Discussion of 2021-1775

EFFECT OF ANTIBIOTIC DURATION IN EMERGENCY GENERAL SURGERY PATIENTS WITH INTRAABDOMINAL INFECTION MANAGED WITH OPEN VS CLOSED ABDOMEN

**DR MARTIN A CROCE** (Memphis, TN): The authors set out to determine if antibiotic duration impacted outcome in emergency general surgery patients managed with open abdomen vs closed abdomen. They did this with an observational, prospective, multi‑center study using 21 sites. I will freely admit that I am not a fan of these observational multi‑center studies, especially involving a particularly sick patient population. It is usually secret code in research for, "Here's how I do it at my institution, so there!". Despite that, I think Dr Diaz and the investigators did a nice job with a difficult problem. I firmly believe that the published data supports the conclusion that unnecessary and indiscriminate antibiotic administration is harmful to patients. The present study also reached the same conclusion, and for that I applaud the authors. My only dyspepsia with this study is the fact that I do not think their data supports that conclusion. Perhaps a few questions can clarify things and they can prove me wrong. I sincerely hope so.

First, the study design. Was there any standardization of the patients? Were the intraabdominal catastrophes all managed in a similar fashion with standardized protocols understanding that there must be some wiggle room since all patients are not the same? Without some standardization, it is extremely difficult to tease out the contribution of the myriad of variables present in these ill patients. Instead of the existing groups, maybe they could have looked at short vs long antibiotics in closed abdomen patients only and short vs long in the open abdomen patients. Comparing outcomes in closed vs open patients is a fixed game, and open will lose every time. The open abdomen patients are simply sicker and will have more infectious morbidity. And perhaps the study design necessitated the need for the complex statistical analysis. I went to school for a long time, and I am clearly not smart enough to understand CART or GLMM. But I do know that they are used to account for missing variables, typically when more than 10% are missing. In this prospective study, why were there so many missing variables?

Second, were there standard definitions for the secondary infections? The authors looked at surgical site infection, pneumonia, urinary tract infection, and blood stream infection. It seems simple to look at these as outcomes, but sometimes the definitions are problematic. Were most of the pneumonia patients on the ventilator? Did any of the bacteremic patients have central lines? Did any patients have their skin closed, causing a superficial incisional infection. That would be less of an antibiotic issue and more of a basic surgical tenet issue.

Third, most patients (54%) had 1 to 5 days of antibiotics, the rest had greater than 6 days. What were the reasons for prolonged antibiotic administration? Did these patients develop the secondary infections while receiving their initial antibiotics after the first operation? Or did the infections develop after the initial treatment was stopped? Unfortunately, it is extremely difficult to determine whether this is a chicken‑egg phenomena.

Finally, I do want to compliment the authors in their attempt to answer a common yet difficult question. I believe their conclusions with all my heart. Dr Diaz and colleagues should be commended for trying to make this a science‑based decision rather than a faith‑based decision. I look forward to further work on this difficult problem.

**DR NICHOLAS NAMIAS** (Miami, FL): Dr Diaz and colleagues in the DaMage control in Emergency General SuRgery with Intra‑abDominal Infection and course of ANtibiotics (MERIDIAN) Study Consortium, comprised of 21 centers with thought leaders and experts in surgical infection, hypothesized that management of intraabdominal infection with an open abdomen technique would be associated with more secondary infection than management with a closed abdomen technique, regardless of duration of antibiotics. This hypothesis is different than the goals set out in the title of the paper, outcomes of interest were secondary infections to include surgical site, bloodstream, pneumonia, and urinary tract, as well as mortality. Not surprisingly, patients with intraabnormal infection managed with open abdomen had higher rates of secondary infection and increased mortality compared to closed abdomen. This is to be expected given the inherent selection bias in choosing the patients who would be managed with an open abdomen. Also, patients with a longer duration of antibiotics had more secondary infections, but this is also possibly due to selection bias. Something bad was happening that led the patient to get more antibiotics, and maybe that bad thing was just a harbinger of the brewing infection. I am a believer in shorter courses of antibiotics, but do you think you have told the readers what the optimum course of antibiotics is for the EGS patient managed with open abdomen? Maybe there would have been even more secondary infections in the long course patients, who got a long course for a reason, if they had gotten a shorter course. You will likely only answer that with an RCT.

The real burning question would be outcomes in the open abdomen group, comparing short course antibiotics vs longer course antibiotics. Do you have that data? Right now, I am left with "people with open abdomens have more complications and longer length of stay," which is somewhat intuitive and had to be the expected outcome. Figure 1 sheds some light on the effect of duration of antibiotics on secondary infection in the open abdomen group; the error bars for all the open abdomens in Figure 1 all seem to overlap, so it appears there is no difference in outcomes based on antibiotic duration in open abdomens. The figure and that data are presented without much fanfare.

So, my first question is, should that be the thrust of the paper? The title led me to believe that was what I would be getting. After all, the choice of open abdomen management is most likely not modifiable. While the outcomes of non‑modifiable factors may be interesting, outcomes of modifiable factors, like duration of antibiotic therapy, lead to change in practice.

Table 3 shows antibiotic management in outcomes, but it does not show the presence of secondary infection in open vs closed abdomen stratified by duration of antibiotics. Again, I feel like the title promised me that data. Your discussion states that you cannot examine the effect of antibiotic duration within the group of open abdomens and that would have to await the prospective randomized controlled trial. Could you have addressed this question preliminarily in your prospective observational study? Why not clearly demonstrate in some form the open abdomen patients, broken down into short and long duration antibiotics, and show the numbers? If the numbers are there, you are not shining a light on them well enough. That golden nugget is hidden, and that is the one of most interest. So, I have two more questions.

Why did you study secondary infection as your primary outcome? The outcome measure for treatment of intraabdominal infection is resolution or persistence or recurrence of the intraabdominal infection. So why did you measure a composite outcome of multiple secondary infections?

With such a large dataset, why not go ahead and shine a light on whether or not the antibiotics for a complicated intraabdominal infection management with an open abdomen can be truncated? I cannot help but think that was a goal at the inception of the idea for this study, but it got overshadowed along the way with a sophisticated prediction model. Just like the STOP‑IT dataset spawned literally dozens of secondary papers from its dataset, I suspect this one will, too, and I bet some of the authors are already working on the next abstracts. Hopefully your data on duration of antibiotics and increased secondary infections can improve antibiotic stewardship, but I eagerly await the subsequent analyses of this data that are sure to come.

**DR HIRAM POLK, JR** (Louisville, KY): Over the last 30 years, there have been dozens of papers dealing with intraabdominal infection that shows no advantage to prolonged antibiotics. What is wrong with this paper is the use of generic "antibiotics." There is a huge difference in drugs and how they enter the wound and how they enter the blood. I would be very interested in learning which antibiotics were used and how prevalently across these several arms of study. Without that, you cannot make more conclusions.

**DR PATRICIA M BYERS** (Miami, FL): This is a very tough topic, but I have a very easy, quick question. I did not understand the course of antibiotics being the initial course of prescribed antibiotics for that initial infection vs redosing for a second operation. I am hoping the authors could clarify, because that would make a difference. If you are reoperating someone for open abdomen, you give an extra dose of perioperative antibiotics as well. This is what I was trying to understand. Perhaps it was mentioned, and I missed it.

**DR AMANDA CHIPMAN** (Baltimore, MD): We did recognize that with a large multicenter study in a variety of very sick patients that there would be a great deal of heterogeneity of the patient population. We did try to narrow this down to some degree, so all of our patients ultimately had a laparotomy. There were no patients that had a minimally invasive or IR‑guided procedure to deal with their infection.

We also purposefully excluded things like patients that were treated with direct peritoneal resuscitation to try to decrease the heterogeneity. That being said, I do think the heterogeneity of the study does allow in some cases for a broader applicability, given that ultimately treatment will regress to the mean.

Regarding the CART analysis, there were some missing variables. Primarily these were laboratory variables, and so there were some sites that did not routinely, for instance, get arterial blood gases, which were one of the data points that we collected preoperatively. And so that was the main area that was excluded. Our definitions were the NNIS definitions of surgical site infection. We do have some further ability to look at the granularity of infections with bloodstream infections, pneumonia, patients on the ventilator, but I will say that greater than two‑thirds of patients, the secondary infection was a deep organ space infection, sort of as suspected.

Additionally, I do agree, there is some chicken and the egg here that will probably only be answered with a randomized control trial.

Regarding Dr Namias' comments as far as open vs closed abdomen stratified by antibiotic duration, while I think this is interesting data, we started out with about 800 patients and just shy of 200 ended up with secondary infection, and so when you further stratify this to open abdomens and then by antibiotic duration, I think you lose a great deal of power, and so your ability to draw any specific conclusions outside a randomized control trial are quite limited.

I think we have shown here, though, that longer duration of antibiotics does not at least improve outcomes in these patients. It could be argued that the patients would have done worse without a longer duration of antibiotics, however, I think with more emerging data about the microbiome, dysbiosis, and resistance as that emerges, I think it will be seen that ultimately the longer duration of antibiotics is not helpful to the patients and may be detrimental.

Obviously, as mentioned, there will be many more studies on this, and we have a lot more data to analyze, and so we do have the ability to look at specific antibiotics, when they were started, what types of antibiotics, and other data as well to give some more information on sort of the specifics of this.