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Pain Management in PKD



Dr. William Bennett

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CME-related Information

This talk is not presently accredited for Category 1.0 CME credit.

Program Objectives and Goals: The primary target audience is nephrology health care professionals. The educational objective is to understand the pathophysiology of pain in PKD, to identify its main causes, and to understand how pain should be approached diagnostically. A further goal is to understand use of pain medications and other therapy options to treat chronic pain in PKD. Posting date: November 11, 2001.

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About the Speaker: Dr. William M. Bennett, M.D. is Retired Professor of Medicine, Oregon Health Sciences University, and Medical Director of the Solid Organ Transplantation Program, and Director of Renal Research, Legacy Health Systems, Portland, Oregon.

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Moderator:

Please take your seats. We are ready to begin. The topic for this presentation is "Pain Management". My name is Marlene Yeldell; I am the coordinator for the Central Ohio FRIENDS Chapter. I am also on the FRIENDS Advisory Committee. It is my pleasure to introduce Dr. Bennett.

Dr. Bennett completed his Bachelor's and Medical degrees from Northwestern University in Chicago. He did his internship at the University of Oregon Medical School and his residency at the VA Research Hospital, Northwestern University. His fellowship was at Mass General in Boston. He is currently the Medical Director of Transplantation and the Director of Renal Research at Legacy Health Systems in Portland, Oregon.

I have his 63-page CV here, so I can attest to his vast accomplishments. I won't mention all of them, but I will mention a few. Dr. Bennett belongs to 28 professional societies. He has been the principal investigator in about 100 different research project grants. He has had 407 medical journal publications and has written chapters or entire texts in 140 different text publications. In addition, he has received numerous awards and honors. In 1998 he received the Jared Grantham Distinguished Achievement Award, which is presented by the PKD Foundation. He has even been listed as one of our nation's top physicians in several guides and publications. I hope you are as impressed as I am. Please help me welcome Dr. Bennett.

Pain Management

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Dr Bennett:

Introductory remarks

Thank you very much. That is softening me up for giving this particular topic, which is Pain Management. Before I start, I would just like to tell you how I would like to do this. I am going to give you about five minutes of philosophy and show you some medical slides about different options and different medications, etc. Then I would like to hear your specific questions because if you have a question, it is liable that somebody else does, too. That, I think, is the best way to get out what your concerns about this issue are.

So first the philosophy. As a practicing physician dealing with kidney patients, I see a lot of patients with polycystic kidney disease. Most of them... it is an unusual patient who doesn't have pain in some form. Just as we are all different in every other respect, the pain is always different. It is different in one individual versus another; even in the same family the pattern of pain is different. And as is true with all pain, the perception on the part of the patient of that pain is the important thing--how they feel, how it interferes or doesn't interfere with their lives--all of those things. So the doctor or whoever it is that you are working with for your polycystic kidney disease, and it may be more than one person... I think the first philosophical thing is, that you need to find somebody whom you are comfortable with and will work with you on your own particular problem. I know somebody is going to ask "How do you do that?", and I don't know. But there are a lot of resources. I think one of the things when you are picking a physician is not so much what discipline they come from or will they work with you? This is a real symptom. It is not anything anybody imagines. It is something that is part of the disease and it is to a greater or lesser extent depending upon the individual. I think as we get into this you will see that I want to make the point that even in the same individual over time those symptoms can change. It takes patience on the part of both the patient and physician to work through to a reasonable satisfactory conclusion to these issues.

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Renal Manifestations of ADPKD

- Hematuria
- Nephrolithiasis
- Flank, abdominal pain
- Infection

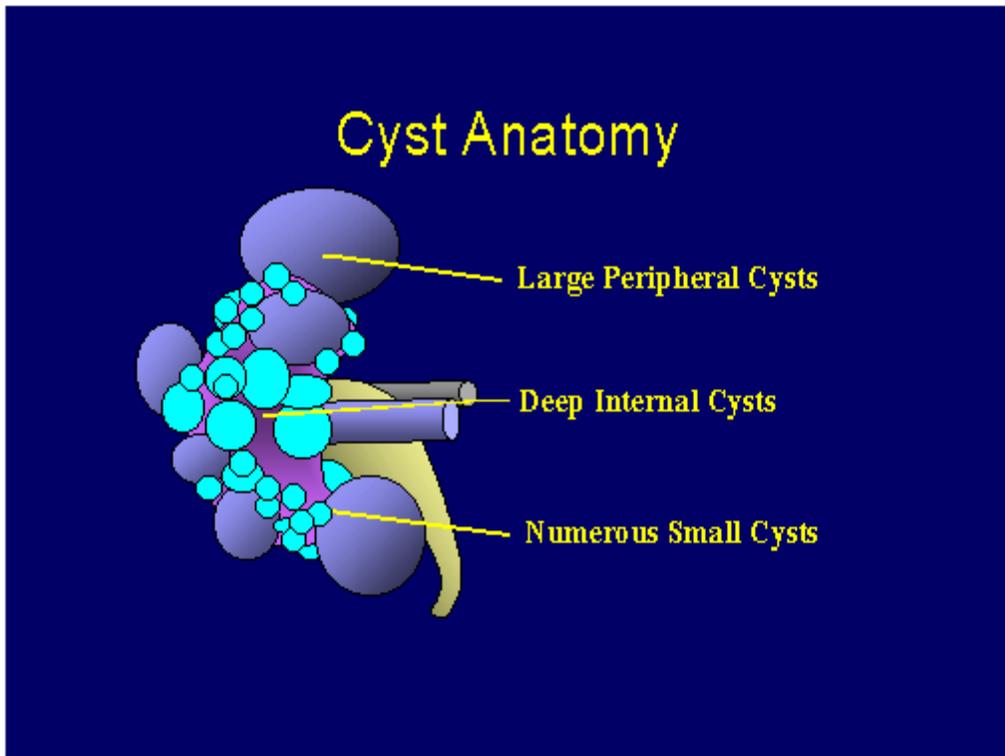
Renal manifestations of ADPKD

Let me just start by hoping the slides advance. The second one is blank because it is in your handout. When I was coming I picked up the wrong slide. So I don't want to show you the slide I had, but the slide that is in there, the second slide. That slide is entitled, "The Renal Manifestations of Polycystic Kidney Disease", meaning those things that are happening within the kidney.

One is hematuria, which is blood in the urine. Blood in the urine can produce pain. It can produce pain because sometimes that blood clots, and those clots have to be passed. When they are passed and they go through the tube that leads from the kidney to the bladder, the ureter, they can produce acute pain. It sometimes can mimic stone pain. So all pain that you have may not be due to the same thing all the time. Most of the time blood in the urine is associated with an aching pain in the back and then people pass either gross blood or clots and it goes away after a few days. The management of that is like you would manage any other acute kind of pain, mostly with analgesics like acetaminophen and other non-opioid or non-narcotic types of analgesics.

The second thing on that list is stones. About 20 percent of people with polycystic disease will pass stones. The stones can be of any kind. They are usually made up of a substance called uric acid. Uric acid is particularly insoluble in urine. When you get dry and dehydrated if you have uric acid in your urine it concentrates and forms a little stone. That, too, can produce severe pain, and usually one passes a stone after a few days. The management of the pain that goes along with polycystic disease stone formation is sort of a subset of all pain, and that is managed differently. What I am going to talk about mostly, though, is the day-to-day, on-and-off pain that you experience with polycystic kidney disease that is not due to an acute event but sort of goes along with the disease.

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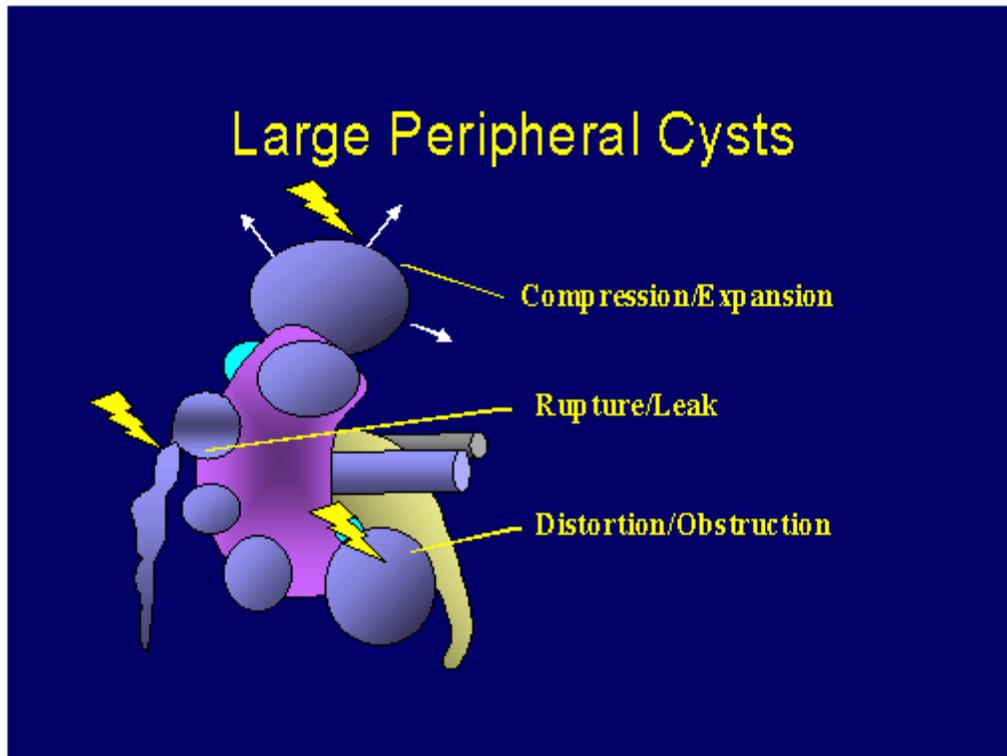
Cyst anatomy

If we look at the anatomy of cysts, you can see that the cysts come in all sizes and shapes. This is important when we think about why pain develops. You can have very large cysts that are on the periphery of the kidney, towards the outside of the kidney; you can have cysts that are internal in the kidney; you can have cysts that press on this tube that goes from the kidney to the collecting duct; and you can have tiny cysts. So each patient with polycystic kidney disease has different sizes and shapes of cysts.

It matters to the physician dealing with you what the anatomy of your particular cysts is. For example, if you had a big cyst like this and it was hurting and you could localize the pain to that cyst, you could simply under ultrasound go down, aspirate the cyst, and some people put in sclerosing solutions that cause the cyst walls after it is collapsed to stick together, and that is it. If you have tiny cysts that are in the middle of the kidney, it is a little more difficult to do that kind of procedure. When you are working with a doctor about pain, they often will want you to get imaging studies so they can tell what the anatomy of your own particular cysts are. And those imaging studies can be either an ultrasound, a CAT scan with dye injected into the patient or not, or sometimes a magnetic resonance study.

It isn't the test that is important, it is who is doing the test and what the facilities are that are doing the tests. So in some locations in the country, the radiologists are very, very good with CAT scanning. In some sections in the country, the equipment for magnetic resonance imaging is sophisticated. In some places in the country, they don't have much of either, and ultrasounds are used. Ultrasounds are very operator dependent. The skill of the radiologist in doing the procedure is important. So it is the skill of the radiologist plus the procedure that makes a difference.

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How large peripheral cysts cause pain

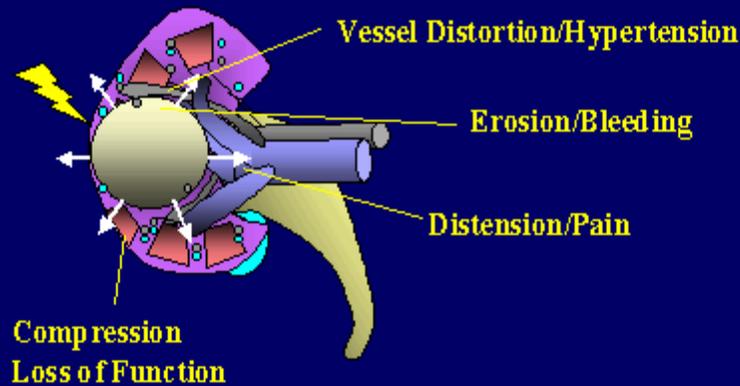
How do these things cause pain? The peripheral cysts tend to cause pain by compressing and expanding adjacent tissue. Sometimes these cysts can rupture and leak, and you know about that. When that happens, you know about it. It is rather severe, acute abdominal pain, and it sometimes goes through to your back, it sometimes radiates around to your groin. Fortunately that acute pain doesn't last too long.

Sometimes when it is happening it is very hard to distinguish from other things that cause acute pain. For example, if the cyst ruptures on the right side and it is in the back, you could have pain in the right lower abdomen and somebody could think it is appendicitis. That isn't so bad. It's the other way around--when you have appendicitis and you attribute it to cystic disease. Just remember that not all pain is the same.

If you've never had one and it happens, probably a medical encounter is a good thing to have. If you've had them all the time, is this the way it has behaved before? Most of these symptoms are treated conservatively, again with sort of low-level analgesics and just time. In a few days, the symptoms go away. Sometimes these cysts can press, as I said, on the ureter, the tube that goes from the kidney to the bladder. If that happens, the flow of urine can be obstructed, and that can give you symptoms. This is usually a more dull, constant pain that goes through to your back.

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Internal Cysts

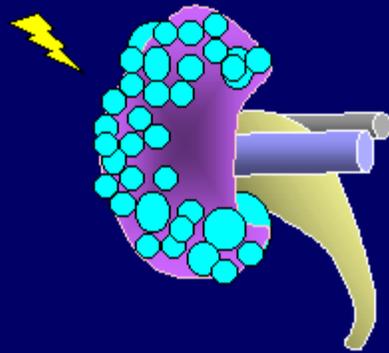


Internal cysts

I put this slide in just to mention that the cysts can be internal in the kidney. If they expand, they can do a number of things--compress on adjacent structures and cause loss of kidney function; they can distend and so the kidney capsule, having some limited ability to expand, can produce increases in pressure inside the kidney; they can erode into blood vessels and cause bleeding; or they can distort vessels and contribute to your high blood pressure. The important thing about these cysts is to know what their anatomy is. There are some techniques now that are available to decompress these kinds of cysts if you got to that stage.

00:00

Numerous Small Cysts



Gradual Replacement
Of Functional Kidney

Significant Capacity
For Pain

Infection Risk

Numerous small cysts

Many patients have very small, large numbers of cysts. They are not spectacular in that the kidneys aren't large and distended. But these kinds of people tend to have lots of pain and are the most difficult to treat because there is something about their kidney that doesn't distend as the cysts distend. This builds up a lot of pressure inside the kidney and seems to be very, very difficult and causes significant capacity for pain. Don't let anybody tell you, "Gee, your cysts aren't so big. They shouldn't hurt. Your kidneys aren't so big. It shouldn't hurt as much as you're hurting. You must not be telling me the truth." The fact is that the pain is real, you are experiencing it, and it is how you experience it, not what the doctor or anybody else thinks you should be experiencing. It is different for everybody. These kinds of patients are a big challenge to treat.

00:00

Treatment Options

- Analgesics
- Cyst Aspiration
- Cyst Aspiration with Sclerosis
- Cyst Reduction Surgery
 - Laparoscopic
 - Open

Treatment options

What are the treatment options that we have? I will be more specific in a minute. We have various kinds of pharmacologic medications that people use to treat pain, with some adjunctive medicines that are used along with them, sometimes which make your response to them more complete or better. Depending upon your anatomy, your individual anatomy, you can have some of these cysts aspirated. This is particularly appropriate in patients with a few huge cysts. You can tell that by the imaging studies. That often works very well. You can aspirate the cysts and you can put sclerosing fluid in there. The sclerosing fluid that is used is either fluid with a high concentration of alcohol, which scleroses things and scars things down inside the cyst, or some people use different kinds of antibiotics that they put in the cyst that causes inflammation and scarring.

This is graded in the order of less to more invasive and serious. The pain that would be required to do these things, working with your physician, would be appropriately severe. The last step is cyst reduction, surgery, and this can be done now laparoscopically or open.

I want to put a few caveats in here. Everybody with polycystic kidney disease who has pain doesn't have their pain due to the polycystic kidney disease. Unfortunately as human beings, you are not spared the ills that befall the rest of mankind. Low back pain and back pain is one of the most frequent reasons why people visit physicians regardless of what else they have. We have learned in some of the studies that Dr. Chapman has done that our back muscle thickness is increased in patients with polycystic kidney disease, probably because these large muscles in your back are trying to cope with an increased volume of something inside your abdomen. So you can imagine if you walked around carrying bowling balls all the time that your back might hurt. Well, you carry bowling balls--some people do--all the time, and your back may hurt. It may be back muscle pain and have nothing to do with the kidneys themselves except that they are there. Likewise, many people, particularly men...even without polycystic kidney disease,

who get a little soft, like I am, and their stomach muscles aren't very flat any more and the go out and they lift up things and they get back pain. Having your stomach muscles not in good shape, which doesn't support your back muscles, can give you low back pain. So I think you need to keep an open mind about what the pain individually is due to. Again, you need to work with somebody so they get to know and you get to know what your own individual symptom complex is.

00:00

Analgesic Medications for PKD Pain

- Aspirin
- Acetaminophen
 - Combinations (ie. Fiorinal, Midrin)
- NSAIDs: Cox-1 Inhibitors/Cox-2 Inhibitors (Selective)
- Opioid Analgesics
 - Combinations (ie. Percocet, Percodan)
- Adjunctive Medications: Antidepressants/
Benzodiazepines, etc.

Analgesic medications for PKD pain

Let's go through the classes of medications. There are so many medicines that are used for pain that I couldn't start to list them. The non-narcotic analgesics are really grouped in the first three: aspirin or acetylsalicylic acid, which is aspirin; acetaminophen, which is the active ingredient in Tylenol; and non-steroidal anti-inflammatory drugs, and they are of two flavors, which I will talk about in a minute. And then there are combinations of these medications in the same pill. Fiorinal is a combination of acetaminophen, a small amount of barbiturate, and caffeine. Especially when these drugs are taken over-the-counter, be sure and look at the label so you know what is in them. Sometimes, and I can't keep up with it, the brand name won't change over time, over 5 or 10 years, but the ingredients will change. So Excedrin in 1980 is not Excedrin today. It just changes. They change with the fashion and the amounts and stuff like that.

From the kidney standpoint, the safest analgesic to take is acetaminophen alone. But as most of you already know, that doesn't work very well. So every nephrologist says, "If you've got to take a pain medication, take acetaminophen." Great. But it doesn't work very well. It does work for some things, and it is worth trying. If you try it, you should try it the way people use it for acute pain. That is one to two tablets, which are usually 500 mg tablets, every 4 to 6 hours. That is the way it will work, and then you will know if it isn't working, as well. So acetaminophen in all of its brands, and there are multiple brands, is very effective for pain, but it has to be used right. You can't take a Tylenol and two or three hours later you say, "Well, the pain hasn't gone away and therefore it is not

working," because that is not the way it is prescribed.

Likewise, aspirin is very effective again used as it should be used for acute pain. It has the downside potentially, in cyst patients, of increasing your tendency to bleed. If you haven't had bleeds, that is not so bad. It won't do it unless you've got something to bleed from. It interferes with the platelet functioning in the blood. In high doses aspirin can act like this class of drugs, which I will get to in a minute. So aspirin is okay to take. There are a variety of brands of aspirin. Sometimes they are combined in the same pill--lower doses of each and they are used together.

Analgesic nephropathy

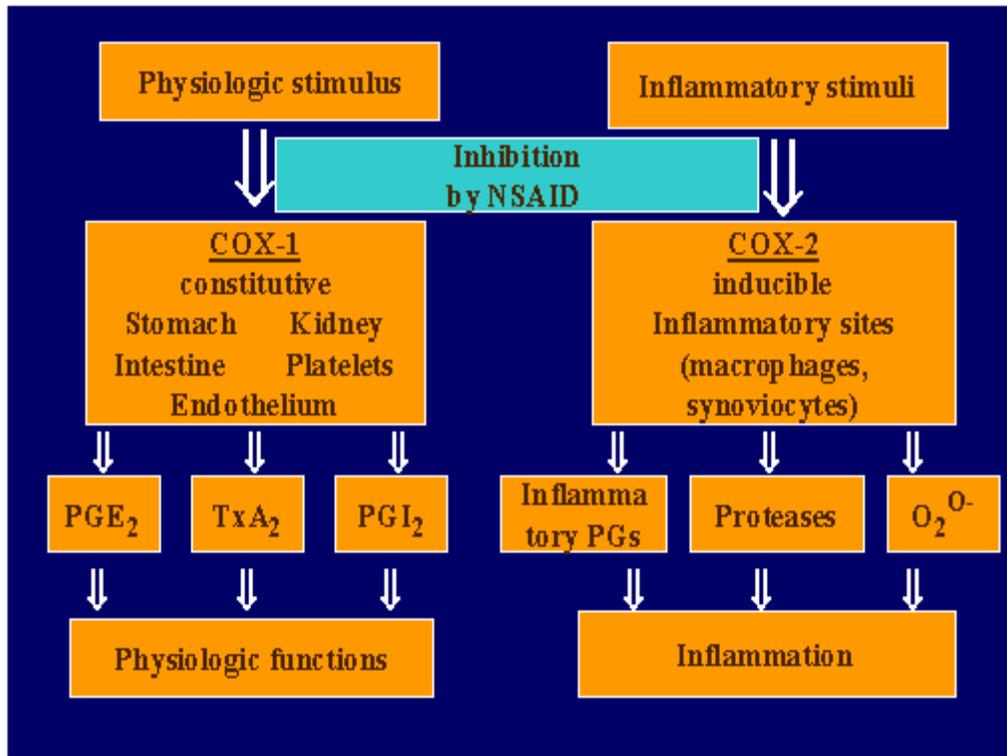
You say, "Well, I have heard that analgesics are bad for your kidneys. How can you stand up here and recommend that?" Well, the reason I can is there is an entity called analgesic-associated nephropathy, meaning kidney disease caused by analgesics. It is quite uncommon in the United States. It is more common in other places in the world. But it takes massive doses over long periods of time to produce that entity. And so on a short-term basis or even relatively short-term basis, these two, the first two, are very, very safe to do. I know it is heresy for a nephrologist to say that, but they are. If you think about it, you have to do something. Unfortunately those are the cards that are dealt at the present time.

NSAIDS

What about non-steroidal anti-inflammatory drugs? These are the drugs like ibuprofen that you can get over-the-counter, plus naproxen, Motrin--there are millions of them. There are two kinds. One is called a COX-1 inhibitor, and I will tell you what that means in a second; and the second type, of which there are now two and there are going to be more, are called selective COX-2 inhibitors. These two drugs right now are Celebrex and Vioxx. These drugs are potent anti-inflammatory drugs. They are very good for acute pain. They are used by doctors in people who have acute sports injuries, they are used to treat acute gout, they are used by most urologists to treat pain associated with passing of a kidney stone, and they are very, very effective.

You are going to say, "But, Dr. Bennett, even you have written papers about how dangerous these drugs are for your kidneys." And I have, and they are. But when they are used for short periods of time in a patient with a doctor who knows what they are doing, they are very, very safe. It is long-term use, use without any limits on the dose, use when you are dehydrated and depleted of electrolytes--that is what is dangerous. So like most potent drugs, they have good sides and bad sides. So I am not afraid to use these drugs in patients with polycystic kidney disease if you are working with somebody for acute pain that you really have to do something about. The alternative may or may not be to give that patient narcotics.

00:00



Cox-1 vs. Cox-2 inhibitors

Let me just show you one slide about the COX-2 and COX-1 business. These drugs work by inhibiting an enzyme called cyclo-oxygenase. So COX is an abbreviation for that. There are two forms--cyclo-oxygenase-1 and cyclo-oxygenase-2. The reason why the new drugs have come into vogue and are highly promoted even on regular commercial television stations is that they seem to be selective for the COX-2 enzyme, cyclo-oxygenase-2. The reason why that is interesting is this enzyme goes up in people who are having acute inflammation and acute pain, usually inflammatory states at the joints, in the shoulders, or wherever you are having it. So the theoretical thing is if you can give a drug that just inhibited this thing that went up with acute pain and spared the one that was found as part of the substance of the kidney, stomach, intestine, and other things, you might be able to reduce the pain without producing the side effects. Unfortunately, the COX-2 inhibitors, Vioxx and Celebrex, in some dosages are nonspecific and they inhibit both COX-2 and COX-1.

Why don't you want to inhibit COX-1? It is too early to throw things at me yet. What cyclo-oxygenase does in the body is very important. It is an enzyme that produces substances called prostaglandins. When you have a decrease in your blood flow to your kidney or any other place, these prostaglandins help dilate those blood vessels back to normal. So they serve a useful function. If your blood flow drops, these prostaglandins help it be maintained as normal. And that happens in the kidney. So you are going along and you have a drop in kidney blood flow for some reason...you're exercising, you're depleted. Just think about it. What do your kidneys do. They save your electrolytes and water, and that is a good thing. You don't want to keep peeing out salt and water if you are dehydrated. The kidney has a very fine-tuned way to regulate blood flow, and the prostaglandins are important for that.

Now if you have a stimulus that says, "My blood flow is decreased; I want to get it back to normal" and you use COX-1 to make all these prostaglandins and that works to get it back to normal, and you come along in those circumstances and give a drug that inhibits

this enzyme, you block the production of these prostaglandins and your blood flow keeps going down and you get kidney dysfunction due to the nonsteroidal anti-inflammatory drugs. So the nonsteroidal anti-inflammatory drugs, like ibuprofen--I will use that as an example, only cause decreases in kidney blood flow when the kidney is under some increased stress. The most common one is diuretics or depletion of body fluids. Under normal circumstances, they don't do much of anything. So if your doctor wants to put you on one of these drugs because you have acute pain for a few days or even a week, you want to make sure that your body fluids are repleted and that you are in good fluid balance. That will make these drugs relatively safe to use for a short time.

There is another kind of kidney toxicity due to these drugs, and that is allergic. But you can't predict that, and it is a very tiny fraction of people who take the drugs. Then there is a third form, and we don't know even whether this form exists. There is a lot of law suits eventually about this. That is, if somebody takes these drugs, not a cystic patient but anybody... takes these drugs for long periods of time because they have arthritis, say, or whatever. Will those drugs act the same as those other analgesics and cause kidney failure just due to those drugs? Most of us think that they have the potential to do that. But because they are released on the market already, nobody is ever going to find that out because the companies that make them have no incentive to find any long-term side effects from them. So you have to be careful.

What I would say to patients about nonsteroidal anti-inflammatory drugs is they are very good pain medications taken with common sense, under the control of your doctor for specific indications, you can use them very, very safely... but not taken for long periods of time on your own without checking in and making sure it is alright. The other thing those drugs can do is they can cause some salt and water retention, and they can raise your blood pressure a little bit. That is another reason why you have to work with your doctor about that.

00:00

Analgesic Medications for PKD Pain

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- NSAIDs: Cox-1 Inhibitors/Cox-2 Inhibitors (Selective)
- Opioid Analgesics
 - Combinations (ie. Percocet, Percodan)
- Adjunctive Medications: Antidepressants/
Benzodiazepines, etc.

Opioid analgesics and other classes of analgesic medications

Let's go backwards. That is the first three groups of drugs. Then we get into drugs that are of the opioid class. You have to develop a little bit of a philosophical thing about using narcotics for pain. Narcotics are great for pain. That is what they are for. I don't think anybody should feel like a criminal or that they are doing something bad if they are using narcotics for pain that they have. They are effective. They work. Used under medical circumstances, they are very safe.

The addiction potential of narcotics when used in conjunction with medical conditions is actually extremely low. The people who get addicted to bad things mostly get addicted when they are taking the drugs for pleasure and have nothing to do with a medical indication. So get that out of your mind. You are not a bad person because you need narcotics to control pain. And there are a variety of drugs and a variety of people who are expert in those kinds of drugs. Some people's pain is such that they need the specialist care of somebody whose professional career is devoted to pain, who know all the tricks. There are skills about giving pain medication. It isn't just, "Here is the pill. Take it." There are various combinations that work better or not so good on certain kinds of patients.

There are many of these drugs you can take orally. There are many of these drugs that are combined with acetaminophen. Percoset is basically oxycodone, a codeine derivative, combined with acetaminophen. Percodan is oxycodone combined with aspirin. There are various brands of these drugs. I didn't mean to promote these. I am just saying there are combinations of codeine, morphine with these analgesics of this class. Again I approach it, personally, in a step- wise way. You don't have to take the medication all the time everyday. You take it in conjunction with what is going on with the patient. There are other things that are called adjunctive medications. What are those? Again, we use these things in non-polycystic kidney disease, as well. Sometimes an analgesic combined with an antidepressant makes the pain better. It isn't that you are depressed or you are in some way flawed because you are taking an antidepressant, it means that drug... and the one that is used commonly is called amitriptyline... is adjunctive to the analgesic property and makes the pain better. There are some people who get pain and get tremendous anxiety with the pain. Anxiety by itself sort of reinforces the pain. And so there is a drug class called benzodiazepines. The drugs in this class are valium, Xanax--drugs like that. They can be very useful. Again, in certain situations to get you over a pain crisis that is worse or better than others.

Now I don't have on this list, because there are too many to put on the slide, the other adjunctive things that people do for pain relief. This includes biofeedback, relaxation therapy, herbs of various kinds, acupuncture--that sort of thing. My view on that is if you have somebody who knows what they are doing and it isn't going to hurt you and you tell your doctor that you're doing it so that you can work with the doctor with it, I think it is okay. And if it helps you, great. We are just starting to learn about these kinds of therapies, and some people are uncomfortable with them because they don't know the mechanism by which they work. Some of the people out there, frankly, who are practicing these alternative things are not the most ethical people in the world and they are happy to take your money. But so are some doctors, I suppose, would be the comeback. I have nothing bad to say about them. They can be helpful in some situations in some people. But you have to be aware of the practitioner. I would try to find out as much about them as you find out about your doctor. There is a woman in Portland, where I live, who is an acupuncturist. We have shared some patients. Sometimes she helps, and sometimes she doesn't help. But that is the nature of the beast.

Key Elements of a Renal Cyst Reduction Procedure

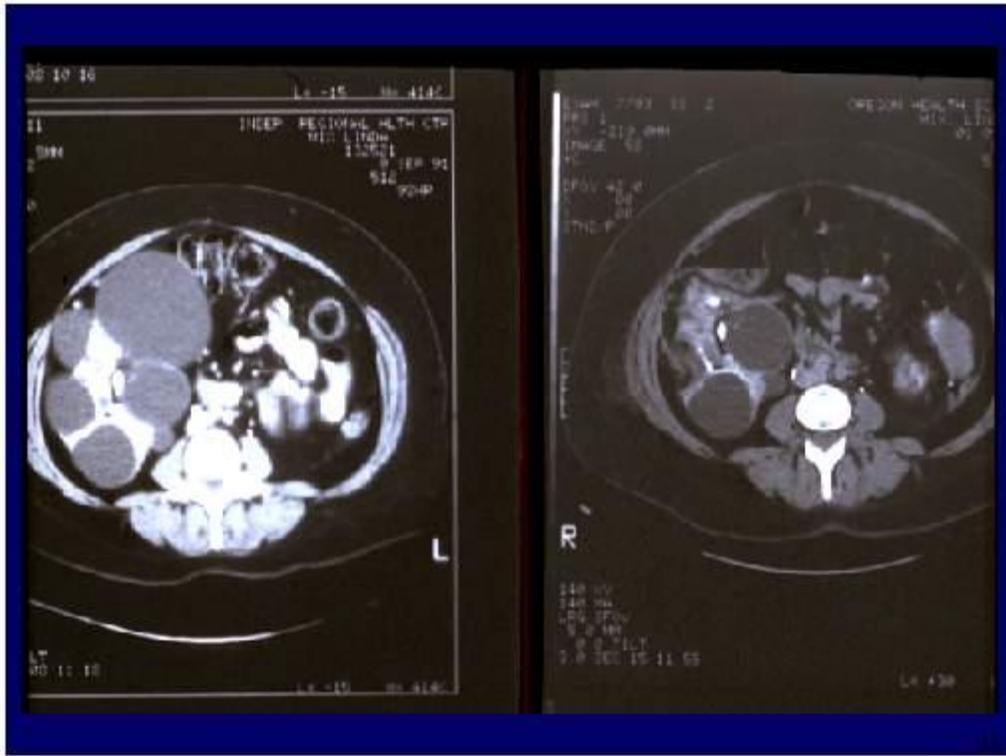
- Preservation of renal blood flow
- Complete exposure of kidney(s)
- Resection of peripheral cyst walls
- Judicious ablation of cyst lining
- Duplex examination of intra-renal vessels
- Aspiration / fenestration of central cysts
- Ablation / sclerotherapy of central cysts

Renal cyst reduction procedures

If you have worked with your doctor and you have tried everything and the quality-of-your life, only you can judge, is being affected by the pain you are having with polycystic kidney disease, then you might be ready for a procedure to reduce the size of the cysts and the cyst volume in an attempt to make your symptoms better.

These are the elements of things that one tries to do. You like to preserve the blood flow to the kidney when you are doing these things. You like to have the kidney well exposed because if you don't see where you are going, it is tough to know the extent of your cystic disease. That is why people will ask you for road maps, namely really good imaging studies. You like to make sure that the cyst walls when you ablate them are removed and try to get the lining of the cyst because the epithelium that Dr. Torres was talking about this morning can secrete fluid and the cyst can come right back if you don't get the lining. We now have this technique where you can look at the inside of the kidney cysts with an ultrasound kind of probe that you can do at the time of laparoscopic or open surgery. For some patients you want to get rid of those central cysts that may be the hardest to get at that are causing the most chronic pain.

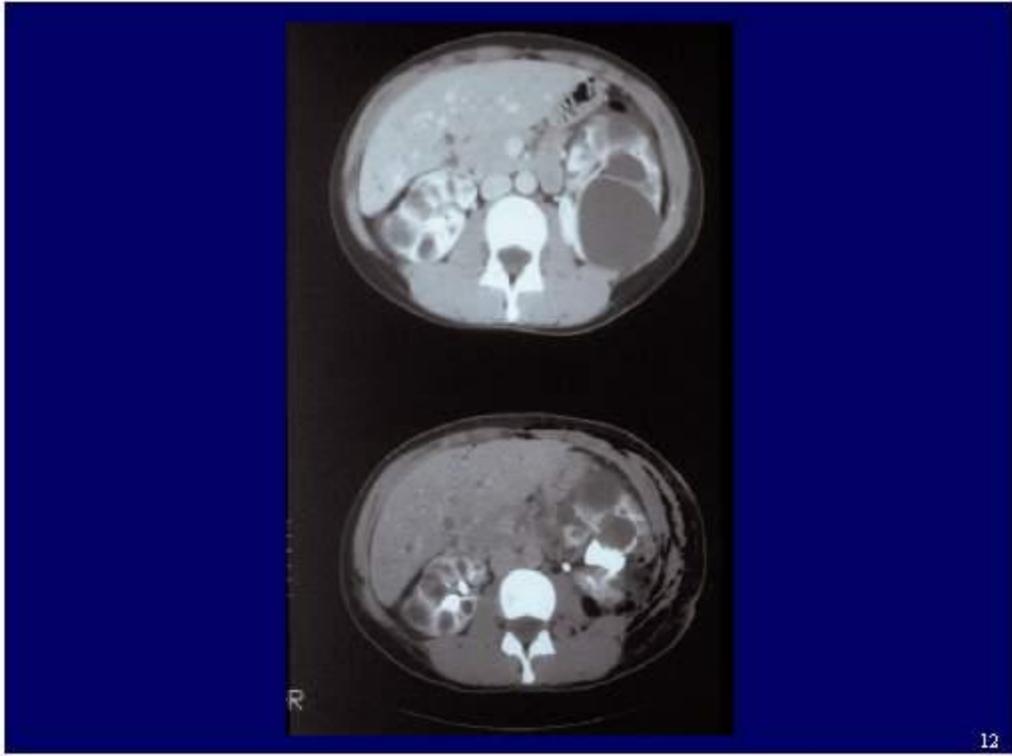
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Cases of renal cyst reduction, before and after CT scans

I will just show you a little show and tell. On your left is a patient with cystic kidney disease. The grey areas are the large cysts. This patient had her cysts reduced laparoscopically. So a laparoscope was put into the abdomen. The abdomen is blown up with some CO2 gas, under anesthetic of course. It is blown up with some CO2 gas so that you can see. The image is projected on a large screen. This is really microsurgery. They get in there and they laparoscopically reduce the cysts. Here is the spine, so this is the back, and here is the front... up here. Here is the stomach. They cut through a section of the bowel. So here is the before, and here is the after. You notice the absence of this particular cyst in this section. This patient did very, very well, was in the hospital for about two days. That was awhile ago, so it might even be shorter now. She recovered without incident and stayed pain-free for about three years. Then she came back with some more pain, and we worked on her again. I think you see it anyway. Sorry, this is off the wall.

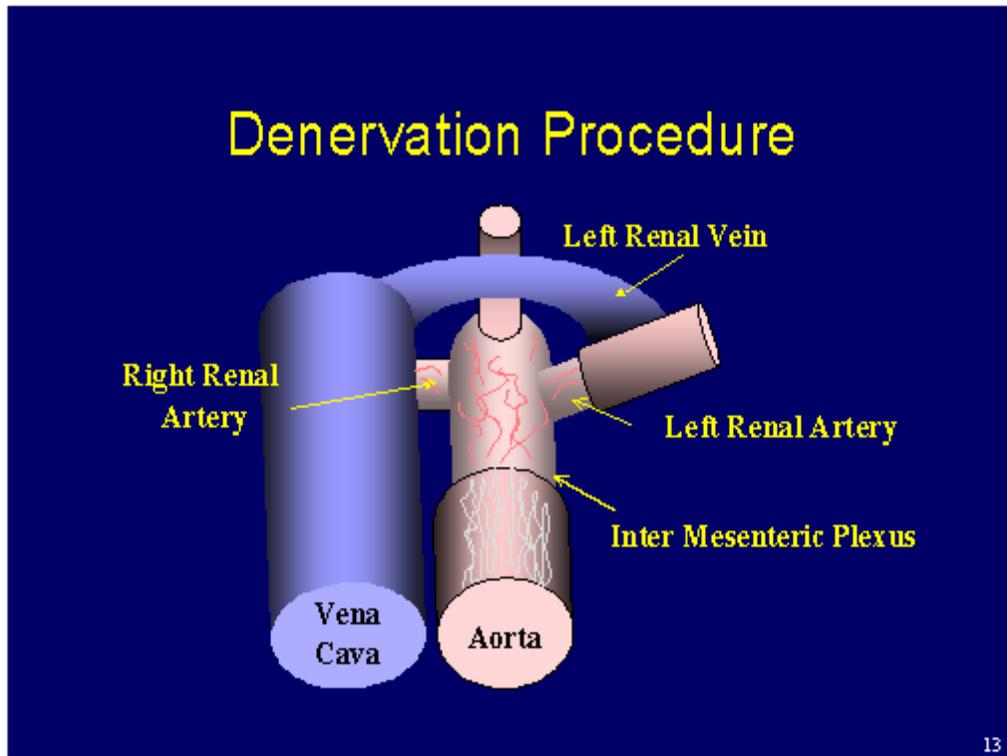
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Cases of cyst reduction: continued

Here is another patient, cysts on both sides but this huge... this is the spine here, so a huge posterior cyst. This is actually a piece of cake for a laparoscopic surgeon. They go in... because it is in the back. Here is the before and here is the after. This cyst was reduced. Having said that these techniques are available, they certainly are not available everywhere. Unfortunately, like with most things in life, you've got to get to the right place and be there at the right time. There is a growing adoption of these procedures at many, usually major medical centers around the country. Probably one of the best in the country is where Dr. Torres works, at the Mayo Clinic. It is probably the best for everything, but it is also the best for this. It is a very good place for these things, and there are other places around the country that do them.

00:00



Denervation procedures

Another little wrinkle that we have added, unfortunately the surgeon who developed this left Portland and is now in Cleveland. The nerves that go down the arteries to the kidney go along the aorta and go down the kidney artery. You can laparoscopically actually cut these nerves that go down to the kidney. With a patient with small, tiny cysts, many of them, there is very little else to offer the patient. The man we did this on first was 42 years old, his serum creatinine was 0.8 mg/dL, he had normal blood pressure, he lost his job because he just couldn't sit there and do his job. Saying to him, "There is nothing we can do" was just not acceptable. He had a family. And so we tried an open surgical procedure. It worked for about a year, and then his pain came back. We did this denervation procedure. It is very laborious. Again, you need a surgeon who knows how to do it. He has been pain-free now for about two years and is back to work and doing fine.

Audience member:

What is this surgeon's name?

Dr. Bennett:

He is in Cleveland. You can ask me privately. I don't want to advertise for him or anything.

Audience member:

Does denervation affect kidney functioning?

Dr. Bennett:

No, it doesn't. Nobody is quite sure what the nerves there do anyway except cause you to have pain. But it doesn't affect kidney function. This fellow's kidney function was fine.

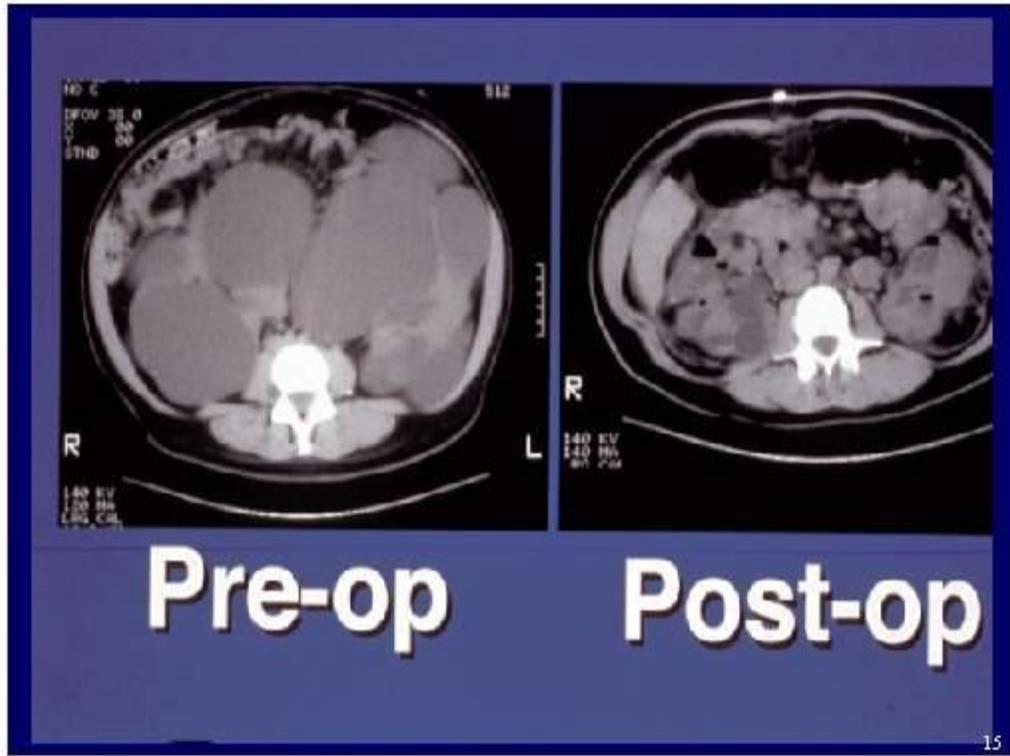
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Surgical cyst removal: examples

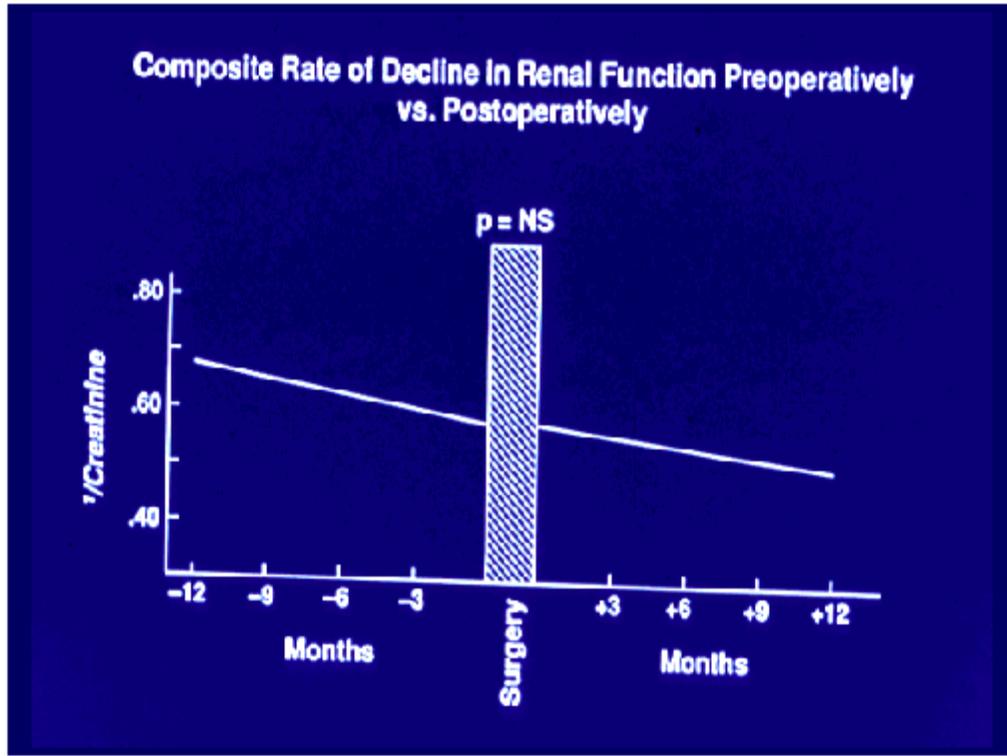
Then if your pain is so bad that it is really interfering with your life and you want the most definitive procedure, then you do an open surgical operation. This is a woman, you can't see the rest of her on the table. This is just her abdomen. This is the head end and this is the bottom end, as you can see. This is preop; this is postop.

00:00



Here is her CAT scan. Most of her kidney tissue was replaced by these cysts. Her serum creatinine was 1.0. Unbelievable. This is a postoperative picture. She had been divorced some time before this was done because of actually the stress and strain of her disease and looking like she was pregnant all the time. She looked like she was 9- months pregnant. She sends me a Christmas card every year. She is about 12 years postop with this procedure. She never had anything else. Her creatinine is still 1.0. She got remarried. I don't know if she is happy or not, but she got remarried.

00:00



Effect of cyst reduction on renal function

One of the things about all of these surgical procedures that is important is what is going to happen to your kidney function when they are done.

We can measure the filtering function of the kidney as the reciprocal of the creatinine. If you just look at this as kidney function, it really doesn't affect it. Initially we had hoped that it would make it better. Unfortunately we've done a lot of surgery now, and it doesn't make it better, but it doesn't make it worse either. The best kinds of patients to do this on who will get the most benefit are people whose quality of life is terrible because of the pain of polycystic kidney disease and who have relatively well preserved kidney function. When you start to get out to massively reduced kidney function, then you have to worry that any stress on the kidney could make it worse and is it really worth it? But we've had gratifying results.

Again, this is a small population of all of those people who have PKD and pain. I think, just to summarize this part, it is very important to find somebody whom you feel comfortable with. It doesn't have to be a nephrologist. It could be a GP, it could be a nurse practitioner, anybody you can work with about these problems because they are real problems. They are just hard to manage. That is all I can say about it. That is why I don't like to give this kind of talk...because it is hard to manage.

00:00

Infection

- Some antibiotics penetrate cysts poorly
- Usually need drug that is somewhat fat soluble
- Not all infections involve cysts
- Can have infection with a negative urine culture

Infection in renal cysts in PKD

Let me just close with a final renal manifestation of polycystic kidney disease. That is infection. This also can cause pain in people with PKD. The pain here is usually either symptoms of a bladder infection, like burning when you urinate, frequent urination, spasms in your bladder, and/or fever. When the cysts are infected, then you are really sick with high fever, severe flank pain. It is one of those things like passing a stone. In polycystic kidney disease, some antibiotics don't penetrate cysts very well. You usually need a drug which is somewhat fat soluble as opposed to water soluble. Unfortunately most of our really good antibiotics for urinary tract infections are more water soluble than fat soluble.

Not all the infections that a patient with cystic kidney disease can get can involve the cysts. Sometimes they involve the substance of the kidney and not the cyst. It is very hard to tell that apart clinically. Just remember, you can have infection in your kidney with a negative urine culture. So if you're doing poorly, losing weight, bad appetite, just sort of chronically ill and your doctor has looked for a kidney infection and the culture has been negative, you still could have an infection. Sometimes these cysts, as you can see by their anatomy, they pinch off and don't communicate with the collecting system in the kidney so the bacteria aren't excreted in the urine, and you don't culture them. That is something to keep in mind.

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Treatment of UTI in ADPKD

- Uncomplicated lower tract: short course oral antibiotics
- Uncomplicated upper tract: hospitalize, parenteral antibiotics → oral
- Complicated upper tract: cyst penetrating, parenteral antibiotics 3-6 weeks

Treatment of urinary tract infections in patients with PKD

How do we treat urinary tract infections in patients with PKD? A lower urinary tract bladder infection should be treated like you would treat any other bladder infection. You don't need a specific antibiotic that will concentrate in the cysts of the kidney. The important thing is to get it treated and treated promptly. If that lingers and it goes upstream, and most urinary tract infections go up into the kidneys from the bladder, that can be a serious thing. For an upper urinary tract infection, which really means kidney infection, that is significant: Most people need to be hospitalized and at least get a few days of antibiotics IV and then switch to oral. If the infection persists and is complicated, that is where you need one of these cyst- penetrating antibiotics, and you need antibiotics for a long term. They don't need to be IV all the time. You can switch to outpatient antibiotics. But that is a serious thing and can cause you to lose kidney function over the long time.

00:00

ANTIBIOTIC CONCENTRATION IN ADPKD CYSTS (N)

| <u>Poor</u> | <u>Fair</u> | <u>Good</u> |
|-------------------------|------------------|-------------------------|
| ** Aminoglycosides (31) | Erythromycin (8) | Metronidazole |
| * Cefotaxime (43) | Vancomycin (43) | Clindamycin (21) |
| * Ampicillin (23) | | * Chloramphenicol (43) |
| ** Ticarcillin (69) | | * Trimethoprim (40) |
| * Tetracycline | | * Sulfamethoxazole (85) |
| | | ** Norfloxacin (91) |
| | | ** Ciprofloxacin (80) |
| * Favorable spectrum | | |

Antibiotics that can be used

What are those antibiotics? This is the list. You don't have to copy this down. I think I gave you a slide. The numbers here just relate to the studies we did to find out if the antibiotics got into the cyst and the number of cysts that we actually did. So they are unimportant. The important thing is some of the antibiotics that normally are used to treat urinary tract infections, like ampicillin, like amoxicillin, like various cephalosporin antibiotics--Keflex (cephalexin), drugs like that--are great urinary tract antibiotics, but they don't get into cysts very well. The antibiotics that get into cysts quite well...some of them get into cysts, but they don't kill the bacteria once they are there. So they are useless. These top two drugs are great, but the bacteria that are there aren't sensitive to the antibiotic. The biggies are trimethoprim/sulfa-methoxazole, which as you know is in one pill and that is Septra or Bactrim; and drugs like norfloxacin or ciprofloxacin or any other kind of -floxacin, which is a group of drugs called the quinolone group of antibiotics. There are some new ones...Levaquin, other drugs. They are good for getting into cysts. As a fall-back position, and hopefully you will never be in this situation... this is a golden oldie that only went out of date when I was finishing my training in the late '60s. It is still around and used in various parts of the world. It is a terrific drug for refractory cyst infections. Unfortunately it has to be given IV.

I think I will quit there. I have left a long time for questions. I would like to hear what you have to say, and we can go from there. Thank you very much.

Discussion

Audience member:

Is Ultram (tramadol) useful to manage pain in PKD?

Dr. Bennett:

Ultram is a possibility. I am embarrassed that I didn't put it on my slide, actually. Ultram is sort of midway between a non-narcotic analgesic and a narcotic analgesic. Altram, I thought, was going to get me off the hook in polycystic kidney disease at one point about five years ago. I thought it was perfect for use in PKD patients. In some people it just doesn't work. In some people it works very well. It is very safe. I think you can use it. It does have the same risks as opiates do in terms of you should take such drugs for defined indications and for a limited length of time, but in the aspirin-allergic asthma situation, I think that would be a good choice.

Audience member:

Where are the best centers specializing in PKD pain management?

Dr. Bennett:

Pain clinics exist all over the country. They are in a lot of places. These procedures are surgical procedures, and they are done by either urologists or general surgeons who are interested in this problem. Besides the Mayo Clinic, there is Oregon Health Sciences University in Portland. The institution where I now work is down the street, but the surgeon who I mentioned that we had who was doing this went to Case-Western Reserve in Cleveland. St. Louis has a very good center for this. As these centers train people, they are in other centers in the United States.

You just have to keep persisting and asking. There is nothing magic about it. It is just that you have to have somebody who knows how to do the techniques or is willing to call somebody who knows how to do them. The techniques are pretty standard. As you know, they do laparoscopic surgery to remove donor kidneys for kidney transplants. In this you don't really have to remove anything. You just have to put the laparoscope in and isolate the kidneys and resect the wall of the cyst. I am sorry I am not giving you a complete answer. There may be other places that are wonderful that I haven't mentioned or don't even know about.

Audience member:

Do people do that cyst reduction procedures post-transplant?

Dr. Bennett:

That's a good question. Most people with PKD who are approaching transplant or are going on dialysis like to have their kidneys because they make some urine. In many people they make normal amounts of urine, and life on dialysis is better if you make urine than if you don't. The indications for removing polycystic kidneys before transplant are infection... if you've got a kidney with chronic infection in it, it best be out before you go on immunosuppressive drugs. The sheer size of the kidney sometimes can interfere with a place to put the transplanted kidney. And that is really a decision that the transplant surgeon has to make. Severe high blood pressure that you can't control by any other means may be another indication for kidney removal, but I've not seen that happen in the last 10 years, the latter.

After transplant, strangely enough, most people with PKD kidneys get smaller and bother them less. Sometimes even if they don't get smaller, they bother them less. Why could that be? Some of the medicines we use for immunosuppression after transplant are derivatives of drugs that suppress cell growth, and that may be a reason. Steroids, as you know, are anti-inflammatory. One of my little tricks, which I didn't put on the slide because only I do it, in somebody who has really severe pain that I think is inflammatory in nature... they've got a little low- grade fever, etc., I will give them a short course of steroids (don't broadcast this to anybody) just to turn off the process for a few days until it gets better. Maybe that is the reason. Most of the kidneys stop bothering people after the transplant.

If it does continue to bother you, you can go back and have the kidney taken out laparoscopically. You say, "How could you get this huge thing out laparoscopically?" You have to remember that when you are doing a donor operation, you want a good kidney. When you are doing a laparoscopic nephrectomy, taking out the old kidney, you can take it out in pieces. You don't care what it looks like once you get it in the bucket. So polycystic kidneys have been taken out laparoscopically. You can do it.

Audience member:

What about coffee and kidney pain?

Dr. Bennett:

I come from the Pacific Northwest. If you can't drink Starbucks, the whole economy of the area goes. There are two things about caffeine. One is the theoretical, and Dr. (Grantham) isn't here, but he is a big believer in this and he said this at one of these conferences about 10 years ago and everybody stopped drinking their coffee. Coffee is a stimulator of this cyclic-AMP that Dr. Torres talked about this morning. So theoretically if you drank enough coffee to stimulate cyclic AMP, that would make your cysts grow and could hurt. That is really a theoretical thing; and I think with the amount of coffee most people drink, it's not really a relevant thing.

Sometimes, though, caffeine acts as a mild diuretic. A mild diuretic in some of those kidneys that have cysts pressing on the collecting system out of the kidney, like any diuretic, can cause acute pain. Urologists, when they are working up patients with obstruction in their urinary tract, often give them a diuretic challenge to see if they will get pain with the diuretic, which means that the narrowing may be brought out and be made symptomatic by the diuretic. So if you have noticed a relationship between caffeine drinking and pain, by all means I think I would stop coffee intake.

Audience member:

If you denervate the kidney, will you have trouble diagnosing other causes of pain, like stones, infection, etc.?

Dr. Bennett:

That is a theoretical risk. We haven't done enough of those, I don't think, to say. In the patients we've done it on, I can't remember that this has happened. But that remains a theoretical possibility.

Audience member:

Why not use the cyst reduction surgery as a treatment for the disease?

Dr. Bennett:

Dr. Torres explained this morning that you have a million nephrons in each kidney. The estimate is that about 5 percent, tops, are cystic. So a million nephrons in each kidney, 10 percent would be a million. Right? No, it would be 100,000. And 5 percent would be 50,000. So if you are going to reduce them all, you would have to find 50,000 of them. They are small, medium, large, very large. The process doesn't stop because you reduce the one cyst and collapse; other cysts are going to grow and take its place.

We thought though originally that that is what would happen-- that we would stabilize kidney function if these cysts, these big ones, that were pressing on adjacent normal tissue were removed, but it just didn't happen. It happened in isolated patients. But we have done about 100 of these procedures over the last 10 years or so, and it just doesn't affect kidney function either way. Before we started this in 1980, it was said in all the textbooks that you shouldn't touch the kidneys, shouldn't do anything because it is going to reduce kidney function. We at least disproved that. But I can't honestly say that we make people better, and probably the reason is that there are just so many cysts.

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