Periprosthetic Joint Infections

New Generation of Treatment Strategies, Antibiotics, and Outcomes

Part 2: New Strategies for PJI

00:11

Dr. Jane Caldwell

In part two, we'll look at new strategies for PJI prevention and treatment. Once again, we're speaking with Dr. Jessica Seidelman and Dr. William Jiranek. Both work at the Duke University School of Medicine in Durham, North Carolina.

Gram-positive bacteria are responsible for many orthopedic infections and account for 60 to 80% of all etiological pathogens. Emergent concerns of orthopedic and infectious disease specialists involve PJIs caused by antibiotic resistance and or biofilm forming pathogens as both present significant therapeutic challenges. Dr. Seidelman, could you address these concerns more specifically?

Dr. Jessica Seidelman

Sure, thanks so much, Jane. You know, I think the first thing I want to mention is that it's really important to recognize that most bacteria have the ability to form biofilm. It's not that we just worry about Gram-positives, we just worry about *Pseudomonas*. I think that the ability of bacteria to again form this very protective habitat for themselves is present in most of the bacteria that we know cause infection. So again, that's gram-positive and gram-negative. And biofilm formation is really considered, I think in general, a universal bacterial trait.

Although the capacity and mechanisms vary among species and strains. So, I think there are some that may form it more readily, particularly staphylococcal species that we use to study in the lab because they form it so efficiently and well. But I think that when it comes to the microbiology of PJIs, you know, it's really dominated by gram-positive bacteria, particularly coagulates negative staphylococci. So notably *Staphylococcus epidermidis, Staphylococcus aureus*, and then some other important pathogens that we always consider include streptococci, enterococci, cutibacterium, particularly in shoulder prosthetic joint infections. And then, I would say that there's fewer gram-negative bacilli infections, such as enterobacterial and pseudomonas species. And then, anaerobes, fungi, non-tuberculous mycobacteria, and even mycobacteria tuberculosis, much, much less common that we see. But again, you know, with the amount of antibiotics folks are getting, we're seeing that the microbiome on folks' skin is changing. And that's also, I think, going to evolve over time in terms of what causes prosthetic joint infections. But I think if you look at recent trends, it really indicates a rise of incidence among, again, more resistant organisms like multidrug resistant, gram-negative organisms or ESBL-producing enterobacteria, even carbapenem-resistant strains. And again, this is more happening in geographic areas, tertiary care centers and patients who have been, you know, maybe treated with a lot of antibiotics previously because that's changing the microbiome of their skin. And again, that's where we really think these infections tend to come from, from the patient's own endogenous flora. But I would say that, again, these gram-negative PJIs, these resistant PJIs, fortunately are still pretty small in terms of incidence, in terms of overall 10 to 20%. But again, I think that over the next decade or so, if we continue with the trends we're seeing, we're probably going to see that number rise as

more and more people continue to get more treatment with antibiotics for various infections, both viral and bacterial.

4:23

Dr. Jane Caldwell

Dr. Jiranek, how about fungal infections?

Dr. William Jiranek

I think we all worry about fungal infections because they're some of the most difficult for Dr. Seidelman to treat in terms of, and also for the surgeon to debride. A lot of what the surgeon is doing in a PJI is trying to get rid of the infected organism. And you can do that with debridement, both in bacterial infections and fungal infections. The problem with fungal infections is it tends to be an opportunistic infection that occurs when the patient is pretty debilitated. So, we know that we've got an infection that we're going to have to manage in a very debilitated patient. We're worried. We know that's going to be a difficult go. And the other thing that I would say is, yes, the microbiome identification has changed. We used to think it was mostly staph and didn't worry about too much of the rest, but as our diagnostic capabilities have improved, as we're able to identify, it used to be that 20 to 25% of patients had culture negative infections, which means we weren't smart enough to figure out what was causing the infection. That is changing with better techniques. And I think it's an important change because it allows us to tailor an antibiotic strategy to that bacteria or bacterias, because some of these infections are multi-organism. Again, another sign of a more difficult infection in a debilitated host. And those kind of keep us up at night.

Dr. Jessica Seidelman

If I can add on just to that a little bit, you know, I think that those of us who have treated a lot of these PJIs, we typically see the fungus set in after a patient has been treated for one, two, three, four PJIs in the past. And so, it's almost a sign of someone who has had a lot of recurrent UTIs. You've treated all the bacteria and now the fungus is kind of settling in. And the other thing I'll say is that, you know, we talked a little bit about biofilm in the first part. If you look at biofilm of fungus compared to biofilm of bacteria, biofilm of fungus looks incredibly different under an electron microscope. So, it looks almost like tangles and whorls of hair compared to more of like a lattice structure of bacteria. And I think that also has to contribute in terms of how difficult the fungal infections are to treat in terms of prosthetic joint infections.

07:39

Dr. Jane Caldwell

Methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis* are among the top concerns in the treatment of PJIs due to antibiotic resistance and the ability to form biofilm. Dr. Seidelman, how do we combat these infectious agents who are resistant to traditional antibiotics?

Dr. Jessica Seidelman

So, I do think that we are seeing a fair amount of methicillin-resistant *Staphylococcus epidermidis* or methicillin-resistant coagulase-negative staph. I feel like the MRS or the methicillin-resistant *Staph aureus* members are probably, in general, not rising as quickly. I still think that most of these, even though they have this methicillin resistant name to them, right? They still remain susceptible to a lot of the antibiotics that we have, like good old vancomycin, know, an oldie, but a goodie. And the issue I think really comes back to biofilm, the implant and the host as opposed to this antibiotic resistance pattern. For instance, patients who have more antibiotic allergies, drug-drug interactions, that may make the treatment more challenging. And again, when it comes to the resistance profile of these organisms, we are lucky in that we aren't seeing a lot of what we call vancomycin-resistant staphylococcus or vancomycin-intermediate staphylococcus,

which does make it harder to treat. I think honestly, when it comes to the antibiotic choices, if you're, if you're taking the biofilm and the surgery completely out of it, it's more a challenge for us clinicians in terms of does the patient have significant antibiotic allergies? Can the patient take these antibiotics because of issues with their kidneys, their liver, concomitant medical problems or medications? And then lastly, like I keep mentioning, has this patient been exposed to a whole lot of oral antibiotics? So, their endogenous bacteria is now resistant to that, making it more difficult. But I'm not sure that just the fact that we're seeing more methicillin resistance is necessarily the problem.

9:55

Dr. Jane Caldwell

Lipoglycopeptides are a relatively new class of antibiotics that inhibit cell wall synthesis and disrupt cell membrane integrity. The three drugs of this class, dalbavancin, oritavancin, and telavancin, have recently been suggested for the treatment of PJI in cases where a Gram-positive biofilm-forming pathogen is suspected. This new class of antibiotics addresses many concerns in PJI, including antimicrobial resistance. All three are effective against MRSA and other resistant pathogens. While there is little data regarding resistance to lipoglycopeptides, vancomycin-resistant strains of enterococci and *S. aureus* may have a low level of resistance to all three agents and vancomycin-intermediate strains of *S. aureus* may show non-susceptibility to dalbavancin.

Dr. Seidelman, there are reports of successful outcomes from this new generation of antibiotics in PJI. Can you share your thoughts?

Dr. Jessica Seidelman

Yeah. So, I am really excited about the class of antibiotics that comprises of, know, oritavancin, telavancin, dalbavancin. Dalbavancin and oritavancin are long acting, lipoglycopeptides, and they have potent activity against a broad spectrum of gram-positive organisms, including MRSA, including VRE, which is vancomycin-resistant enterococci. and they've been increasingly used off label for prosthetic joint infections. And I think that the most robust data actually exists for dalbavancin. Multiple observational studies and meta-analysis, a propensity-matched cohort study demonstrate that dalbavancin achieves clinical success rates comparable to standard of care regimens in bone and joint infections, including PJIs, with success rates typically in the 70 to 80% with a favorable safety profile. The other thing I really love about dalbavancin is that it's a long-acting antibiotic, right? So, typically when Bill and I have these patients or clinicians in general have these patients, you're putting a PICC line in them. You're sending them out with IV antibiotics. This is a huge burden for patients. For dalbavancin, typically what you're doing is giving two or three 1,500 milligram doses one week apart. So, the patient gets a dose in the hospital, hopefully a dose or two as an outpatient, but it saves the patient and their family you know, a lot of time, a lot of effort, a lot of stress about the PICC lines. I mean, I think that some people feel safer, quote unquote, on intravenous antibiotics. But the fact of the matter is that having a PICC line or a central line in your body actually can create a lot of other problems. And we see that, you know, not to go back to part one, but we see that with readmission issues, returns to ED because the PICC lines aren't working, they're having an issue. And some of these longer acting antibiotics really do ameliorate that issue. And I think that there's some growing data regarding the fact that these antibiotics probably have some good activity against these gram-positive bacteria within the biofilm as well.

When it comes to oritavancin, there's less published clinical data, but systemic reviews in a recent case series suggest it may be as effective particularly for salvage or suppressive therapy with VRE bone and joint infections. But again, that data is really small, but it's another long-acting antibiotic and particularly helpful for, again, some of these more resistant pathogens. I'm not aware that telavancin has really been

systemically studied in the prosthetic joint infections. And it's one that I haven't really used a lot myself, but I think again, these three agents are really exciting, particularly for those of us in infectious disease and biofilm treatment, because again, they offer the opportunity perhaps to better treat biofilm and then free the patient up from needing intravenous antibiotics for long periods of time.

14:22
Dr. Jane Caldwell
Dr. Jiranek, on the surgery side, how did choice of biomaterials affect infection rates?

Dr. William Jiranek
Well, I think a lot of people say, is one biomaterial more susceptible to biofilm formation? And the answer is yes, there are biofilms formed more easily on some materials, but it's not a big degree. So, any biomaterial that's not biologic is going to have an increased risk of biofilm formation in the correct bacteria.

And I think we worry about resistant bacteria in our surgery. And I think surgeons tend to groan because they know the results are not going to be as good and nobody wants to pick a patient that's not going to do well. But I think sometimes that's our case. As far as surgical treatment, I think if you were to ask most surgeons what makes the biggest difference, it's not the biofilm buster that you might pour into the wound. It's not the antibiotics. It really has to do with getting rid, decreasing the bacterial load in the joint. And if you are doing something where you're retaining the implant, obviously there's a, but only so much biofilm that you can eradicate. And that's why perhaps the debridement, antibiotics, impact, retention, i.e. DAIR, that we see done an awful lot, has varying rates of success. And those don't approach resecting the implant, cleaning the joint and putting in another joint. So, I think most surgeons would agree that the most important thing is debridement though. You have to get rid of the tissue that's containing large amounts of bacteria around the implant. You do as good a job as you can on the actual biomaterials if you're not swapping them out. But I think to just say, yeah, we drained the pus and then poured in acetic acid or betadine, or some other agent that's been shown to disrupt biofilms is probably not going to be as effective because you're leaving a lot of tissue containing bacteria that's just going to make new biofilms behind. And so, I think as we're training the next generation of how to manage these, adequate debridement strategies are critical.

17:11
Dr. Jane Caldwell
All right, thank you for that information. We'll talk again in part three where we're going to discuss the Clinic of Hope.