Osteomyelitis:
Achieving Antibiotic Penetration

PODCAST 21

00:22
Dr. Jane Caldwell:
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Dr. Adam Bressler is an infectious disease specialist affiliated with Emory Hillandale Hospital and Emory Decatur Hospital. He has been in practice for over 20 years with special interests in antibiotic trials, fungal infections and osteomyelitis. In 2022, he received the Atlanta Business Chronicle Healthcare Heroes Award. Dr. Bressler is with us today to talk about the role of antibiotic resistance and other complications in current treatments for osteomyelitis. He will discuss the novel glycopeptide antibiotics and a multidisciplinary approach to treating these infections.

Hello Dr. Bressler and welcome to *On Medical Grounds*.

Dr. Adam Bressler:
Glad and honored to be here.

01:57
Dr. Jane Caldwell:
Dr. Bressler, can you tell our listeners about osteomyelitis? What causes it, and why it can be tough to treat.

Dr. Adam Bressler:
Sure, osteomyelitis refers to infections of the bone and may involve bone as well as the adjacent tissues, which could include joints or any associated prosthetic material.

These infections are extremely difficult to treat for a lot of reasons we can discuss further but including the environment of where these infections occur being sometimes difficult to access or being difficult for antibiotics to penetrate, they often require prolonged treatment to have successful resolution period.

They also are often due to antibiotic-resistant organisms, especially methicillin resistant *Staph aureus* (MRSA), which is one of the more common causes.

02:53
Dr. Jane Caldwell:
What is the role of antibiotic resistance in current treatment regimens for the disease?

Dr. Adam Bressler:
Well, I think, like all infections that we have to deal with now, multidrug resistant organisms or other resistant organisms do play a prominent role in osteomyelitis also. Again, as I mentioned methicillin resistant *Staph aureus* is probably one of the most common causes of osteomyelitis and has to be taken into account when considering these types of infections.

We do see other resistant organisms showing up in certain situations, and one of the issues is that we really have limited data or indications and how to treat these persistent infections within osteomyelitis.

03:37
Dr. Jane Caldwell:
What are some challenges in treating bone tissue?

Dr. Adam Bressler:
I think a lot of the challenges arise from the nature or location of the infection bone tissue tends to be relatively avascular or have poor blood flow which can make penetration of antibiotics difficult.

These infections often occur because of areas of traumatized tissue or bone, whether that be trauma or spread of infection from more superficial areas or post-surgical types of infections, and so the tissue environment is often difficult to treat. They may be in difficult to reach places in terms of trying to have surgical or other types of mechanical interventions within the area. One of the other concerns, as I mentioned, is also that these infections typically require prolonged treatment. Sometimes six weeks or more, and so maintaining effective therapy for a long period of time comes with a lot of complications, and difficult issues for the patient, inpatient care, concerns for side effects or toxicity, and things like that.

04:45
Dr. Jane Caldwell:
Biofilms and chronic infection. Can you elaborate on these and how they happen?

Dr. Adam Bressler:
So yeah, biofilms have become one of the hot topics in infectious disease in a lot of realms, and this does include osteomyelitis. Biofilms are basically sort of microenvironments where colonies of bacteria adhere to tissue or sometimes prosthetic material.

And they create a layer made out of sort of a combination of polysaccharide, extracellular protein and genetic material that form something like a slime layer around these bacterial colonies. And these biofilms make treating the infection that much more difficult because of the sort of nature and value within these biofilms. They make it difficult for antibiotics to penetrate to the bacterial colonies. Within these biofilms

you may have alterations of things like the pH of the environment or other attributes which might decrease the activity of the antibiotics that do reach the area the bacteria themselves within these biofilms tend to be metabolically less active.

You can sort of think of it as hibernating bacteria, so they're not replicating or as metabolically active, and therefore making the antibiotics that we utilize that may have mechanisms with action that actually require active replicating bacteria may be less effective in these environments.

So these, as well as some other factors have really helped shape our understanding of why some of these difficult infections, including osteomyelitis, sometimes don't respond very well to antibiotic treatment or require difficult and prolonged treatment.

06:30
Dr. Jane Caldwell:
It's unclear that first line Gram-positive antibiotics such as vancomycin can penetrate bone. How often do these first line treatments fail?

Dr. Adam Bressler:
Yeah, I think that's definitely a relevant point that we see and again gets to that idea of, you know, osteomyelitis treatment is often prolonged and not always successful. The data is very inconsistent across studies because osteomyelitis is such a difficult entity to study and it encompasses so many different types of infections in so many areas.

But certainly, depending on the series you're looking at and looking at some of you know the older studies where vancomycin has been utilized. You may see failure rates, sometimes up to 40% with either failure or recurrence. So I definitely think that we have some significant gaps in in our ability to always successfully manage these infections.

07:28
Dr. Jane Caldwell:
What are some of the antibiotics effective against Gram-positives that have been introduced in the last few years?

Dr. Adam Bressler:
Well so I think, you know I give talks about bacteria and antimicrobial resistance a lot in relation to our hospital's antibiogram. And for years I always have a section where I discuss, the "old" versus the "new" antibiotics active against MRSA. And actually, even some of the new ones aren't so new anymore, but in general we're kind of thinking about the "new" antibiotics that we have in the Gram-positive spectrum, especially active against MRSA.

Some of the drugs that have come in in more recent times include daptomycin and which is a lipopeptide. We have what we call the newer glycopeptides or lipoglycopeptides, like telavancin, dalbavancin and oritavancin.

We also have a beta lactam drug, a cephalosporin, ceftaroline, that is active against MRSA, which is unique to that class. We also have what I call sort of the tetracycline or glycylcycline derivatives, drugs like tigecyclin, apocycline, and omadacycline which are active against gram positive organisms including MRSA. There are some other drugs that are less frequently used or in development, but for the most part, these tend to be our go-to options for IV therapy. We also have some oral drugs that are again what I call that relatively "new" class of drugs active against MRSA which includes linezolid and tedizolid.

09:15
Dr. Jane Caldwell:
These guidelines for treatment haven't been updated in many years, correct?

Dr. Adam Bressler:
We actually don't have a lot of guidelines for work with for osteomyelitis. We do have 2015 guidelines for vertebral osteomyelitis, which is a very difficult entity to treat, but not as common. There are also newer guidelines for pediatric hematogenous osteomyelitis, but for the majority of osteomyelitis that we treat in adult infectious diseases we don't have really, any active guidelines to fall back on because it's such a difficult entity to study and get good data on.

10:35
Dr. Jane Caldwell:
Do you think the glycopeptide antibiotics as a class may be more useful in osteomyelitis than the more traditional antibiotics?

Dr. Adam Bressler:
Well I think because methicillin-resistant *Staph aureus* plays such a prominent role in osteomyelitis that antibiotics in general that have activity against MRSA, say are essential, and so to that extent the glycopeptides or the newer lipoglycopeptides, I think certainly play an important role for treating this kind of infection.

11:08
Dr. Jane Caldwell:
I understand that they have a dual mechanism of action inhibiting both cell wall synthesis and cell wall function.

Dr. Adam Bressler:
Yeah, so the best characterized dual mechanism of action is for telavancin a lipoglycopeptide, and it does both inhibit cell wall formation, typically similar to vancomycin, which is sort of the parent molecule but also interacts with the cell membrane, and it is thought that this dual mechanism of action may also be helpful in what we call the bactericidal effect or the ability of these antibiotics to not just to inhibit growth but to actually kill the bacteria and they play a role in being effective in the biofilms we're talking about.

11:55
Dr. Jane Caldwell:
You have published two journal articles on a retrospective medical chart review called the Telavancin Observational Use Registry or TOUR for short. Can you tell us about the objectives of TOUR?

Dr. Adam Bressler:
Sure, the TOUR database was a large retrospective trial, although some patients might have been enrolled prospectively, the data was all collected and entered retrospectively, really, the goal of which was to look at the clinical real-world use of telavancin, so this is all post approval, post marketing utilization by multiple centers across the country or the world, and it really wanted to get a sense of how the medication was being used by clinical providers in situations you know really across all entities.

The trial ended up enrolling over 1000 patients across many different infection types, including skin and soft tissue infections, for which the drug was approved, pneumonia, certain types for which the drug was approved, but also other off label indications that included osteomyelitis in a large number of patients.

13:03
Dr. Jane Caldwell:
Could you describe the methods used in the TOUR multicenter study?

Dr. Adam Bressler:
Sure, so as I mentioned, the study looked at retrospective data of over 1000 patients. For anybody who had received at least a single dose of telavancin per the investigator's discretion. These patients could not be enrolled in other clinical trials, and they were followed for both efficacy and determination of outcomes of treating their infection as well as any concerning adverse safety signals such as kidney dysfunction and we looked into issues of dosing duration of treatment, concomitant therapies…. You really again try to get a sort of broad view of how this drug is being utilized and performing in real world situations.

14:04
Dr. Jane Caldwell:
And what results were gleaned from the TOUR meta-analysis?

Dr. Adam Bressler:
Yeah, so I think there was actually a lot of interesting findings that it might have been unexpected prior to looking into this. As I mentioned before, I think one of the most interesting findings was that this drug is certainly being used in situations other than the approved indications I mentioned, which were just in soft tissue and in pneumonia. It was used in a large number of people for bone and joint infections, including osteomyelitis, that was about 1/4 of the patients. It was also used in other situations, including bacteremia, endocarditis, as well as some other entities, and I really think the bone and joint utilization as we're talking about that here, was informative because I think that certainly, as we mentioned, it's an area where we don't have a lot of great options or data, so any information that we can gather this large number of patients can be instructive.

I think one of the other interesting findings was that in this real world use it was being used at significantly lower doses than the package insert recommends and yet what we found was that there was really consistent and high success rates across all of these entities or types of infections, there was, in general, about a 75% or so success rate across all of these, despite the fact that the drug tended to be dosed in in this database anyways, at lower than recommended for the package insert.

15:43

Dr. Jane Caldwell:

So what is the recommended dosage and treatment duration for intravenous telavancin for osteomyelitis?

Dr. Adam Bressler:

Yeah, so I think that's a, you know, a little bit of a tricky question in that as I mentioned, there is no indication for osteomyelitis. Really, we don't have an official package insert indication for osteomyelitis for many drugs. Some of the very old drugs like vancomycin have data and indications. The last drug to actually get a true indication for osteomyelitis was ciprofloxacin back in the 1980s. So having said that, we really don't have a true dose or indication for osteomyelitis, but for the things that it is indicated for the recommended package insert dosing for telavancin is 10 milligrams per kilogram. In the TOUR database, what we saw is that across all of the types of infections where it was used, the mean dose was about 750 milligrams, which corresponded more like about 8 milligrams per kilogram.

16:46

Dr. Jane Caldwell:

A once daily intravenous dosage may be problematic for non-hospitalized patients or people that have inflexible work schedules or transportation issues. Are there alternatives to an infusion center such as home health care providers or self-administration via an infusion pump?

Dr. Adam Bressler:

Yes, that is that is certainly an option that we have. So when we work through outpatient infusion centers, sometimes that does mean having a patient come on a daily basis. But we are often able, depending on the patient's comfort level and ability, and certainly their insurance or payer coverage attributes, were able to have them treated at home with either self-administered home infusion or home health infusion and that is important.

You had asked earlier about the duration, again, although there's no indicated duration for osteomyelitis, most of the time we're treating osteomyelitis we are talking about prolonged treatment, which can be, you know, up to six weeks in many situations, and so having that kind of flexibility when it's available for the right patient makes a lot of a lot of sense.

17:58

Dr. Jane Caldwell:

In both TOUR articles, patient demographics were broken down and listed. What do you say to the critical observation that most of the data came from males, about 53% or for white non-Hispanic patients, 83%?

Dr. Adam Bressler:

Yeah, I think that's an interesting observation, realistically, one that we've seen across many types of studies across all drug classes, and certainly that you know in more recent times, that's been an issue that in drug trials that we're trying to remedy by having representative populations. Having said that, I would say that osteomyelitis is disproportionately a disease of males for various reasons, and so having 53% in the scheme of things is probably not inappropriate. Uh and of note, African Americans did represent about 10 to 11% of the patients in the TOUR data, so that's fairly representative of their demographics within the population.

18:58

Dr. Jane Caldwell:

In the TOUR study, 29% of the patients were over 65 years of age, the average age being 55. Is this disease, a disease of the middle age or the elderly?

Dr. Adam Bressler:

Well, I think as I've alluded as I have alluded to, osteomyelitis is sort of a varied entity, and it can sort of manifest in different ways and come from different situations. So what I'd say is it's a disease that can affect all age groups, but its presentation or its underlying cause is different. In pediatrics it is more commonly what we call a hematogenous or blood borne infection, and we mentioned the guidelines that came out recently to address that. And sort of the younger to middle age adults is where we see situations that might include trauma or injury subsequently leading to osteomyelitis and then in the middle age, the older patient is where we see things like underlying diabetes or vascular disease leading to skin and soft tissue infections, ulcerations that then progressed to osteomyelitis or perhaps post-surgical infections following knee replacements, hip replacements, things like that. So it can be really seen in all age groups but tends to be a little bit of a different manifestation.

20:20

Dr. Jane Caldwell:

How about in those that are immunocompromised?

Dr. Adam Bressler:

Yeah, I think that what I'd say the relative immunocompromise of diabetes is the most important way that that shows up in our clinical practice. Undoubtedly in that middle age and older population, diabetes is one of the more important risk factors, and there is a degree of immunocompromise that comes with that. In thinking about what I would call traditional causes of immunocompromised, whether it be malignancy or steroids or chemotherapy or AIDS or other things like that, I don't particularly think of osteomyelitis as being more prominent in those situations.

21:05

Dr. Jane Caldwell:

Besides diabetes, are there other comorbidities associated with it?

Dr. Adam Bressler:

Yeah, and I think a lot of those are the same comorbidities that we see running with diabetes in the general population. Vascular disease, which again you know that is important because of that limitation of blood flow to the area to impede healing, is a common cause, obesity, smoking…. Another important entity that we see is injection drug use is one of the underlying risk factors, again, because in that case the hematogenous spread of infection combines.

21:42

Dr. Jane Caldwell:

So as an infectious disease specialist, could you summarize your recommendations for osteomyelitis management?

Dr. Adam Bressler:
Well, I guess if I if I could summarize them that well, I'd make my own guideline. But I think the important point is that osteomyelitis is a varied entity. It is not a sort of single, easily definable condition that has simple or you know necessarily reproducible answers all of the time, so I think one of the important things to recognize is, is that osteomyelitis has as much do the underlying situation.
That leads to it again thinking about diabetes or vascular disease, or some of these other risk factors post-surgical situations, obesity, things like that because I think the important thing to recognize is that the underlying issue, often with osteomyelitis, model osteomyelitis, is that there is a significant degree of tissue compromise and whether that be due to vascular status or non-healing wounds or mechanical aspects, that's really a lot of what makes osteomyelitis difficult to deal with and so while it's easy to think about, well, what's the right antibiotic and how much and for how long? That is often only a part and sometimes a small part of the equation. You have to think about things like what we call source control, which essentially means is there a way through surgical debridement or other methods to remove that devitalized tissue or unhealthy tissue to think about appropriate blood flow delivery to think about mechanical offloading, to think about proper wound care, and so all of that is important in the management of diabetes.

And then we have to think about some of the things we were talking about earlier, recognizing that some of these difficult to treat organisms like MRSA say are often involved, and so you have to have not only medications that are active against these bacteria, but also are able to be successfully delivered, so to speak, for a long period of time, and that's as much a logistical issue as it is a microbiological spectrum issue, so again things like infusion ability, infusion time, number of infusions per day, access duration, all of these things come into play because we have to treat these patients often over a prolonged period of times for six weeks or more.

24:18
Dr. Jane Caldwell:
Could you describe the multidisciplinary approach to osteomyelitis diagnosis and treatment?

Dr. Adam Bressler:
Yeah, I think that's exactly sort of the issues that I was, you know, kind of alluding to in the last question is that you know our role in infectious disease is often thought of as sort of the you know, "What's the bug and the drug," and that kind of thing, but in reality, successful treatment of osteomyelitis requires this multidisciplinary approach. I'd say this has really come into play for me in my career because we also do wound care and work at the wound care clinic in our hospital. And so we really get to see all of the different facets of osteomyelitis and where it's approved from. We also have a podiatry residency program and so we work with them a lot, and osteomyelitis is one of the most common things we deal with and it is definitely clarified for me that these other issues such as having the right collaboration with surgical teams, whether it be podiatry, orthopedic surgery, or vascular surgery, is critical because to the extent that source control is available for these infections, the more you can do, the better.

The wound care aspect, which can include appropriate management of the wounds dressings offloading mechanical offloading. Some of the other things that we really have to do to think about long term maintenance to enable successful therapy are critical and so being able to work with wound care centers and nursing home health is really important.

And then, in terms of the actual antibiotic treatment, again because we're thinking about long-term treatment, you have to be able to work with pharmacists, home health, delivery, outpatient infusion centers, vascular access if you're having to think about PICC lines or other long term access devices like that.

And the reality is that you know, it really does take all of these entities to get successful treatment, as we sort of alluded to earlier, the failure, or at least recurrence rate with osteomyelitis, can be significant, and this can have really devastating and debilitating consequences, including limb loss and mobility, recurrent infections and hospitalizations. And so you know, I often have conversations with my colleagues, that sort of you know, we have one chance to get this right. We have to kind of throw all of these things together in the right way with the right team to make it happen.

26:53
Dr. Jane Caldwell:
Last question, what were you hoping I would ask you today about osteomyelitis?

Dr. Adam Bressler:
You know, I, I think what whether you intended to or not, all of all of the questions that you did ask really helped get at some of the messages that I want to convey, especially those questions at the end about the multidisciplinary approach and really, you know the way to address osteomyelitis, sort of globally, as opposed to thinking about it in isolation, as sort of a drug bug problem. I do think also, as we alluded to, it would be great if we could ever get some guidelines put together to help manage this, uh, I think the issue that you know that we've kind of touched on is that it is sort of literally and figuratively a quote, dirty diagnosis, and so it's very hard because of this to come up with standardized algorithms for diagnosis.

Dr. Jane Caldwell:
Well Dr. Bressler, we appreciate your work in infectious diseases such as osteomyelitis. Thank you so much for taking time out of your busy schedule today to speak with us.

Dr. Adam Bressler:
Thank you, it's a pleasure.

Dr. Jane Caldwell:
And thank you for listening to *On Medical Grounds.* We know your time is valuable.

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