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February 2013

INFECTION PREVENTION: SSI PREVENTION FOR COLECTOMY

Hello everyone. This is Patchen Dellinger from the University of Washington, and I'm going to talk today about surgical site infection, prevention for colectomy, and I want to cover bowel prep, yes or no, oral antibiotics, and is there a best IV antibiotic or not.

On this first slide we have a look at the rate of infection reported for various types of operations when prophylaxis is used compared to when placebo is used. And you can see that there's quite a range reported, but in all cases prophylaxis results in lower infection rates than placebo, and this is referring to intravenous prophylaxis. And in the last column over here on the right you see the number needed to treat with intravenous prophylaxis in order to prevent a single surgical site infection. And if we focus on colectomy there's a high rate of infection when prophylaxis is not used, and so you need treat only a relatively small number of patients to prevent an infection.

Now when I started my residency in 1970 all patients having colectomy got a bowel prep as in-patients before their operation. And we had just seen the first widely believed paper that demonstrated the beneficial effect of intravenous antibiotics. In those days oral antibiotics were not being used for colectomies. And in the early '70s Ron Nichols did the paper referenced here, in which he showed that even if you cleaned out the colon quite significantly with a good bowel prep so that there was no gross feces evident, it did not change the actual numbers of bacteria present in what fluid remained. And so the question arose as to whether it would be beneficial to reduce those numbers using oral antibiotics.

The first study done was by John Washington and colleagues at Mayo Clinic. And they compared patients getting a placebo, getting neomycin alone, or getting neomycin and tetracycline. And what you can see is that neomycin and tetracycline resulted in a dramatic reduction of surgical site infections, from more than 40% down to 5% only. What you also see, as illustrated here, is that giving neomycin alone was basically not much better than giving a placebo. Now neomycin covers the aerobic and facultative bacteria like *E. coli* and other gram negatives. And the tetracycline covers the anaerobes. So what this study showed was that you really need to have an agent that is effective against both the aerobes and the anaerobes in order to achieve significant reduction in surgical site infection.

The next study was a study done by Clark and colleagues, including Bob Condon and Ron Nichols, and they used neomycin and erythromycin compared to placebo and showed a similar reduction in infection rate from more than 40% to less than 10%. This was followed by a study looking at neomycin and metronidazole, again, with significant reduction in infection rates, and then a study of kanamycin and erythromycin, again, getting very low infection rates.

So in a five-year period there were four studies done, all showing dramatic reduction in surgical site infections caused by oral antibiotics compared to placebo. And in these four studies, only oral antibiotics were used and not intravenous antibiotics.

Now a little bit later this very interesting study was done by Allen Kaiser and colleagues, in which they compared intravenous cefoxitin for one group of patients and oral neomycin and erythromycin for the other group of patients. What you see is that for short operations lasting less than four hours there was a



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similar efficacy of preventing surgical site infections. But for long operations the oral antibiotic group actually did better than the intravenous antibiotic group. Now this is just an observation, and we don't have an official explanation, but one plausible explanation for this is that cefoxitin has a relatively short half-life. So for long operations there were no longer effective drug levels available at the end of the operation, and this exposed the patient to infection from the bacteria that still remained at high levels in the colon because no oral antibiotic was used. But in the group getting oral neomycin and erythromycin there were low levels of bacteria exposed to the wound, and they continued to be protected.

Now in this interesting study done in England, Dr. Keathley tried to compare, again, oral antibiotics against intravenous antibiotics, but unfortunately there was a significant defect in this study, and that was in the oral antibiotic only they stopped the metronidazole 36 hours before the operation. The idea was that Keathley knew metronidazole could be absorbed, and he didn't want to have any in the system. Unfortunately what that did is it meant that the oral group basically was ineffective, and what you see is there was a high rate of infection. Basically it's as if the oral group was getting neomycin only because the metronidazole was stopped so far in advance of the operation that it was no longer effective.

Sometime in the 1980s most American and Canadian surgeons adopted oral antibiotics, while most European surgeons abandoned oral antibiotics, perhaps because of the results of that badly designed study by Dr. Keathley in 1979. More recently, Ron Lewis in Montreal did a study looking at the infection rate after colectomies and comparing patients who got intravenous antibiotics only against patients who got intravenous plus oral antibiotics.

The first thing that Ron did was that at the end of each colectomy he cultured the subcutaneous fat, and what he showed was that if the culture of the fat was negative there was a 2% infection rate. But if the culture of the fat was positive there was a 17% infection rate. So the number of the bacteria detectable in the wound at the end of the operation clearly made a difference in infection risk. What he also showed is that if the patient got intravenous or systemic antibiotics only, 60% of the patients had a positive culture subcutaneous fat; whereas if the patients got a combination of both intravenous antibiotics and oral preoperative antibiotics, only 30% of the subcutaneous cultures were positive. And so as you might have expected, patients that got intravenous antibiotics only had an infection rate of about 17%, but this went down to 5% when intravenous antibiotics and oral antibiotics were used together.

Ron went on and did a meta analysis, and here you see odds ratio. So one means there was no different between combined regimens or intravenous alone, and you can see that most of the study showed a benefit or a lower infection rate when oral plus intravenous antibiotics were given. And out here we have the combination of all of the different studies together showing a significantly lower infection rate for the combination of oral plus intravenous antibiotics and confidence intervals that do not cross one, P value 0.0001.

Now around this time a number of surgeons, in Europe in particular, were comparing patients who got mechanical bowel prep versus patients who did not get a mechanical bowel prep. But they were studying patients who did not get oral antibiotics, who only got intravenous antibiotics. And this paper in the Annals of Surgery 2009 shows basically that there was no significant difference in terms of anastomotic leaks, and in the next study no particular difference in intra-abdominal abscesses, and no particular difference, no significant difference of surgical site infection when you compare getting a mechanical bowel prep or no mechanical bowel prep in patients who were getting intravenous antibiotics but no oral antibiotics. In



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fact, there is a hint of a suggestion that it might even be beneficial not to get a mechanical bowel prep for surgical site infections. But, remember, none of these patients were getting oral antibiotics.

This was followed with two different Cochrane systematic reviews. The first review by Gwenaga [ph] showed a similar result to what Slim had shown in the Annals of Surgery; that is, if you get a mechanical bowel prep and IV antibiotics, or no mechanical bowel prep and IV antibiotics, there's not a significant difference. And the small differences that do show up seem to favor not getting a mechanical bowel prep. But Nelson did another Cochrane analysis at the same time. He compared patients who got a mechanical bowel prep in both groups, got intravenous antibiotics in both groups, but only one group got oral antibiotics, and the oral antibiotics had clinically significantly and statistically significantly fewer infections than the patients who did not get oral antibiotics. This is true if you look at selected trials or in this slide look at all trials from the Cochrane analyses.

The next bit of information we have comes from the State of Michigan, where a very nice surgical collaborative has been going on for a while. And they looked there at over 1,600 patients having colectomies, and they saw that 11% did not get any mechanical bowel prep. 36% got a mechanical bowel prep and oral antibiotics, whereas almost 50% had a mechanical bowel prep without oral antibiotics. When they looked at the infection rate, mechanical bowel prep without antibiotics and no mechanical bowel prep at all had very similar infection rates, similar to the Cochrane analysis. But mechanical bowel prep and oral antibiotics combined with intravenous antibiotics cut the infection rate in half.

Now some surgeons have suggested that it's nice to avoid oral antibiotics because it might increase the risk of *C. difficile* colitis. And I guess I'm ahead of myself. Here, this just shows, again, deep incisional organ space superficial and overall SSI rates with and without oral antibiotics. And, again, they always were better with oral antibiotics. And when they looked at their *C. difficile* rates, the *C. difficile* rates were actually lower in patients who got oral antibiotics, although this small difference is not statistically significant. And interestingly, the patients who had the bowel prep and the oral antibiotics had a shorter period of postoperative ileus. They published their data analyzed, again, on *C. difficile* colitis, and again showed that there was no deficit. In fact, the patients with oral antibiotics here had a lower rate of *C. dif* than those who did not get oral antibiotics.

Now another study that was done a bit later was this study by Anthony and colleagues from a hospital in Texas. And Anthony read the literature and said, "Gee, I see studies showing that you don't need to use a mechanical bowel prep." And they decided to do a study of what they called a "bundle." And in their bundle they decided to eliminate bowel prep, which they had previously been doing, eliminate oral antibiotics. They added preoperative warming, which is probably a good idea, and intraoperative warming, and they increased the oxygen concentration, which is probably beneficial, and they added a wound protector. And, of course, everybody got intravenous antibiotics.

Well, what they ended up showing was that they basically doubled the infection risk. And probably the primary element leading to an increased infection rate in this study was the elimination of the mechanical bowel prep and the oral antibiotics.

Now in another study Cannon and colleagues published just in the last part of the previous year looked at 9,940 patients from 112 different Veterans Administration hospitals. And again they showed some results similar to the Michigan results. Patients who got a bowel prep without antibiotics, that happened about 39% of the time, and they had a 20% infection rate. Patients who got no prep and no antibiotics, that



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happened about 20% of the time, and their infection rate was similar. So it didn't benefit the patients to get a bowel prep without antibiotics. But bowel prep plus oral antibiotics had an infection rate of about 10%, and that was about a third of the patients. A very small number of the patients got oral antibiotics without a mechanical prep. And this is something that's never been systematically studied, and it happened only in a small number of patients, but they also had a relatively low infection rate. And it makes me wonder whether somebody should do a study of oral antibiotics without a mechanical prep, which, of course, patients would welcome, rather than aggressive bowel cleanout, which nobody enjoys.

Cannon and colleagues also looked at the percentage of cases in each facility that got oral antibiotics, and it varied from zero patients getting oral antibiotics up to 95% of patients getting oral antibiotics, and this blue line indicates the average facility surgical site infection rate, and you can see that there seems to be a clear relationship to more oral antibiotics and lower SSI rate.

In another study, Hahn and colleagues, again, looked at the same VASQIP data in a slightly different group of patients, over 8,000 patients, and showed similar results. 44% of their patients got oral antibiotics and bowel prep, 39% mechanical prep without oral antibiotics, and 17, or one patient in six, no prep at all. And interestingly, they showed that oral antibiotics plus bowel preparation resulted in a shorter length of stay for those patients and a reduced rate of 30-day hospital readmissions. This was recently presented at the Southern Surgical Association and is available only in abstract form at this time. But I got this from the American College of Surgeons surgery newspaper that we all get in the mail.

So my conclusions are that if you're not going to give oral antibiotics then you probably don't need a mechanical bowel prep. But if you're taking my colon out I guess I will choose to suffer through the bowel prep and take oral antibiotics in advance of the operation in order to achieve the lowest possible surgical site infection rate. And it would be great if somebody would study in a systematic fashion whether oral antibiotics work without a mechanical prep. It's hard to imagine, but then in medicine and in surgery we learn over the years that some things that don't seem to make any sense turn out to be different when you study them.

Now what I have here is the patient education brochure we use in my hospital to tell the patient how to do the mechanical bowel prep and how to use the oral antibiotic. And I'm not going to spend a lot of time going over it but just to say this is a typical sort of handout and instruction that we give our patients. I'm also not specifically endorsing movie prep compared to other mechanical bowel preps. It happens to be what our Gastroenterology group had chosen for their colonoscopies, and we decided in the surgery department to go with the same thing so that there would be consistency across services within our hospital.

Now I'd like to spend just a little bit of time talking about parenteral prophylactic antibiotics for colectomy. Are some parental antibiotics better than others? Well, first of all, this study looks at a study done now almost 20 years ago, comparing cefotaxime alone to cefotaxime to metronidazole, and what you see here is a much lower rate with cefotaxime plus metronidazole, indicating that just with the oral antibiotics having a regimen that is effective against both aerobes and anaerobes is important. The cefotaxime has poor activity against anaerobes, so cefotaxime plus metronidazole clearly gives you better results than using cefotaxime alone, which has inadequate activity against anaerobes.

On the other hand, in this study the authors compared ticarcillin, which has reasonably good both aerobic and anaerobe, particularly back in the '80s when this study was done, compared to oral tinidazole alone.



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And tinidazole has activity only against anaerobe, not aerobes, and so you had a high infection rate here, the 20%, when the aerobes were not adequately treated.

In this study, Zilanetski [ph] and colleagues, at the University of Manitoba, used gentamicin and metronidazole intravenously for prophylaxis for patients have colectomy. What this study shows us is that they looked at patients with surgical-site infections and patients without surgical-site infections and looked at the Gentamicin level in serum at the end of the operation. You can see that patients with surgical-site infection had significantly lower Gentamicin levels than patients who did not develop an infection, suggesting that for your intravenous antibiotic it's important to have a good level of drug throughout the duration of the operation. In fact, when the gentamicin level was less than 0.5 at the end of the operation there was an 80% surgical site infection rate.

In this study we see recommendations from a combined prophylaxis guideline that was actually published only about two weeks ago, and this guideline is a joint effort of four societies, the American Society of Health system Pharmacists, the Infectious Disease society of America, the Society for Health care epidemiology of America, and the Surgical Infection Society. And the point made here is that this guideline recommends that we use two grams of cefazolin for any patient above 80 kilograms, and three grams for patients above 120, and if we're using gentamicin as an amino glycoside we'll use five milligrams per kilogram. In other words, the emphasis is on adequate dosing.

Now probably many of you have seen this study by Itani and colleagues, which compared ertapenem with cefotetan, showing significantly better and lower infection rates with ertapenem compared with cefotetan. You will also see that the ertapenem levels were higher than we like, at 17%, and, in part, this is because the patients were not getting oral antibiotics. One explanation for this difference is that cefotetan, which started out many years ago as a pretty good aerobic and anaerobe antibiotic, has had decreasing efficacy against bacteroidetes in recent years at the time this study was done.

Now a number of other authors have looked at large databases. This is a paper from using the Premier database, looking at almost 5,000 patients having colectomy, and you can see if you use odds ratio and you set cefoxitin as one, you get about a 47% better result with ertapenem, but you also get a much better result with cefazolin and metronidazole, or levofloxacin and metronidazole or ampicillin sulbactam, and not such a great weight with cefotetan. So ertapenem is a good intravenous prophylaxis, but so are a number of other choices.

In this study the Michigan collaborative looked at the results of their antibiotic choices again, and found that giving oral antibiotics resulted in a 46% reduction compared to not using oral antibiotics, at the same time as being SCIP compliant was a 33% advantage. Keeping the patient warm was a 60% advantage. Keeping glucose controlled was beneficial. Laparoscopic was better than open, and so on. So you can see that there were many factors that influence the rate of infection.

In addition, Hendren and colleagues looked at the intravenous antibiotic choices in the Michigan database, and, again, you see here odds ratio of one, any line that crosses one is not significantly better than cefotetan or Cefoxitin. But ertapenem, cefazolin Metronidazole, and ciprofloxacin metronidazole were all significantly better than cefotetan or cefoxitin alone, and if anything, cefazolin metronidazole and ciprofloxacin metronidazole looked a little bit better than ertapenem.



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So another thing to remember is that cefazolin and metronidazole are compatible in the same IV bag, and in my hospital, the University of Washington Medical Center. Our pharmacy provides us with a combination of premixed cefazolin and metronidazole in a single bag, which is available in the OR pharmacy, and that is our antibiotic of choice for our colectomy patients.

Now one last thought about colorectal surgery, we're not used to thinking about staph as an important pathogen in colorectal cases, and certainly *E. coli* and bacteroidetes are what we want to focus on. But there's a very interesting lesson by this study done by Morris and colleagues in 1990. They compared the regimen of aztreonam and metronidazole against cefotaxime and metronidazole. Now cefotaxime and metronidazole, we have seen earlier, is a reasonably good intravenous combination. Aztreonam and metronidazole sounds like a good combination because aztreonam has pretty good gram negative activity, and metronidazole has good anaerobic activity; however, metronidazole has no activity against gram-positive cocci. And aztreonam has no activity against gram-positive cocci. And what they found was they had a high rate of gram-positive, many staph infections in this group of patients.

So while staph isn't the first pathogen we think about in colectomy patients, if you completely ignore it, as these investigators did by giving aztreonam and the metronidazole, it will come back to bite you. But all of the standard intravenous regimens we've already talked about, as well as the standard oral regimens we've talked about, do have some activity against staph.

The other thing that I want to close with is duration of prophylaxis. There's been a tendency over the years for surgeons to want to continue prophylaxis postoperatively, but all of the data, not only for colectomy but actually every other type of operation that's ever been studied, show that there is no benefit to continuing antibiotic after the operation is over.

Here we see two studies, done quite a long time ago, comparing a single dose of intravenous prophylaxis with three days worth of intravenous prophylaxis, and you can see that in each study there was no benefit whatsoever to continuing antibiotics after the operation was over. So I would urge you to give high doses of antibiotics during the operation, repeat your antibiotics if the operation goes for a long period of time, use oral antibiotics for your colectomy patients, but stop the drug after the operation is over. Don't bother to order any postoperative antibiotics. If you do that you'll never run into violating the SCIP mandate of stopping within 24 hours, your hospital will thank you for not having them get SCIP misses, which hurts hospital reimbursement.

So with that, I want to say thank you for your attention, and I hope that this has been helpful, and I'm going to sign off at this point. Thank you very much.