMR develops, what are the different mechanisms, and these are all available on the CDC website.

I would also encourage researchers that are maybe just studying one organism and one particular infection threat to maybe zoom out and take a holistic view of the problem as a whole in terms of the community of microbes and how aspects of resistance, AMR, are shared among microbes, for example, and how the interconnectivity of our modern world plays a role in the spread of AMR and really makes this a global problem and not just a problem in the United States.

[Candice Hoffmann] Whether you're a longtime or a first-time listener, we hope you'll want to read more.

[Mike Mangalea] Yeah, I'm a regular reader of EID, and I'm a regular listener of this podcast. So, I guess I could say, longtime listener, first-time caller. It's really an honor to be here. I think the journal has a wide readership in terms of clinicians, microbiologists, and it really represents the important work that CDC does to not only combat AMR, but tackle other important issues related to healthcare and infection control.

[Candice Hoffmann] We hope that you will also become a regular reader of the EID journal.

The June 2024 issue of *Emerging Infectious Diseases* has more about AMR and other public health issues.

[Candice Hoffmann] Thanks for listening to our podcast. You can read the *Emerging Infectious Diseases* journal at cdc.gov/eid. You can also follow EID on X and Instagram @eidjournal, and on LinkedIn @eid-journal.

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