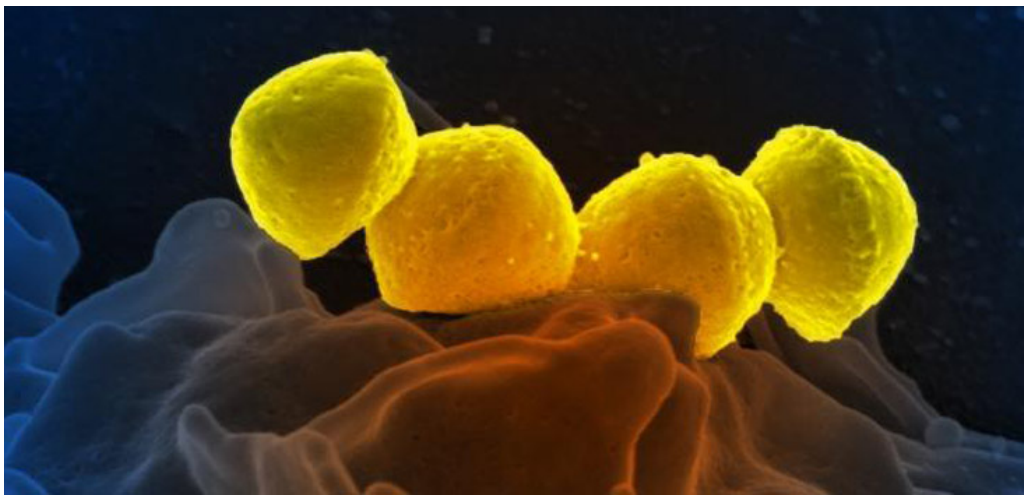
Orthopedics This Week



INFECTION BREAKTHROUGH AT ROTHMAN

Elizabeth Hofheinz, M.P.H., M.Ed. • Wed, May 9th, 2018

Javad Parvizi, M.D., orthopedic surgeon at Rothman and one of the most prolific infection researchers in orthopedics, has made a significant and very novel breakthrough in the understanding and treatment of infections.

As he described the problem to *OTW:* "Traditionally, diagnosing infection from bacterial cultures has come with the downside of false positives and false negatives. These rather crude efforts are giving way to the field of genomics, an interdisciplinary field where we use next generation sequencing to pinpoint the organism(s) in patients with periprosthetic joint infection (PJI)."

"What makes the diagnosis of joint infection particularly difficult is that the organisms are usually in biofilm form—not floating around. Our current detection techniques are only effective 60-70% of the time…and that is a conservative estimate. It's unfortunate, but we often just don't know what organism we are dealing with. A surgeon may give a

patient an antibiotic and then the patient rightfully asks, 'How can you choose a medication if you don't know what I have?'"

In effect, physicians are playing "guess that organism."

What if there was a nearly fool proof method to identify the infection culprits?

As Dr. Parvizi explains it, he and his team may well have found it.

'23 and me' for Bacteria?

"In the last few years we have attempted to use a more sensitive process—polymerase chain reaction (PCR). It is a very sensitive tool that essentially amplifies the DNA, enlarging a few pieces of the bacteria. The problem with PCR is that you have to know what organism you are looking for (Staph, E. Coli, etc.). We began to realize that this is not going to cut it."

"Recently the cost of sequencing DNA has come down drastically. The initial sequencing of the human genome took 13 years and cost $3 billion; now you can do it in a few hours for $200. We are seeing a lot of companies springing up to participate in the DNA analysis market."

"We began thinking that it would be possible to use a similar type of technology to identify infected organisms. When a company known as MicrogenDx initially approached me about next generation sequencing there was no data on this in orthopedics, so I was skeptical. Several cases changed my mind, however, including one that made it into the *Philadelphia Inquirer*."

Parvizi's Acid Test

Dr. Parvizi told *OTW*, "The wife of one of my knee replacement patients called me and said that his knee was red and swollen and that he had fever. We aspirated the joint and it was clearly infected…but the culture was negative. We sent the same sample to MicrogenDx and they isolated *Streptococcus* canis, something I had never heard of until that day."

"Canis," as in canine.

"Interesting," said the patient's wife. "Our dog scratched my husband's leg and has been licking his wound."

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How It Works

"The process," says Dr. Parvizi, "is to send a sample to MicrogenDx where they sequence every bit of the DNA and remove the host DNA. Whatever is left is run against the genome database and that gives us precise information about what organism(s) are present."

And new research shows that such testing works.

Working with colleagues from the Department of Infectious Disease at Thomas Jefferson University and partners from Tel Aviv University, Dr. Parvizi conducted a prospective study, examining samples from 65 revision arthroplasties (39 knees and 26 hips) and 17 primary arthroplasties (9 hips and 8 knees).

"We took samples of synovial fluid, deep tissue, and swabs while in the OR and then sent them for next-generation sequencing. Deep-tissue specimens were also sent to the institutional laboratory for culture."

Their work, "Diagnosis of Periprosthetic Joint Infection: The Potential of Next-Generation Sequencing," appears in the January 17, 2018 edition of the *Journal of Bone and Joint Surgery*.

The Study Results

Dr. Parvizi told *OTW*, "Next-generation sequencing was able to identify an organism in 9 out of the 11 cases of culture-negative periprosthetic joint infection; the process detected several organisms in most positive samples. However, in most patients who were infected, 1 or 2 organisms were dominant."

"Overall," says Dr. Parvizi, "Next-generation sequencing will identify an organism or a group of organisms in up to 90% of cases. A traditional culture will give you one dominant organism but there are other 'silent partners' that are just sitting there looking for an opportunity to emerge. When a surgeon does a two-stage exchange about two-thirds of those who fail do so because of an offending organism that is different from the initial infective organism. We have been calling these 'reinfections' but this company's work is leading us to think that instead this was an infecting organism that was there all along."

In light of this, says Dr. Parvizi, it's time to reevaluate what we know about infections. To that end, the Rothman Institute is supporting a multicenter, 500 patient study. "What we have learned to date," says Dr. Parvizi, "has been a real eye-opener. The fact is that just one organism does not cause infections…we are dealing with polymicrobial situations. We are fortunate that the DNA leaves a signature behind and the next generation sequencing can pick that up."

More Than a Gut Feeling

"We are taking a much closer look at the science of the microbiome," says Dr. Parvizi. "Our bodies have three times more organisms, germs, and microbes than cells…for every cell we have three germs. They typically live in a state of equilibrium but when this is disrupted then a state known as dysbiosis occurs and disease emerges."

"Everyone has a very specialized microbiome which is determined by our genes, food we eat, and the environment. Using next generation sequencing, we have found that in about 30% of people there are organisms living in the joints."

"The way our body handles those germs could be an explanation for some of the diseases we develop."

“What if osteoarthritis is caused by dysbiosis? In the ‘80s two gastroenterologists postulated that gastric ulcers were caused by bacteria. They were laughed out of the lab, as it were, and 20 years later they were awarded the Nobel Prize (the bacteria was Helicobacter pylori).”

“It could be that things such as osteoarthritis, rotator cuff tears, etc., are all linked to a disruption in the microbiome.”

Alexander R. Vaccaro, M.D., Ph.D., M.B.A., president of the Rothman Institute, told *OTW*, “We believe so strongly that microorganisms play a pivotal role in musculoskeletal conditions that we are actually building a microbiome facility to explore the relationship between the gut and bone, joints, disc space, etc. We should then be able to develop much-needed therapies that improve bone strength and address a multitude of other conditions. This is the next dimension in orthopedics.”

In the not too distant future, schoolchildren might be singing, “The hip bone is connected to the…stomach biome.”