**Episode 5: Pelvic Inflammatory Disease – Part 3**

By Dr. Joe Chappelle

Hello everyone, and welcome back to the OB/GYN Podcast. You are listening to the conclusion of pelvic inflammatory disease where we will be discussing the treatment and prevention of PID. In the last two episodes, we established that PID is relatively common and can have far-reaching and long-lasting consequences. We also noted that although PID is more common in young women of low socioeconomic status, it can affect any woman at any age. In the last episode, we took a deep dive into the history of diagnosing PID and the work still to be done. We talked about how we have no true gold standard for diagnosis, and we touched upon how that makes it so difficult to perform good studies on the topic.

I got some good constructive feedback after the last episode. I was afraid that it might have been a little too dense and hard to follow, and at least some of you expressed that to me. I’m still working on the right balance of scientific details to make it informative but accessible, so I hope you’ll bear with me as I figure it out.

Anyway, let’s get started with Episode 5: Pelvic Inflammatory Disease – Part 3. Just like diagnosis, the treatment of PID has changed drastically over the years. First, I want to go back and start with Bernutz, who we heard about in the first part of the series. In the 1850s, when he practiced, he had few treatments available to him, and so he recommended what was, leeches and rest. The leeches were thought to remove bad blood or infection from the sick, and although they could be effective when placed over surface infections, they offered little to internal infections.

His lack of effective treatments led to a predictably high mortality, which, fortunately for us, he was able to use to give us our first real definition of PID by his numerous descriptions of the autopsies he performed. 20 years later, American gynecologist, Lachlan Aitken recommended transvaginal incision and drainage of pelvic abscesses, which decreased the mortality rate. But again, he had little to offer women if the abscess was not approachable vaginally.

By the 1880s, when Dr. Berry and Freeland published their book, *The Manual of Gynecology*, they had incorporated carbolic acid into their treatment regimen. The antiseptic activity of carbolic acid, or phenol, had first been reported by Lister, in 1867, and by the 1880s was becoming widely used to treat wounds. In their book, they recommended washing drained abscesses with carbolic acid as well as daily vaginal douches with it as well.

Besides the fact that it is questionable that any of the carbolic acid was able to make its way to the upper genital tract, carbolic acid also had the unfortunate side effect of causing second- and third-degree chemical burns. The caustic effects of the treatment most likely cancelled out any of the benefits, but it was a step in the right direction. Doctors were beginning to treat PID as an infectious disease process that could be treated by killing the pathogens, even if they didn’t know which ones they were.

The other treatment that they recommended are more humorous from our perch 125 years later. They included the use of leeches as well as a diet of ice, milk or lemonade and one tablespoon of whiskey to be given every two to three hours. These probably had little effect on the outcome, but they’re interesting from a historical perspective. The caustic effects of carbolic acid pushed the surgical field, of which gynecology is a direct descendant, towards aseptic surgical technique as opposed to post-surgical treatment of infection.

Therefore, beginning in the late 1890s, and continuing up until the discovery of antibiotics, the treatment of choice was laparotomy and surgical removal of the infected organs. This was the approach advocated by Dr. Kelly in his two books on gynecologic surgery published in the early 1900s and was allowed by the proliferation of safe anesthesia and the aforementioned aseptic technique.

The development of antibiotics radically changed the treatment of PID, and there have been numerous studies throughout the years comparing different regiments. The bottom line is that we need to know what we are treating, which antibiotics cover the bacteria that we want to kill, and what aspects of antibacterial resistance we expect to encounter.

Before we get into the current antibiotic recommendations for PID, I want to take that detour into antibiotics that I promised in our first episode. This will not be exhaustive by any measure but will hopefully help us understand why we use what we use.

Antimicrobial substances have probably been used for millennia, and there is documentation about mold and plant-based mixtures in both Greek and Egyptian writings. However, the modern history of antibiotics starts in London in 1928. In September of that year, Alexander Fleming, already famous for discovering lysosyme, returned home from a vacation with his family to find that a plate of staphylococcus was contaminated with a mold, which inhibited the growth of bacteria. He isolated the mold and determined that it was a penicillin mold. In March of 1929, he named that substance penicillin.

His 1929 paper on the finding was mostly ignored, and he eventually gave up his work on it because the mold was very difficult to grow and the antibiotic compound even harder to purify. He was further discouraged because his clinical trial yielded mixed results, most likely because he was trying to use it topically. The first recorded cure with penicillin was in 1930 by Dr. Paine, who used it to cure a gonococcal infection of the eye. Then, in 1939, a group at Oxford were able to cure bacterial infections in mice by injecting them with penicillin. This group discovered how to produce a water-soluble compound that could be mass produced, and by 1944, it was a major factor in the Allied Normandy invasion.

Interestingly, penicillin was not the first mass-produced antibiotic. That honor goes to prontosil, a sulfite antibiotic that was discovered in 1932 in Germany at Bayer labs and first sold in 1935 in the U.S. Although Bayer did not know this, prontosil is actually a prodrug. This prodrug is converted into sulfanilamide after ingestion. Sulfanilamide had been discovered in the early 1900s and the trademark had long expired. When it was discovered that it was sulfanilamide and not the prodrug that had the antimicrobial effects, it set off a goldrush, with hundreds of companies producing it, with various levels of quality.

In late 1937, the Massengill Company started dissolving the sulfanilamide with diethylene glycol, or antifreeze, which as many of you know, is poisonous to most animals. This led to 105 deaths in two months and was the driving force behind the Federal Food, Drug and Cosmetic Act of 1938, which created the FDA to regulate, amongst other things, pharmaceuticals. Over the years, new sulfite drugs have been found, which have less side effects and toxicity, but do all the same fundamental actions.

Alright, so how do these antibiotics work? Well, let’s start with penicillin. Penicillin has a large family tree that remains one of the fundamental pillars of antibacterial treatment. If you remember back to the first episode about PID, when we went over bacteria, you will remember we spent a decent amount of time talking about bacterial cell walls. Now, this comes back into play here.

The bacterial cell wall has many purposes, but one of the most important is to keep the cell from imploding by protecting it from the outside osmotic pressure. Penicillin and its descendants work by disrupting the cell wall, leading to loss of stability and cell death. Penicillin does this due to its beta-lactam ring, which binds to the terminal end of the peptidoglycans that make up the bacterial cell wall. This then inhibits the formation of essential cross links, weakening the cell wall. This does not lead to cell death in and on itself, however.

Bacterial cells constantly remodel their cell wall by degrading portions of it while they replace it with new peptidoglycan. In the presence of penicillin, the degradation still happens, but the new portions do not form correctly, which eventually leads to collapse of the bacteria as the cell wall fails. This action against the cell wall explains why penicillin has strong activity against Gram-positive cells but has little or no action against most Gram-negative cells. This is because, as you might remember from the previous episode, Gram-negative bacteria have their cell wall sandwiched between two cell membranes, and penicillin cannot penetrate that membrane.

Work was done to try to improve the activity of penicillin against Gram-negative bacteria, which led to the creation of ampicillin in 1961. Ampicillin has an extra amino group attached to the beta-lactam ring, which helps it penetrate the outer cell membrane of Gram-negative bacteria. Ampicillin, unfortunately, can only be given IV, as it has poor oral absorption. And therefore, in 1972, amoxicillin was released, which has all the benefits of ampicillin but can be given orally. This greatly increased the availability of antibiotics in non-hospital settings. Penicillins with an even broader spectrum of activity have been created over the years by adding a polar side chain to the compound to facilitate ingress to the Gram-negative cell membranes. These are carbenicillin and piperacillin, but they come with their own drawbacks, namely, sensitivity to beta-lactamases.

Alright, well this brings us to antibiotic resistance. As soon as antibiotics were used, resistance started to appear as bacteria adapted. For penicillins, this takes the form or beta-lactamases. These are produced by bacteria to break down the active beta-lactam ring and prevent their antibacterial action. A number of penicillins were created over the years to resist these compounds and some of them are still used today. These are dicloxacillin, which we use for mastitis, and nafcillin and oxacillin, which are used as the first line treatments of staph endocarditis. Additionally, we have discovered a class of beta-lactamase inhibitors, which allow our previous generation of penicillins to remain effective when given together. These have given rise to some very poplar antibiotics, like Augmentin and Zosyn.

The next class of antibiotics are relatives to the penicillins, and these are the cephalosporins. These compounds also have a beta-lactam ring, but fuse to a six-membered ring as opposed to a five-membered ring in the penicillins. They were first discovered in 1948 by Giuseppe Brotzu in Sardinia, Italy. He found the fungus Acremonium, which was then known as cephalosporium in a sewer and noted that it had activity against Salmonella Typhi, which was known to have a beta-lactamase. It was finally commercialized in 1964 with the first generation of cephalosporins, cephalothin.

The cephalosporins are divided into generations according to their antimicrobial activity. The first generation, which contained cephalexin and cephazolin have good Gram-positive activity but limited Gram-negative activity and no anaerobic coverage. As the generations proceed, they trade Gram-positive coverage for Gram-negative coverage. The second generation contained important surgical prophylaxis antibiotics, like cefoxitin and cefotetan, which are useful because they also have anaerobic coverage. The third generation are potent against both Gram-positive and Gram-negative and include ceftriaxone and ceftazidime. Ceftazidime is important because it also active against pseudomonas, which is a very difficult bacteria to treat. The fourth generation retained all of the Gram-negative coverage of the third generation and also reclaimed the Gram-positive coverage of the first generation, which makes them truly broad-spectrum. This is accomplished by the addition of a zwitterion to the six-membered ring, which gives the molecule both a positive and a negative charge at the same time. The most common example of this generation is cefepime.

There are two more members of the penem family. The first is the carbapenems, which replace the sulfa atom in the ring adjacent to the beta-lactam ring with a carbon, hence the name. They derive from *Streptomyces cattleya* and were released in 1985. These include imipenem, meropenem and ertapenem, and have broad-spectrum activity. Unfortunately, there has been growing resistance to them, and they’re losing their clinical usefulness.

The last group of penems is the monobactams. These do not have a secondary ring attached to the beta-lactam like the other penems. These are only effective against Gram-negative bacteria and are extremely sensitive to beta-lactamases. Aztreonam is the most common member of this group, and despite widespread resistance, it is still useful due to the fact that even people who are allergic to penicillin can take it without risk.

Moving past the penems, we get to antibiotics that act inside the bacteria, on ribosomes. Ribosomes are important to cell health because they synthesize all the proteins needed for cell function, growth and division. Different antibiotic groups act on different ribosome subunits, but they all end in the same outcome. The first group is aminoglycosides. They were also isolated from *Streptomyces*, and the first one, gentamycin, was discovered in 1963.

The antibacterial activity of aminoglycosides is determined by their peak plasma levels, which means that larger doses lead to better activity. Unfortunately, they also have a nasty habit of causing renal damage and hearing loss at high levels, which makes them a little tricky to dose. Aminoglycosides have great Gram-negative activity but no Gram-positive coverage, because the compound cannot penetrate the thick peptidoglycan layer. This is overcome by a fortuitous synergy, where penems can be given to disrupt the cell wall of Gram-positive bacteria, and then aminoglycosides can get into the cell and kill it. This works even if the bacteria has some resistance to penems. The other important members of this group are neomycin, tobramycin and streptomycin.

The second group of ribosome-attacking antibiotics are the macrolides. The two most important of these are erythromycin and azithromycin. These two have great Gram-positive coverage but only slightly better Gram-negative coverage than penicillin. The third group are tetracyclines, which now have limited clinical usefulness due to widespread resistance. The most common example of this group is doxycycline, which is still used today for chlamydia, mycoplasma, syphilis, Lyme disease and malaria. The last group is lincosamides, which includes clindamycin. Clindamycin is important because it has great Gram-positive coverage, including for some MRSA and also, importantly, anaerobic bacteria.

The next class is the quinolone antibiotics, which have gotten a lot of bad press recently due to their unfortunate propensity to make tendons rupture. These were discovered in 1962 and work by preventing DNA from unwinding, and thereby preventing cell division. Like the cephalosporins, these are divided into four generations, but here it’s backwards, where increasing generations have better Gram-positive coverage. First generation are not used anymore. Second generation includes ciprofloxacin. Third generation, levofloxacin. And fourth generation, moxifloxacin. Fourth gen compounds have two targets on the bacterial DNA, which is responsible for its broad activity and lack of resistance.

The almost last class of antibiotics, and I swear we’re almost done, brings us back to sulfonamides. These work by inhibiting folate synthesis, which is essential for bacterial growth. The sulfa drugs have good Gram-positive and Gram-negative coverage, but also have a high rate of allergic reactions, some of which, like Stevens-Johnson’s, can be quite severe.

Now, the absolute last class of antibiotics, and I promise, that I’m going to talk about today is metronidazole. It was first sold in 1960 and works by causing free radicals to disrupt DNA. Interestingly, in order to function it must be partially reduced by a process that only happens inside anaerobic bacteria, and this is why it is only effective against this group of bacteria.

Having this kind of high-level knowledge about antibiotics is essential when choosing the right medication. If you know what you need to cover, then you can decide which combination of antibiotics are needed. Most hospitals also now know what common bacteria are usually resistant to in their hospital, as this can change from place to place. With all of these three factors, you can get it right every time.

Okay. Now let’s go back to treatment. As new more broad-spectrum antibiotics became available, the treatment of PID drifted more and more away from surgical treatment. When choosing antibiotics for PID we must remember that PID can be caused by a lot of different types of bacteria. It can be caused by gonorrhea, chlamydia, aerobes and anaerobes of both the Gram-positive and Gram-negative varieties. This means that we need to use the most broad-spectrum coverage possible. In earlier years, this took several different antibiotics to accomplish, but now, with the newer classes of drugs available to us, it can be done with one or two antibiotics and much more cheaply.

There are a lot of studies involving different treatment options for PID. I am not going to spend any time reviewing these for a couple of reasons. The first is that they’re mostly no longer relevant because they were product of their time in that they compared the antibiotics that were available to them when they did the studies. Additionally, as resistance has grown, some of the antibiotics studied are no longer great options.

There is one study that I do want to touch upon, and that is the PEACH trial. PID was treated was an inpatient admission from the time of Bernutz all the way up until the 1970s. As oral antibiotic choices became more available, considerate effort was made to move treatment outside of the hospital. Although there were many studies examining the efficacy of this approach, it was really the PEACH trial, published in 2002 in AJOG that cemented its efficacy and safety.

In their study they followed 831 women with mild to moderate PID based on clinical findings. Half of the women received inpatient treatment with cefoxitin and doxycycline, and the other half, outpatient treatment with a single shot of IM cefoxitin and oral doxycycline. They found no difference in fertility, ectopic pregnancy rate or chronic pelvic pain between the two groups in the mean follow up of 35 months.

The current CDC recommendations take this into account and therefore recommend outpatient therapy as first-line treatment, except in the following circumstances. One, tubal-ovarian abscess, because higher circulating levels of antibiotics are often needed to treat these, and sometimes, that doesn’t even work, and surgery is needed to remove them. Two, pregnancy, as these rare cases are often much more severe. Three, severe illness or sepsis, which makes sense. Four, if the patient is unable to tolerate or follow an outpatient course due to nausea or social reasons. And lastly, five, if they have previously been in an outpatient regimen and failed to respond.

For IV treatment, CDC recommends the use of second generation cephalosporins like cefotetan or cefoxitin to treat Gram-negative and -positive aerobes and anaerobes, along with doxycycline, for its activity against chlamydia and mycoplasma. If women are clinically improving after 24 to 48 hours of IV treatment, women can be given doxycycline for a total of 14 days orally. If the woman is allergic to penicillins or cephalosporins, then similar coverage can be achieved with clindamycin, which as you remember covers Gram-positive and anaerobes, and gentamycin, which covers Gram-negatives. These women can be discharged home with clinda and doxy for a total of 14 days.

The oral treatment is similar to the PEACH study, with women receiving a single IM shot of ceftriaxone and then doxycycline for 14 days, to which metronidazole can be given as well to better cover anaerobic bacteria.

A couple of other little notes regarding treatment are that all sexual partners within the last 60 days should be tested and treated for gonorrhea and chlamydia, and that all women should be re-tested for these organisms three months after treatment if they tested positive at the initial examination. The last little topic to touch upon is IUDs. There is a common misconception that IUDs increase the risk of PID. This is actually true, but only for the first three weeks after insertion. If a woman with an IUD in place is diagnosed with PID, the CDC recommends keeping the IUD in place unless they do not respond to treatment, in which case they advice pulling the IUD, although they themselves admit that there is no evidence to support that recommendation.

Alright, so the last topic I want to talk about today is prevention of PID. This is an interesting idea, because what this really means is preventing infections with the organisms that cause PID, or at least treating them before it progresses to PID. So, prevention is a little bit of a misnomer, I think. Well, regardless of what we call it, several studies have been done on screening and treating women with asymptomatic chlamydia infection, and they followed the outcomes.

The first study I want to talk about was published in the New England Journal of Medicine in 1996. In that study, 1,009 women were screened and treated for chlamydia at the start of the study, while an additional 1,598 were only screened if they had symptoms or requested a screening. 7% of the immediate screen women had chlamydia. 9 women in that screening group developed PID in the 12-month study, of which 7 of the 9 had tested positive for chlamydia at the beginning of the study. In the usual-care group, there were 33 cases. This translated to an incidence of 8 per 10,000 women in the screening group and 18 per 10,000 in the usual-care group. And although the absolute number of women with PID in the 12-month study is not large, each case represents a significant cost, as we discussed previously.

The second study is from England and was published in 1910 by the British Medical Journal. This is an interesting study, so bear with me a minute while I describe it. The authors randomized 2,529 women into two groups. All women provided a self-taken vaginal swab at the start of the trial. In one group, the samples were frozen, and the women received normal gynecologic care as in the previous study we talked about. In the second group, the samples were tested for chlamydia immediately and the women were treated if positive. They followed both groups of women for 12 months.

At the end of the study period, they tested the remaining samples for chlamydia, the initial rates of chlamydia were similar in each group when compared at the end of the study, with approximately 5.5% of women testing positive. They also found that 1.3% of women who were treated at the beginning of the study developed PID, versus 1.9% in the non-screening group. Interestingly, but not surprising, is that almost 80% of the women in both groups who developed PID were negative for chlamydia at the time of treatment. So, again, there was a very small difference, but 0.6% when multiplied over a population can have meaningful impact.

To try to sum up both papers, I would say that the probability of being diagnosed with PID is directly related to the length of infection with chlamydia or other causative agents. So, not surprisingly, if we interrupt that course early, we will decrease the number of severe infections, or otherwise called, PID. To me, this is a strong call for more aggressive screening and treatment.

Okay, well that’s it. Amazingly, we’ve made it to the end of PID. There are a few take home points from these three episodes that I want to emphasize. The first is that it is so, so important to know how we arrived at our diagnostic and treatment guidelines. In the case of PID, it is valuable to understand that with multiple causative agents, each with their own disease course, that a single definition is going to be problematic. Until we can more accurately determine which bacteria is causing each woman’s symptoms, then we need to continue to cast a wide net, because the consequences of undertreating can be devastating.

Secondly, the idea of a flawed gold standard is also important. When I read papers, I always look to see what test they use, but I rarely take the time to investigate the validity of those tests. My research for these episodes is making me rethink those assumptions. If the foundation we build our studies on is invalid, especially in treatment studies, then the best-designed research is doomed to fail.

Lastly, I now believe more strongly than ever that we need to be more aggressive in offering screening in women and men at risk for gonorrhea and chlamydia. The more we treat asymptomatic people, the more we prevent the downstream and often irreversible consequences, especially infertility and chronic pelvic pain.

Well, thank you for wading through this topic with me. I learned a lot and I hope you did as well. Now, if the starts align-up then the next episode will be something a little different. And I’m excited about that. After that, I’ll be pushing forward to tackle of the nearest and dearest topics to my heart, contraception, and I hope that you’ll join me.

So, until next time, thank you all for listening. And for my U.S. listeners, I wish you a happy Thanksgiving.