#357 Hotcakes: Ultra-short Antibiotics for Pneumonia, Acetazolamide for CHF, Psilocybin for AUD, and Asymptomatic Kidney Stone Removal

THE CURB SIDERS INTERNAL MEDICINE

#357 HOTCAKES

Ultra-short antibiotics for pneumonia

Acetazolamide for acute CHF

Psilocybin for AUD

Removal of Asymptomatic Kidney Stones

[Disclaimer]

[The Curbsiders Podcast theme]

Matt: Welcome back to the Curbsiders. I'm Dr. Matthew Watto here with some great friends. Maybe you can see them, maybe you can't. Paul, how are you doing tonight?

Paul: Yeah, I'm great. Hopefully visible. Thanks, Matt. How are you?

Matt: Good. I'm trying to tease for the audience that we are now putting more stuff on YouTube so they can see our faces. I'm not going to put any adjectives along with that, Paul.

Paul: I'm not going promise any feet or anything. No, that's cool.

Matt: This is a Hotcakes episode. We have some great articles. Before we get into those-- And let's actually let me tease some, we're going to talk about kidney stones. We're going to talk about a short course of treatment for pneumonia. Some magic mushrooms, Paul. It isn't psilocybin magic mushrooms. Am I getting my drugs mixed up, Paul?

Paul: Psilocybin is indeed the active part of magic mushrooms. You're correct.

Matt: Okay, and then we're going to talk about acetazolamide for heart failure. I mean, what an episode Paul. But first, what is it that we do on the Curbsiders?

Paul: Well, I do ask myself that often. We are *the* Internal Medicine Podcast. We usually use expert interviews to bring you clinical pearls and practice-changing knowledge every so often, we'd like to stretch our critical appraisal legs and actually try to look at articles ourselves and try to figure out how we feel about them and then bring them to you, the listener. And happily, we have an expert. We have raconteur, master educator, what else can we say about the amazing Dr. Rahul Ganatra, who also joins us tonight.

Matt: He's a great host. I visited him before. He's a great host. Lovely home. So, yeah, all these things.

Rahul: Thanks, guys. I don't know what to say. I feel like you're setting the bar really high for me.

Matt: [laughs] Rahul, always great to do these Hotcakes episodes with you here. Makes us feel more confident that we can say things, and then just pass it off to you if we don't know something. So, it's great to have you here as backup.

Rahul: Oh, shucks. Thanks, guys.

Paul: Because I will say something patently wrong and you'd be like, "That's a great thought, but," and then you'll sort of finish it off. So, I still feel smart but still you don't let me sound to be too stupid after the fact. So, it's great to have you.

Matt: We get to play the trainee role on these episodes Paul.

[Paul laughs]

Rahul: And I'm the pushover attending who's like, "Yeah, good thought."

[Paul laughs]

Matt: We may be joined by another special guest later on in the episode. But for now, I'll remind you that this and most episodes are available for free CME through VCU Health at *curbsiders.vcuhealth.org*. And with that, we're going to skip over Picks of the Week. Half of the audience is rejoicing at that, the other half is upset. But we're going to start off with an article on ultra-short course of antibiotics. This was from Clinical Infectious Diseases, came out in something like July 2022. And we thought that this was an interesting article. You know, Paul, I like to geek out on stuff like this, shorter courses of antibiotics, anything that might be practice changing. And, Paul, were you excited about this title?

Paul: No, no, no. Not particularly.

[laughter]

Paul: No, [unintelligible 00:03:28] the scientist to Jurassic Park, just because you can do something doesn't mean you shouldn't necessarily do it. But we'll get into it, I guess.

[laughter]

Matt: So, the question they were asking was does mortality or time to hospital discharge differ among adult patients that are hospitalized with the diagnosis of pneumonia, and oxygen sats greater than or equal to 95% if they discontinued antibiotics early? So, that's what they were looking for it, almost kind of the safety of doing this. And this was a retrospective study. So, they looked at it out of a large hospital system, there were four hospitals that they were pulling from, 40,000 patients who were treated for possible pneumonia based on someone checking pneumonia in the electronic health record, when they ordered the antibiotics. And out of that subset, 10,000 patients had sats that met that greater than or equal to 95%. So, they decided, "Let's propensity match just under 4500 patients from that 10,000 patients with the higher sats." And they looked at people treated for two days or less, or people treated for five to eight days. And the results of this, Paul, what do you think Paul? Positive trial, negative trial? We were talking about this a little bit beforehand.

Paul: Yeah, the trial met with my expectations. I would describe this as negative trial, but I don't know what you thought about it. I mean, I know a little bit what you thought about that. Now, I'm pretending to be ignorant, but why don't you tell me what you thought about?

Matt: [laughs] So, basically, I think this was probably a negative trial. They were looking to see is there harm caused by this shorter course versus longer course. And maybe it doesn't matter if we call it a negative or a positive trial. But basically, they found that the patients who were given the shorter courses versus the longer courses, they did not have increased mortality. They had maybe even a little bit less shorter duration of hospital stay, which makes sense, and less exposure to antibiotics. But, Rahul, anything that jumped out to you about the setup of this trial, the things that we need to be cautious of when we're interpreting the results?

Rahul: Yeah, absolutely. You described correctly in the first part of your mentioning this math that this was a retrospective study, so I'll just remind listeners that a retrospective cohort study has a major limitation compared to a randomized controlled trial, which is, by definition, always prospective. And because this was a retrospective cohort study, and not a randomized controlled trial, patients were not randomly allocated to whether they got treated for one to two days versus five to eight days. It was clinicians who made that decision in the real world. And the investigators are now looking back in time to try to figure out comparing those two groups of patients, how did they do with those two strategies.

So, as you can imagine, there's going to be differences between the patients that were responsible for whether a clinicians decided to treat for one to two days versus five to eight days. And this is the central problem of observational research is trying to tease out what really is due to the exposure, in this case, the ultra-short course of antibiotics, and what is due to confounding, which in this case is all of the other things that make clinicians decide to choose to treat the patient for an ultra-short course.

Matt: Rahul, I wanted to prompt here because you gave us a great example before, because I was asking you. So, they propensity match this group, right? So, they could show you this nice table, all these comorbidities and characteristics that they kind of made sure they were similar between the two groups after propensity matching, but I was asking you about residual confounding.

Rahul: Yeah.

Matt: And you made a comparison. I think Ozzy Osborne was involved; can you tell the audience about that?

Rahul: Oh, absolutely. So, to frame this answer to Matt's question, the problem that propensity matching is intended to solve is the existence of residual confounding in an observational study. Because we're not randomizing patients to treatment A or treatment B. We're just looking back at what happened. No matter how good of a job we tried to do to control for confounders, there's always going to be this problem of residual confounding. So, there was a meme floating around Twitter in the past couple days and weeks that I thought just encapsulated this perfectly. And this was trying to find a match for King George III. And it turns out Ozzy Osbourne is a match in the sense that they were both men born in 1948, raised in the United Kingdom, live in castles, married twice wealthy and famous, the list goes on.

But I love the example because it kind of highlights how even if you match on all these things that you can measure, there's still going to be some unmeasurable differences that you're not able to capture with variables like that.

Matt: Yeah, I don't think Prince George snorts lines of ants or whatever [Rahul laughs] Ozzy Osbourne is up to.

Paul: How do we know for sure?

[laughter]

Matt: Paul, but to me, I think that part of the reason they were looking at this, there were some randomized trials looking at this three-day course of pneumonia three-day course versus longer course,

like eight days of treatment that seemed like it was noninferior. And we can link to one of those studies. So, patients who had clinical stability at three days, they decided-- and it sounded like these were more patients we were certain they had pneumonia. In those patients, if there was no difference between or that was least not inferior to stopping at three days versus continuing an extra five days. That's not what this was. This was selected based on the EHR diagnosis of pneumonia. We don't know clinically what was going on. But when you were practicing in the hospital, Paul, did you have patients like this where after two days, you were just like, "Yeah, maybe we should stop antibiotics"?

Paul: I think that's the part that I've sort of struggled with this. I think I might be looking at the question wrong, but I think it's very, very common, at least for me to hedge my bets a little bit, because there's no diagnosis. There's no good building code for just in case. You have a patient who comes in a little bit short of breath, who's got maybe some [unintelligible 00:09:47], but maybe not, who has all the right gestalt for COPD, but they might actually have a bit of heart failure, but also maybe they had a fever at home. So, you just start the antibiotics. And then as they kind of declare themselves after two days, "Oh, that wasn't right," and then stop them. And you treat the thing that's actually going on with them, whether it's that COPD exacerbation or not. So, I can just picture many clinical scenarios where you just weren't sure. So, you start just in case and then deescalate pretty quickly once you actually get more clarifying information. And I don't know how you tease that out, or how you sort of account for that with the data that they were looking at.

Rahul: I sort of feel like this study informs that question very well, Paul, because this study was limited to patients who were saturating 95% and above on room air on all their oxygen saturation values on the first hospital day. So, this study really only applies to patients who are right on the edge, like how you described, these are not patients with dense lobar, infiltrate and hypoxemia on room air. These are those patients who many of whom are unlikely to really have bacterial pneumonia. And this is kind of corroborated by the fact that only 4% of patients in this study had any bacteria identified on a sputum culture at all. And even with the limitations of diagnostics in pneumonia, we know that in community-acquired pneumonia, the rate of culture for bacterial organisms is closer to like 15%. So, the inclusion and exclusion criteria for this study kind of took advantage of selection bias in a way that I think is kind of a strength in that they limited the study population to people who are unlikely to have bacterial pneumonia, and they do just fine without antibiotics.

Matt: So, my take-home from this, about the bottom line, I think that we are good as physicians that work in the hospital of identifying patients when we get that warm and fuzzy feeling, we can stop antibiotics early and looking at people with oxygen sats greater than or equal to 95%. That may be a good way to select out that group or help you think about that. But I do think, listeners, this is why it's important when you see like a top line result, ultra-short antibiotic course is not inferior, you really have to read about it, because this is not telling us that we should just be giving everyone with pneumonia, 2 days of antibiotics instead of 5, 7, 10 days.

Paul: That was exactly the point I was going to make, because the word 'suspected' is in the title and it's doing a lot of heavy lifting there. So, this is not an ultra-short course for pneumonia. It's for suspected pneumonia is specifically what they're looking at.

Matt: I really enjoyed going through this. This gave us a good excuse to go through a retrospective study and talk about residual confounding. I will give this, Paul, three hotcakes, not four or five, three

hotcakes. Definitely an interesting article, and I'll link to the randomized trials that were done with the shorter courses that I had mentioned to in the show notes.

So now, Paul, as I said earlier, I'm curious about magic mushrooms. I don't know too much about them. But tell me what's new with magic mushrooms these days in the world of medicine.

Paul: I'm glad you asked. And I did just want to mention, I'm glad that we skipped past the Picks of the Week because I certainly wasn't going to pick a tangentially related topic to this study. I wasn't going to suggest the David Cronenberg movie, *Naked Lunch*, playing [unintelligible [00:13:11] Film Festival. But anyway, but it's an interesting article, there's always a little bit of sort of low-grade ambient buzz, no pun intended, about management of various substance use disorders with psychedelics. I feel it's always kind of vaguely out there in literature. And this recent article that was in JAMA Psychiatry has looked at the percentage of heavy drinking days following psilocybin-assisted psychotherapy versus placebo in the treatment of adult patients with alcohol use disorder. And this was a randomized, double blind, which we'll get to as much as we're able to, clinical trial in which patients, they received the psychotherapy-- both the control group and the study group received psychotherapy throughout that duration. But the study group received psilocybin at weeks four and weeks eight of their course and they were hoping to see if the administration of psilocybin reduced the percentage of drinking days or [unintelligible 00:14:05] drinking entirely, or even just the amount of alcohol they actually drank. And there's been, again, lots of talk about this. I believe this is actually based a little bit on a proof-of-concept study done by authors a couple years earlier, and they just kind of expanded it and sort of formalized it a little bit.

Matt: Yeah, and I will say if people are interested in this stuff, there is no shortage of podcasts and experts that are making the rounds--

Paul: Ready [unintelligible [00:14:24]

Matt: Talking about various hallucinogenics for substance use disorder, PTSD, refractory depression, all these things. So, it's an exciting area of research. Sorry to interrupt, Paul. So, tell--

Paul: No, no, no, no. It's best to interrupt. There's a lot of me in this-- but in terms of how they did it, there's psychotherapy for all. The study medication was psilocybin, it was given in a plain capsule dosed by weight, so 25 mg/70 kg for the first session, in the study group and then it for the second administration that medication weeks later if they scored low on this test that they gave-- It was actually called the Panhnke, and forgive if I mispronounced this, Richards Mystical Experience Questionnaire. So, if they didn't have a sufficiently mystical experience during the first session, then they got a higher dose for the second session. And then, the control group received diphenhydramine 50 mg the first session and 100 mg the second dose of medications, both groups had to be supervised for eight hours. They were encouraged to lie on the couch and listen to a standardized playlist of music and I would pay so much money to get my hands on the actual playlist. [Matt laughs]

Rahul: It wasn't in the supplement?

Paul: No, was not, I believe I looked. But what they were looking for was basically the decrease in heavy drinking days was their primary outcome. And then, secondary outcomes included things like the mean drinks per day and the percentage of drinking days. And then, they assessed based both on

patient recall of alcohol use, and they did some testing of hair and nails just to see, just to confirm if there's absence or not.

Matt: We should email the authors and ask for the playlist. Rahu., you think they would answer us? I mean.

Rahul: I can't think of a better use of [laughter] our email address than this question.

Matt: I think it was either Weird Al or Pink Floyd Paul, that's my guess. Or maybe a mix of both.

Paul: It's a combination of both. Yeah. All right. I'm not going to editorialize psilocybin and weird out. But I will ask you, Matt, what do you think happened? What would you expect the outcome to be?

Matt: Well, I'd be curious because, Paul, they had a lot of psychotherapy sessions, which I feel like that could bias towards the no hypothesis, meaning it'll be hard to prove a treatment effect if you did a really good job with psychotherapy. Are you going to tell us? Was this a positive trial?

Paul: Yeah, it was a positive trial, and I think will talk a bit more about this, but both groups did better. Both arms, whether you got diphenhydramine, or whether you got psilocybin. Especially in the ramp-up period, even before the medication, just with the psychotherapy alone, both groups actually had a significant decrement in the percentage of drinking days. But then over the course of that 32 weeks, which was the length of the study, there was a greater decrease in alcohol use in the psilocybin arm compared to the diphenhydramine arm. So, both arms, by the way, did better overall, though kind of tapered off, and you had some diminishing returns, but the psilocybin group actually had a greater decrease in the percentage. So, arguing that there is efficacy to administering psilocybin to help manage alcohol use disorder, especially in combination with psychotherapy, if I'm interpreting-- Does that sound right, Rahul?

Matt: Yeah, I think your interpretation is right. I like that you just picked a handle of calling this a positive trial. I agree with that. With respect to the primary outcome, a difference was shown. And then, thinking about what are other sources of chance and bias that could explain that, is the whole point of critical appraisal, in my view, is just asking, like, how could this be wrong? What are the ways in which I could be wrong about my interpretation of this study. So, reading this positive study and looking for sources of chance and bias that could explain that positive finding. And I'll just give one example of each.

In terms of chance, you can actually see in figure two in panel A for those of you following along at home, there is a big drop in the percentage of heavy drinking days from the screening visit, to weeks one to four, the first assessment in both groups. And there's probably several factors contributing to that, one of which might be the Hawthorne effect. People probably behave differently when they know they're being observed. Another factor is something that we've discussed on previous episode of Hotcakes, and that's something called regression to the mean. Anytime you define enrollment in a study based on an extreme value of some variable, you're always going to see that variable go back to its central tendency towards the mean of follow-up. So, this is one example of why it's so important to have a control group. Didn't really matter what the control group is. And I found myself wondering, when reading this paper, "Okay, why diphenhydramine? Is there some secret benefit of diphenhydramine I don't know about?" But really, I think the value isn't just having a comparator, because this way, you know that you're not getting fooled by seeing a big initial decline in patients' percentage of heavy

drinking days. So, that's one example of how chance could create a positive finding. That sort of I think inflates some of the effect size of the change that's seen from the very beginning at the screening visit.

And then in terms of bias, we talked a little bit before getting on air about how blinding was just totally impossible in this study. And, Paul, I know that you had some reactions to the blinding integrity assessments that they did. I don't know if you want to talk about that.

Paul: Yeah, certainly not a criticism because I just don't know a way around it. I'm not sure that you can compare adequately dosed psilocybin to diphenhydramine. And it sounds like, just based on and even the author has mentioned that this is a limitation, it sounds like they've tried in the past things like methylphenidate or niacin or low-dose psilocybin compared to high dose to see if they could mitigate some of that recognition of the treatment arm but it doesn't seem like there's a good way to do it.

Matt: You have to give a hallucinogen, Paul, that you knew didn't work for this. So, they would still be hallucinating. But you knew it didn't work for this, which I don't know that we have that information.

[laughter]

Paul: You're someone who volunteers tribute but yeah, that's exactly right.

Matt: Yeah. And the effect size, Paul, of this, it was more pronounced early on and then towards the end around week 36, the graphs are a little closer together as far as number of drinks per day, heavy drinking days. So, I'm not sure if it's just that they needed to be-- if the treatment effect wore off over time as they got further away, but it did seem like early on there, the graphs, there was more spread between them, and it seemed like it was helping people. But do you think this would be practice changing, or can you talk about the practicality of that?

Paul: Yeah, thanks for sticking around for the bottom line. I think this is exciting. I think anything that we have an armamentarium to deal with alcohol use disorder is exciting. I will say, logistically, these patients were sat with for eight hours at a time for safety's sake. There was fairly intensive psychotherapy that happened over the course of time. So, it involves a lot of resources that I even now don't have access to. I don't know how it would actually be operationalized. And especially since we don't do a particularly good job of prescribing medications that we know work for alcohol use disorder as it is, like they are already widely prescribed, so if you make it even more complicated with something that has a lot of stigma already kind of attached to it, I'm not sure that's going to be happening anytime soon. But I do find it exciting that there might be something we can eventually add to our toolkit. I just don't know what that will look like in the immediate short term.

Matt: And this is another one of those headlines that I just worry about the public is going to be like, "Oh, magic mushrooms. I'm going to just--" People are just unsupervised going to be taking magic mushrooms thinking it's going to treat their alcohol use disorder, when these patients were in very serious psychotherapy, and having very guided, safe-- I guess, as safe as you can, trips with the medication. So, it would be exciting. I think what's this going to look like in the future is there's going to be centers where you can go to and programs that will have to be developed where people can get referred to do this, because the average primary care office isn't going to be able to do this.

Paul: Right. Yeah, and I think even sort of our rudimentary sort of centers for stuff like this are not that great. So, this feels like it's asking for a lot of resources, but I think it's going to be helpful.

Matt: It seems like a lot of people are pumping money into it because it's-- Yeah, I think there's public interest in this if pop culture and the podcasts I listened to are any indication. There's a lot of people very interested in this. And we have to do something about mental health. So, and it's substance use. So, it's good to have tools,

Paul: Anything to pause the conversation, I think, is good. I think that's exactly right.

Matt: Yeah.

Paul: And I will for what it's worth give this three-- we're calling it three savory mushroom hotcakes. So, not really practice changing but I think at least very interesting and may change practice in the future.

Matt: Now, Paul, Rahul has a trial here and, Rahul, is this the ADVOR trial? Because Paul, how do you rate this trial name?

Paul: I am shocked that a cardiology trial [Matt laughs] just dropped the ball on the one-yard line like this. I feel there were so many probable options. Maybe they just ran out of words. I mean, I guess that's possible, but it's not great, Matt.

Rahul: I think it sounds good. It sounds like a Transformer or something.

Matt: Yeah, well, Paul is a big trialhead, Rahul. So, I don't know that you are qualified. I know you have some chops in critical appraisal, but Paul is really-- and ADVOR is just not doing it for him but it's an interesting name.

Paul: I mean, we got [unintelligible [00:23:44] out there and this is just an abject failure. I'm sorry.

Matt: Maybe ADVOR AF is better. Does that make it better?

Rahul: There we go.

Matt: [laughs]. Okay, all right. Rahul, tell us about this study.

Rahul: I love it. Okay, so the name aside, the question that this study was asking was does acetazolamide when added to usual care, which is loop diuretics, among patients who are admitted to the hospital with acute decompensated congestive heart failure, does acetazolamide improve the incidence of successful decongestion by day three? And in this study, successful decongestion was defined as the absence of signs of volume of overload other than trace edema. And this was as assessed by a cardiologist by third day after randomization. There were some important secondary outcomes that you can read more about in the paper, but they included mortality, readmissions. and adverse events.

So, the comparison in this study? The study was done at 27 centers in Belgium, and it included a little over 500 patients out of about 3000 who are screened, so just under 20% of screened patients were included. The patients all had to be hospitalized with decompensated heart failure and they had to have at least one sign of volume overload. They all had to have biochemical evidence of volume overload, so

an elevated NT-proBNP or BNP, and they had to be on the equivalent of an oral dose of furosemide at least 40 mg a day for at least a month. Couldn't have been on acetazolamide or an HLT2 inhibitor. Couple other exclusions in there too. Patients were randomized in a one-to-one fashion to get either acetazolamide 500 mg IV once daily or placebo, plus IV loop diuretics in the total daily amount of two times the patient's usual home dose. So, kind of similar to what we do here.

Overall, patients were pretty well balanced. There is one exception, I'll talk about my interpretation. But just to tell you who these patients were, the mean age was in the high 70s. Basically, everyone was white. The baseline congestions score was a 4/10 in both groups. Everybody had edema, but half of patients had pleural effusions. These patients were decently sick, 30% of them had NYHA Class IV heart failure, and 80% of patients in both groups had CKD.

Matt: And you mentioned the congestion score. I just wanted to highlight what that was. This is a bit different. We talked with Dr. Kittleson about this. And typically, we monitor like JVP we monitor the patient's weight, how the patient's feeling, those are some of the things that I would monitor. If you're into POCUS, you might monitor B lines and JVP with that as well. I mean peripheral edema is something I monitor a little bit, but they were talking about pulmonary edema, or pleural effusions, ascites and peripheral edema here. So, it was a bit of an odd way-- and the scoring system, it seemed like you'd have to be a little bit subjective, and I'm not sure how they were tracking the pleural effusions and the ascites, but it would almost seem like it'd have to be POCUS or-- I don't know, Paul, do you have thoughts on that? I didn't see it.

Paul: I was going to ask the same question, but I was scared to feel dumb. Especially the pleural effusion, I don't know if we're percussing out an air fluid level or the level of crackles, I don't know what that looks like, specifically.

Matt: They had a cardiologist from 1950 and he--

[laughter]

Paul: Three of them.

Rahul: You bring up a good point, though, in terms of how similar or different is this to what our practice is. And I think you're right, Matt, I think a lot of us are much more comfortable kind of thinking about changes in weight, assessing a jugular venous level. And there's sort of a tradeoff between the subjectivity of an assessment and kind of the ease of measurement.

Matt: Yeah.

Rahul: I think this was probably just sort of a practical tradeoff in terms of what can be reasonably assessed.

Matt: Right. So, the congestion score, they gave numbers to edema 0-4, ascites 0-3, and pleural effusion 0-3. So how they did that may be subjective, but the results, I interrupted you there, keep--[crosstalk].

Rahul: Not at all. As Paul said, there's a lot of me in this, [Matt chuckles] so [crosstalk] good. Let me tell you what happened. So, the results of this trial, successful decongestion by day three, the primary

outcome, happened in 42.2% of patients who were randomized to acetazolamide in comparison with 30.5% of patients randomized to placebo. So, that is an absolute difference of 11.7% and that corresponds to a number needed to treat of nine patients to achieve decongestion over three days. And the relative risk ratio for that difference is 1.46. So, about a 46% relative increase in the number of patients who are getting successfully decongested by day three.

The secondary endpoints, I'm not going to spend much time on, but length of stay was shorter by about a day, more patients randomized to acetazolamide were decongested at discharge. But there was no difference in endpoints at three months that included death, rehospitalization for heart failure, and there were no glaring safety signals.

Matt: It wasn't significant, but I noticed that the adverse kidney events and the hypokalemia, hypotension, they trended more towards the treatment group, which I guess you'd expect, but they weren't statistically significant. So, I'm not sure if we had a bigger group, if we would detect that if we started to do this widespread in practice, if that could be a concern, but that just kind of piqued my interest, that signal.

Rahul: Yeah, I think your caution is well deserved. I mean, anytime you're talking about adverse events in the single digits range, one or two adverse events on either side could make the difference in whether or not something is statistically significant. I do think that kind of careful monitoring of this strategy, if implemented in practice would be absolutely required to make sure that we're not overdoing it with patients more effectively decongesting them. Absolutely.

Matt: Is there anything else that you wanted to mention about this? We mentioned that the congestion score was a little bit odd. But I think like-- so maybe if the way that we normally measure congestion, maybe we don't know how this strategy would have performed if we were trying it that way. But would you think this is going to change what you're doing in practice as a hospitalist?

Rahul: Yeah, well, I mean, that is the million-dollar question. And to put my money where my mouth is and walk you through my thinking, this was a positive study, because they did show that the trial drug was associated with some benefit. So, what are the things that could make that wrong? What are the sources of chance and bias that could explain that?

The primary outcome was unchanged from the protocol to the paper. So, that's good, nothing concerning there. I did find one source of chance that could bias towards a negative finding, which actually increases my confidence in these findings. And that's that the patients in the acetazolamide group at baseline required a higher cumulative dose of maintenance diuretics. They were on a median of 60 mg of furosemide equivalents a day as compared to 40 mg a day in the placebo group. So, why would this matter? Well, the subgroup analyses kind of support that acetazolamide might work better in less severe CHF. And this is totally a hypothesis for my part, and I would welcome anybody with more content expertise kind of helping us learn more about this. But looking at the subgroup analyses, the magnitude of the treatment effect was greater in people with LV ejection fractions greater than 40, people who are on less than 60 mg of furosemide for maintenance daily, in people with a baseline congestion score of less than four.

So, those all seem like patients who are presenting with less severe heart failure. And some of the supplemental data really makes it clear that acetazolamide in these patients was really just providing more effective diuresis. They had a cumulative urine output of about half a liter per day or half a liter over the course of the three-study day period more, they had more sodium natriuresis, more sodium loss in the urine. So, I can't really say whether the difference that we're seeing in congestion is really due to acetazolamide or due to just more effective diuresis, regardless of the method.

Matt: Yeah.

Rahul: So, the fact that patients in the acetazolamide group did need a higher maintenance dose of loop diuretic does make me think that, "Okay, maybe we saw a little bit less of a benefit in those patients than we would have seen had that been distributed evenly across groups." So, if anything that kind of increases my confidence in these findings.

Matt: All right. I was going to say, hotcakes. What's your--?

Rahul: Yeah. Absolutely, all those things considered, I'm not really seeing anything to make me worry that this is a very highly selected patient population. It is a limitation that all of these patients are white. So, replication of these findings in a more diverse setting is definitely needed. All of that considered, I think I am ready to give these four out of five hotcakes, because it doesn't take much to get me to use a safe and effective drug. [Matt laughs] So, yeah, four out of five.

Matt: Now, the great Dr. Nora Taranto, our chief editor of the Curbsiders Digest, which comes out twice a month, she was supposed to present an article, but I will try to present it and, Rahul, you can help me out here with the statistical analysis. But this was a trial looking at removal of small, asymptomatic kidney stones. So, they were looking at these small stones, 6 mm or less, and seeing if this improved the primary outcome, which was relapsing stone disease. And that was basically patients who went to the ER for stone, needed surgery for a stone or if there was growth of secondary stones.

This was a randomized trial. It was relatively small trial, 38 patients in the group where they remove the stones and 35 patients in the control group. These were adult patients. But it was a positive trial, there was 75% lower incidence of relapsing stone removal at this 4.2-year follow-up. There was about 16% of patients in the treatment group had a relapse versus 63% of patients in the control group. So, Rahul, anything about the setup of this trial that that you see as a limitation that could have been a source of chance or bias, making this less likely to be practice changing?

Rahul: Yeah, as you were listing the primary outcome, I had to do a double take because this is huge. That's like an absolute risk reduction of like almost 50%, 40-47%. So, you don't see that every day. That's kind of a really large effect size. So, to answer your question, what are the features of this study, in terms of the design and the interpretation that could threaten that really, hugely positive result. So, the only things that really stuck out to me, I always like to verify that the press primary outcome in the study is the same as what was initially registered in the ClinicalTrials.gov Protocol. Or if it's different, that we've at least got a compelling explanation for kind of why that was done. And in this study, the primary outcome was changed. But to my eye, it looks like they actually made it more stringent, because they included some sort of clinical criteria to stone growth, like patients needed to present for

an emergency department visit if they had pain rather than just growth of a stone. And that's something that's pretty patient centered. So, to me, that seems okay.

So, I'm not really finding any sources of chance. You were talking a little bit before we aired, Matt, that because the number of patients in this study was so small, if there really is a big effect out there in nature, you don't need a lot of observations to see it. But anytime you're dealing with a small number of observations, you're really vulnerable to the impact of any one of those things changing. So, replicating this in the real world would kind of increase my confidence that there is a big effect of removing asymptomatic stones.

And then in terms of sources of bias that could explain that positive result, the biggest weakness that I saw here is in their CONSORT diagram, the number of patients who were randomized is reported, but the number of patients who were screened was not reported. So, you really need to know how many patients were screened for enrollment to get even the roughest idea of a quantitative measure of selection bias. Because if this study represents only the smallest number of really highly selected sort of model patients for this intervention, that kind of raises your concern that selection bias could be explaining some of this effect size, you might not be able to replicate these results in the real world. So, very big effect size. Even if this is an overestimate, I'm kind of hopeful that in the real world, there's going to be some benefit to removal of small kidney stones. But I think I'm going to have to wait for somebody with some content expertise and urology to tell me what to make of these findings.

Matt: Yeah, and from what I was reading about this, in the literature, it seems like maybe this is going to be like a shared decision with the person doing the procedure. There's about 25 minutes extra time in the OR on average for patients who are having these asymptomatic stones removed, and they mentioned that was about a 38% increase in time. So, in real world, what would that translate to complication rate wise, and they did a dollar cost analysis of it, and it seemed like it was cheaper than ER visits and recurrent procedures for stones and things. But it's interesting.

For us, we don't have the power to remove these stones, Paul, certainly I would say this is not practice changing for me, but I didn't even know this was like an option that they could do this. Before we had talked to Dr. Goldfarb, he was telling us that they can actually in some cases go up into the calyces and remove stones and discard quickly, which was news to me at the time.

Paul: I do. I'm excited because I feel like there is now a growing body of "while we were in there" literature, between--

[laughter]

Paul: --between left atrial appendage closure for patients with Afib and now this ureteral stone, yeah, we mess around there anyway, I think, as evidence builds, the surgeons [unintelligible 00:38:14] just kind of mess around and take off stuff that bothers them aesthetically, is great. So more of that. Best of luck to all the surgeons out there.

Matt: That's one of my favorite things you said in a while, Paul. There's a growing body of "while we were in there." I like it. I like it. Yeah, we were just, Paul and I Rahul we were recording filming Afib earlier this week, talking about the left atrial appendage surgical closure and they're just like, "Yeah, while we're in there, we'll just sew that thing up." That I still find that funny.

Paul: Just freestyle, man. Patients do better.

Matt: All right, Paul. Well, it's been a long night, Paul. It's a weeknight, it's late. We've done hero's work, four for great articles. And, Paul, can you take us to an outro?

Paul: Happy to. This has been another episode of the Curbsiders bringing you a little knowledge food for your brain hole.

Matt: Yummy.

Rahul: Yummy.

Paul: I thought-- okay, I was waiting for Rahul. It was a good time to shine, man. Get your show notes at *thecurbsiders.com* and while you're there, sign up for our mailing list to get our weekly show notes in your inbox. Plus, twice each month, you'll get our new Curbsiders Digest recapping the latest practice-changing articles, guidelines, and news in internal medicine.

Matt: And we're committed to high-value, practice-changing knowledge. And to do that, we want your feedback. So, please subscribe, rate, and review the show on Apple Podcasts or now on Spotify. You can also email us at ask*curbsiders@gmail.com* And a special thanks to PodPaste who does editing and production for the show. Elizabeth Proto runs our social media. Stuart Brigham's composed our theme music. And until next time, I've been Dr. Matthew Frank Watto.

Rahul: I've been Dr. Rahul Balvant Ganatra.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

Matt: And Paul, I forgot the CME announcement. VCU Health does our CME. Go to *curbsiders.vcuhealth.org*. Paul, you want the last word?

Paul: Still goodbye.

[laughter]

[music]

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