biology,” convened last May in Denver during the 2013 ASM General Meeting. Thus, they say, when urine specimens from healthy patients test positive for bacteria, it may no longer be acceptable for clinicians to dismiss those results as mere contamination or “asymptomatic bacteriuria.”

The microorganisms that one detects in urine depend on how it is analyzed. Because *Escherichia coli* accounts for upwards of 90% of all acute cases of urinary tract infections (UTI), clinical laboratories typically analyze urine under culture conditions that favor this well-known pathogen. Also, labs tend to reject any culture result that falls below an arbitrary threshold, which may be as high as $10^9$ CFU/ml. Further, labs typically disqualify mixed growths because they are deemed more likely to reflect contamination or to contain bacteria that are not common pathogens of the urinary tract. No wonder so many doctors have little idea what might be hiding behind “negative” culture findings from clinical lab urine analyses.

Better analytic tools not only could change those reports but also are providing a different view of what urine contains under ordinary circumstances, according to symposium participant Paul Schreckenberger of Loyola University of Chicago in Maywood, Ill. For example, after subjecting urine specimens from healthy donors to 16S ribosomal RNA gene sequencing and to analysis by matrix-assisted laser desorption ionization mass spectrometry, he says that he was amazed to find a large array of rare and exotic microbial genera, including *Aerococcus*, *Actinobaculum*, and *Alloscardovia*, many of which cannot be readily cultivated.

Deep-sequencing techniques are also helpful for uncovering microbial species in urine, says symposium participant David Relman of Stanford University in Stanford, Calif. This analytic approach uncovers remarkably complex microbial communities within the human urinary tract, whose composition can shift depending on whether the microbial community is in a pathogenic or benign mode—similar to what occurs, for example, in the gut with Crohn’s disease or in the vagina with vaginosis.

Understanding the bladder microbiome is not merely an ecological exercise. Importantly, some culture-negative patients complaining of lower urinary tract symptoms are infected, but with levels of bacterial pathogens that fall below the routine threshold set for diagnosing UTIs, according to Linda Brubaker, who is Schreckenberger’s collaborator at Loyola, and also James Malone-Lee of University College in London, United Kingdom, a pioneer in this field.

In such clinical cases, sensitive detection to determine whether pathogens are part of the mix and then deciding which individuals need antibiotics can be crucial in terms of outcome, Brubaker continues. Perhaps the urinary microbiome, even if ephemeral, is itself protective and thus antibiotic treatments sometimes might cause more harm than good, she points out. Further research to learn which microorganisms occupy this environment could help in guiding such treatment decisions.

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**RESEARCH ADVANCES**

**Gut Microbes Affect Host Responses To Two Oral Vaccines**

Carol Potera

Among their diverse activities, the microorganism of the gut apparently affect the host immune response to orally administered vaccines, say Claire Fraser, director of the Institute for Genome Sciences at the University of Maryland (UM) and her collaborators at its Center for Vaccine Development (UM-CVD) in Baltimore. After being vaccinated, cynomolgus macaques with a highly diverse gut microbiota resisted infectious challenges and dis-
MINITOPIC
Promising Vaccine Developments
Cover Range of Diseases

Here are examples of promising developments involving vaccines for a range of diseases and pathogens:

- Designing vaccines to incorporate a multiple antigen presentation system, or MAPS, could bring together the benefits of whole-cell and acellular or subunit vaccines and possibly defend simultaneously against several different kinds of pathogens, according to Richard Malley of Boston Children’s Hospital in Boston, Mass., and his collaborators. Details appeared July 29, 2013 in the Proceedings of the National Academy of Sciences (doi: 10.1073/pnas.1307228110).

- PfSPZ, an experimental malaria vaccine, consisting of live but weakened sporozoites of Plasmodium falciparum and which is administered intravenously, proved safe for recipients in a phase-1 clinical trial and generates a protective T-cell and antibody response, according to Robert A. Seder of the National Institute of Allergy and Infectious Diseases in Bethesda, Md., and his collaborators. Details appeared August 8, 2013 in Science (doi: 10.1126/science.1241800).

- Adding a Toll-like receptor agonist to a malaria vaccine broadened its coverage and improved its capacity to neutralize antigens from the parasite that causes this disease, according to Darrick Carter of the Infectious Disease Research Institute in Seattle, Wash., and his collaborators. Details appeared July 27, 2013 in Science Translational Medicine (doi: 10.1126/scitranslmed.3002135).

- Rice that produces a rotavirus-specific antibody fragment protects mice against that virus, even when the rice is boiled or after long-term storage, according to Yoshikazu Yuki and colleagues at the University of Tokyo in Tokyo, Japan. Details appeared August 8, 2013 in the Journal of Clinical Investigation (doi:10.1172/JCI70266).

A more robust immune response than did animals carrying fewer types of gut bacteria, they report. Details appeared June 5, 2013 in PLOS One (doi:10.1371/journal.pone.0064212).

Fraser and her UM-CVD collaborators are evaluating two separate experimental vaccines for their ability to protect against infections by either Shigella dysenteriae or Salmonella typhi, bacterial pathogens that are acquired orally. The former mainly disrupts the gastrointestinal (GI) tract, whereas the latter disrupts the GI tract and also causes high fevers and other systemic symptoms.

One set of tests began by inoculating cynomolgus macaques with an orally administered, live-attenuated Shigella dysenteriae-1 vaccine and then analyzing their feces to identify bacteria of the gut microbiota. Much like in the human gut, Bacteroidetes and Firmicutes are the most abundant phyla, according to Fraser. However, the gut microbiota of macaques and humans vary greatly at the genus and species levels, both in terms of the types of microbes and their relative abundances. “This raises the question of whether we should take these differences into account when we use nonhuman primates as models and extrapolate data back to humans,” she says.

About two months after vaccination, the macaques were challenged with an infectious dose of wild-type S. dysenteriae-1. Animals with the most diverse fecal microbiota resisted the pathogen better than those with less diversity, and animals in the former group also mounted stronger IgA and IgG antibody responses, Fraser and her collaborators report.

These findings “add a new dimension to the study of enteric diseases and vaccine approaches,” says Martin Blaser, a professor of microbiology at New York University, New York City. “The authors show that microbiome composition is related both to the resistance of the host to the infection, and also to the ability to produce an immune response. The good news is that these characteristics are potentially malleable, which could improve outcomes.”

Treating individuals with probiotics to modulate the intestinal microflora and enhance the immune response when they are administered oral vaccines is an example of a “malleable” intervention, Fraser says. Other researchers report that the probiotic Lactobacillus GG specifically increased IgA after individuals received an oral typhoid vaccine, and this same probiotic also improves the immunogenicity of influenza vaccines, she points out.

In another study, Fraser and her collaborators measured changes in fecal bacteria of 13 individuals who were immunized with Ty21a, an experimental typhoid vaccine also being developed at UM-CVD. Samples were analyzed 1 week before individuals received the vaccine and at regular intervals for 8 weeks. Here again, vaccine recipients whose gut microbiota were more diverse mounted stronger S. typhi-specific, cell-mediated immune responses, she says. Details appear April 24, 2013 in PLOS One (doi:10.1371/journal.pone.0062026). The results from these two separate evaluations of orally administered experimental vaccines offer “preliminary evidence that the gut microbiome affects the immune response,” Fraser says.

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