



## ORIGINAL ARTICLE

# Antibiotics and the transplant patient: The good, the bad, and the ugly

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## Abstract

As a heart transplant recipient for 34 years, I have been asked to write an experience-based opinion on antibiotic stewardship programs (ASPs) in the transplant setting. The aim of this piece is to provide real-life examples—the good, the bad, and the ugly—to help contextualize the potential impact of an effective transplant-specific ASP model. The exigency of transplant ASPs is illuminated, and suggested changes that can help patients right away are provided.

## KEYWORDS

*Clostridioides difficile*, infection in transplant recipients, patient advocacy, transplant antibiotic stewardship

In 2021, I was asked to provide a patient's point of view for a draft-form paper on transplant antimicrobial stewardship programs (ASPs).<sup>1</sup> Not surprisingly, the paper made cogent arguments to highlight the necessity of data-based, handshake ASPs. What I did not expect were the medical memories it would conjure up, going all the way back to my heart transplant in 1988—an unfolding of my antimicrobial life. And so, more recently, when I was invited to write this opinion piece, I decided to use those experiences to share a patient's view of what might be considered “the good, the bad, and the ugly” of antibiotics over the course of 34 heart transplant years.

Although this title references a Clint Eastwood western, it also evokes some soap opera drama, which I think is apt. Because the management of antimicrobials in transplantation can be viewed as a saga of sorts. Antibiotics have an irresistible quality. As a vulnerable population prone to infections, we feel compelled to chase the prospect of their cure. These drugs have a talismanic effect for doctors and patients alike, warding off fear from the moment their names appear on the prescription form.

But antibiotics are fraught entities. Without deliberate and prudent handling, they can become mistakes with far-reaching consequences. It's General Hospital all over again, as I see it—characters under pressure, trying to do their best while swirling in a vortex of incomplete, outdated, or poorly communicated information. Soap opera mishap weaves a story, not unlike that which occurs in the absence of antimicrobial stewardship. Quiet errors. Perpetual incidence. Insidious harm.

You cannot help but wish someone would step in and impose order (or at least a word from our sponsor).

I certainly have wished for an order in the transplant setting at times.

From a base of personal experience with antibiotics, I provide here just a few examples to help contextualize the potential impact of an effective transplant-specific ASP model. Admittedly, this is an N-of-1 viewpoint. But I would hope that three decades on the transplant survival circuit bestow some worthiness of consideration, even though the content is anecdotal and lacks data from a sizeable cohort.

I should state here that I did interview a few recipients of different transplanted organs before sitting down to write, but only so I could get some general footing. My hope is that by contributing to this special issue, my experiences and ideas might augment the more broad-based, scholarly articles that follow and, together, illuminate the exigency regarding ASPs in transplantation.

We patients really need your help.

## 1 | QUIET ERRORS

It's 1988, just a few months into my life as a heart transplant recipient. I'm hospitalized with a cough and low-grade fever. X-ray doesn't show any sign of bacterial infection. But nonetheless here comes a big pink tablet in a paper cup—an antibiotic. I ask the nurse for the name of the prescribing doctor. She shares it, adding that he's a “young hotshot.”



After two pink doses, I start vomiting. By the third, it is dry-heave hell and I've got a headache so severe it raises the question of meningitis. Dr. Hotshot saunters in. He looks to be about my age: 25 years. I shift the vomit-tinged basin away from my face and squint up at him, embarrassed.

"Hey there!" he chirps, head down, flipping through clipboard pages before landing on one with an *Aha!*

"Aha? What do you mean?"

"Okay, it's like this ... we put you in the hospital and toxify your liver with antibiotics. That's our job—*ha!*" The nurse beside him smiles. "Look at that ALT," he says to her, pointing to a page.

I'm lost. I don't know this ALT word or what antibiotics have to do with the liver. But this doctor sure pierced my gut with "toxify." I jolt away from the propped pillows, "Toxify my what? What!"

"Whoa, hey, no worries. Happens all the time. No more erythromycin for you, that's all."

"But, but ... I'm immunosuppressed. I need this antibiotic!" I am not aware that there are several classes and generations of antibiotics to choose from. I've had almost no bacterial infections in my life—not even strep throat as a kid.

"I'm going to switch you to a different one. Let's see ... um ... er ... how about, say, tetracycline?"

*Is he asking me to weigh in?* "Well, ah, it seems I'm allergic to erythromycin, you know, with the vomiting, so I guess ..."

"Ha, no, not exactly. Look. I have to run," he says, handing the clipboard to the nurse and heading for the door. "But I'll come back tonight and explain everything."

He doesn't.

Decades later, I would work alongside this same physician on the thoracic committee of a major transplant organization. I noted that the affiliation on his badge showed that he'd attained a top position at a big transplant center in a different city. The young doctor who'd once casually joked about liver toxicity at my bedside had come a long way over the years. And as he launched into a committee presentation with jargon that might set a new transplant fellow scrambling for a medical dictionary, it occurred to me: *So have I.*

I understood every word.

It's a story that, even decades later, compels me to break into fantasy for a moment, re-imagining how the 1988 cough/hospitalization/antibiotics encounter might play out today with my years of transplant experience (or how it might be for a brand-new patient if there were a transplant ASP to guide them):

*Me: You gave me an antibiotic I've never taken before and it's making me vomit like mad.*

*Dr: Sorry. Your liver doesn't like this drug.*

*Me: What's my ALT?*

*Dr: Two hundred ninety.*

*Me: Yikes. Hey, does erythromycin inhibit Cytochrome P450 3A4? Because we both know what that does to CNI's.*

*Dr: Seems to be the case. I can switch you to ...*

*Me: Question, please. Did you run a cyclosporine level on me? It's probably sky high from inhibited metabolism, and I need to skip a dose. We don't want to spike my creatinine. And this headache, whoa, neuro effects going on.*

*Dr: Can't run a level 'til morning. I'll switch you to tetracycline.*

*Me: For what infection exactly? Nothing showed up on x-ray. Maybe this is viral. And besides, doesn't tetracycline inhibit CYP3A4, too?*

*Dr: Need to check that, but I must run. I'll come back later and explain everything.*

*Me: No need to come back. Please call in the transplant antimicrobial stewardship team.*

But this is where my fantasy turns to impossibility—because there would be no transplant ASP. And the reality—back then, and now—is that many if not most transplant recipients would not be inclined or able to advocate for themselves this way. I may have had the will and backbone to speak up in 1988, but I hadn't garnered the transplant knowledge that would help me self-advocate with meaningful medical insights. And so, the rest of this antibiotics story had to unfold just this way:

- I switched to tetracycline; it made me sick.
- No one suggested an interaction with cyclosporine could be the culprit.
- No one questioned the presence of bacterial infection.
- I left the hospital a day or so later feeling more debilitated than when I was admitted.
- I stopped the antibiotic prematurely at home and felt better quickly.
- It was probably a viral cough after all.

No serious harm to the patient. No grievous foul by the doctor.

But it was one of those quiet errors that I warned about above: a slip-up that could have used someone to step in and impose order. And with the continued absence of devoted ASPs over my transplant years, quiet errors like this one began to stack up for me like a house of cards.

## 2 | PERPETUAL INCIDENCE

Heart transplant was just becoming routinely successful-ish in 1988. Even the most knowledgeable physicians at a busy heart transplant center in New York (where I was a patient) lacked sufficient information/data/science to navigate the complex contours of post-transplant antimicrobial care. It is no wonder, then, that medical practitioners whom I had seen in my healthy/normal woman years regarded my new

heart recipient status warily. After my transplant, my dentist and gynecologist told me in a skittish panic that they could not take care of me anymore. With some effort, I was able to connect with new, more courageous ones. But I could not find a primary care physician (PCP) who was not irremediably spooked. "I had a kidney transplant recipient a few years ago," they told me, "But *heart transplant?* I just, well ... I can't."

Consequently, my transplant physician (a highly-regarded, niche cardiac-transplant specialist—let's call him Dr. Niche) became my PCP. For the next three decades, I sought his medical advice for everything from intractable pinkeye to searing sore throat. Looking back now, I understand that this arrangement was flawed from the get-go.

Against this backdrop, my transplant antimicrobial life ensued.

In the first 26 years that followed my heart transplant, I took well over 100 courses of antibiotics (yes, I counted—it's annotated in a detailed medical notebook I started in 1988). Heart transplant recipients were kept at high levels of immunosuppression in the eighties and nineties—not all that different from what is given today, except that the CNI was cyclosporine, and the anti-metabolite was azathioprine, plus a 10 mg maintenance dose of prednisone. There was no such thing as a CD4 T-lymphocyte assay, as far as I knew (and if there were, it was not used to help balance infection/rejection risk at my transplant center). Vigilance regarding bacterial infection in patients like me seemed appropriate. And if Dr. Niche was a little too quick to scribble *Omnicef* or *Lorabid* (remember those?) on his prescription pad, and if I was overly eager to fill and ingest his Rx's, well, chalk it up to fear and a "better safe than sorry" non-stewardship approach.

The target of these prescriptions included an inordinate number of acute bacterial sinus infections. Or were they? Best to call them instances of sinus pain for which Dr. Niche gave me 14 days of broad-spectrum antibiotics. And when this did not bring relief, he wrote an additional prescription for another seven days, which I took willingly. When the pain returned a few weeks later, there was another antibiotic prescription for the full 21 days straight away. This cycle occurred six or seven times a year for almost two decades. After a while, I got the sense that Dr. Niche's penchant for long, repeated antibiotic courses might be based on how he had treated his own infections. (My notes from October 1995: *Doctor told me, "Less than 21 days never works on my sinuses" - Wait, he's using his nose as a PDR?!*)

Meanwhile, urinary tract infections (UTIs) flourished. Sort of. Even my brave new gynecologist succumbed to a quick-draw prescription pad reflex in my presence. When the bacteria count on a routine urinalysis/culture hovered on the judgment-call line, she urged me to be cautious and take a course of antibiotics even though I had no UTI symptoms. "The course for normal women is three days, but I want you to take seven," she told me. "You're immunosuppressed. We can't risk a kidney infection."

Kidney infection? Did I even have a UTI? And did I really need a longer course of antibiotics than "normal" women? It seemed to me that bacteria are bacteria—a specific dosage of antibiotics is needed to kill them off, no matter the normal or abnormal body they're located in. Right?

I had questions.

*Hey, let's ask the transplant antimicrobial stewardship team! I'll just call my transplant center and ...*

Nope.

Again and again, I took extended courses of antibiotics for what I now understand were mostly viral sinus infections (some of which were bacterial and were helped, eventually, by endoscopic sinus surgery) and chimera UTIs made up not of harmful bacteria, but my well-meaning gynecologist's fears. There were other antibiotics instances as well: some of them clearly necessary (pneumonia, ear infections, etc.) and some probably not (sore throat, a hint of possible paronychia, little diarrhea after Mexico trip). There was hardly a month where I was not taking a course of antibiotics for some infection, real or hypothetical.

Also, down this rabbit hole was a myriad of questionable antibiotic prophylaxes. After my transplant in 1988, my dentist instructed me to take antibiotics before all cleanings and procedures. Get ready for the prescribed dosage: six antibiotic tablets prior to the dental visit followed by five tables after. I don't remember the milligrams (it is not in my notes), but you might want to sit down before I tell you which antibiotic Dr. Niche and my dentist decided upon together: clindamycin. (It will become clear later why this was such a poor choice for me, but I imagine that if you are in the infectious disease field, you already have an idea.)

There was also antibiotic prophylaxis for many of the 29 angiograms I had at my transplant center in New York. For a few years, it was IV vancomycin given during closure. But when a fast drip caused what a nurse called "red man's," I was given cefuroxime instead, which I had to swallow while lying flat on my back (because my femoral artery had just been sliced open). After a decade or so of choking down giant pills on the catheterization table, I asked, "Is this really necessary?"

The response: "Not for normal patients. But in a transplant recipient ..."

It wasn't until 26 years after my heart transplant that I would learn that antibiotics were not necessary for post-angiogram closure. This information came my way in 2014 when I received a second heart transplant across the country at a medical center in California. Imagine my surprise when, during my first angiogram at this new center, no nurse appeared at my side with an antibiotic. Apparently, a glove change between procedure and closure prevents infection splendidly. "It's evidence-based medicine," the freshly gloved interventional cardiologist explained to me. "And we don't want to give transplant recipients unnecessary antibiotics."

I had never heard a physician say this before.

It is notable that in the nearly three decades between my heart transplants I experienced no improvements or advancements in my antibiotic-related care. It took a change of transplant centers from the east coast to the west for me to benefit from modernized medical and procedural approaches that would end the antibiotic pummeling in the catheterization lab and my day-to-day life.

And now, settled into the enlightened practices of my California transplant center, I know that when I ask my transplant cardiologist a question that begs an antimicrobial answer, he will say, "Let's reach out to ID." While there is no transplant-specific ASP at his disposal (yet),



infectious disease physicians are an integral, active part of the heart transplant team—thank goodness.

I know too well what can happen when they are not.

### 3 | INSIDIOUS HARM

There is a kind of harm that is not highlighted in transplant infectious disease journals. Nor is it top of mind when thinking about the damage that transplant ASPs are meant to minimize or avoid. But for patients, it's crucial. I'm talking about what antibiotic side effects can do to a transplant recipient's life.

It is one thing to read a list of side effects. It is another to experience them for yourself, over and over, in combination with powerful transplant medicines that are difficult to tolerate even on their own. Side effects can turn to harm. Not just harm that occurs as an isolated, discrete instance, like liver toxicity from an errant erythromycin prescription. I mean harm that is cumulative. The house-of-cards kind. The harm that is not documented in studies, is not contemplated when antibiotics prescriptions are written and is not articulated by transplant patients who have become inured to taking medicines with ill effects (and whose gratitude for life can sometimes act as a silencer of complaint).

Side effects profiles for antibiotics do not speak to what transplant recipients experience when they take these drugs. There might be a recommendation for monitoring calcineurin blood levels (if a physician opts to check for it). But there is no data that details what it feels like to combine courses of antibiotics with powerful transplant immunosuppression medications—and, in my case, to experience this more than 100 times. If there were reports, they might read something like the antibiotic-laden cry that appears repeatedly in my medical notes from 1988 to 2014: *If I could transfer into someone what I am feeling in my body right now, they'd shout for me to Stop! Stop!*

I am not seeking sympathy. I am a grateful, incredibly lucky woman who has been blessed with two magnificent donor hearts, and I have never expected transplant life to be a cakewalk. But all organ transplant recipients have limited post-transplant survival years. Every week or month that is spent white-knuckling it through exacerbated side effects is a loss of treasured time. The lack of ASP guidance during the decades of my first heart transplant enabled a sickening excess of problematic antibiotic prescriptions that eviscerated my quality of life and nearly crushed me.

This might seem like an exaggeration. But so far in this piece, I've simply listed antibiotic experiences as punctuated dramatic reports and tallied numbers. These events did not happen in a vacuum, however; they occurred in the broader context of a transplant medical life. This brings me back to the house of cards and, this time, its collapse.

Here is how the cards were stacked in 2011:

- 78 routine heart biopsies over 23 transplant years cause repeated trauma to my tricuspid valve
- Tricuspid leaflet severs, necessitating open-heart tricuspid valve repair on my transplanted heart

- Long post-surgical hospitalization
- Diarrhea starts one week later
- Clostridioides difficile (*C. diff*)
- Vancomycin. Recurrence. Vancomycin. Recurrence.
- Seven months of severe diarrhea, weight loss, exhaustion
- I spike a fever and spiral down—emergency

If not for a fecal transplant done stealthily by a general gastroenterologist who proved to be an intrepid pioneer (an unregulated fecal transplant on a heart transplant recipient in 2011—wow), I might have died. And what would have been the root cause of death, exactly? Hospital-acquired *C. diff* infection that was particularly virulent? Microbiome flattened by decades of excessive antibiotics?

Probably both.

Imagine if there had been a devoted ASP in place at my New York transplant center starting back in 1988. How different the variables might have been. The illness and trauma I might have been spared.

### 4 | TOWARD MEANINGFUL TRANSPLANT ASPs

When thinking about antibiotics in transplantation, I envision a giant Venn diagram with the intersection lit in neon: here is where the need for transplant ASPs shines for every organ recipient. We're all immunosuppressed. We all want to live well and avoid harm. And we all want to hit the sweet spot when it comes to antimicrobials.

But how to do this most effectively?

Transplant ASPs are a critical answer to this puzzle, but they may not be enough. ASPs live in hospitals. For most transplant recipients these days, however, almost all antibiotic prescriptions come from PCPs or other medical practitioners outside the transplant setting. Any antibiotics prescriptions I've received since my re-transplant in 2014 (except for post-surgical prophylaxis) have been written by my PCP. This is also the case for the transplant recipients I interviewed. I asked if their PCPs reach out to their transplant centers when writing antibiotics prescriptions for them, and everyone said no. But they told me that sometimes they reached out themselves before taking what their PCPs prescribed.

This leads me to this observation: For hospital-based transplant ASPs to benefit patients routinely and reliably, there must be a system for communicating and applying transplant ASP practices outside the transplant setting. Patients need to play a key role, then, as they are the ever-present connectors between their transplant and non-transplant medical professionals. Accordingly, patient self-advocacy regarding antimicrobials must be woven deliberately into the fabric of post-transplant wellness early on.

This means that in addition to giving patients written information about recognizing signs of infection and rejection, transplant programs should provide a simple chart highlighting important facts/warnings regarding antibiotics, antivirals, and antifungals, and encourage patients to share this chart with their non-transplant medical providers. Even if patients do not appreciate or understand every detail, much good can come from them knowing, at least, that their use of antimicrobials requires some special attention.

Of course, communicating current transplant-specific ASP information to the medical community—within and outside the hospital setting—is imperative as well. But an ASP model that acknowledges and incorporates the importance of informed, self-advocating patients, is poised for the greatest impact.

## 5 | IMPOSING SOME ORDER—NOW

Just how urgent is the need for change in the current management of antimicrobials in transplantation? The experiences I have detailed herein appear to be nestled safely in the past. And given that I am still alive after 34 heart transplant years, one might question whether transplant ASPs are all that crucial for long-term survival.

But wait—I got *lucky*. I eked by so many times. And if you think that some ghosts from my antibiotic past haven't left deep scars, then I should add this: When one of the transplant recipients I interviewed told me that his dermatologist gives him clindamycin prophylaxis for skin cancer removals, I lost my breath for a few seconds. I should have warned him: *Tell your dermatologist No! You don't need antibiotics if he uses sterile procedure. And if he insists, tell him there's an alternative antibiotic that's safer for transplant recipients—tell him to give you...*

But I didn't know him well and I'm not his doctor, so I said nothing. Instead, I dove into writing this piece. Because this patient doesn't need my help. He needs yours.

The sooner the better.

Here are four changes that could help patients right away:

1. **Institute antimicrobial timeouts in the hospital setting:** Like pilots before they fly or surgeons before they operate, transplant physicians should have an antimicrobial safety/appropriateness/effectiveness checklist to review before procedures and at the bedside for drug interactions, side effects, necessity of prophylaxis, intent to treat infection or colonization, etc.

2. **Update antimicrobial practices to the current era:** Unite transplant centers for the purpose of sharing best antimicrobial practices across the board. Investigate and eliminate protocol that is continued because “We've always done it this way.”
3. **Establish incentives (through government agency or professional association):** Reward centers for ASP-based metrics such as low *C. diff* rates, reduced fluoroquinolone prescriptions, appropriate use of short-course antibiotics, etc.
4. **Encourage patient involvement and advocacy:** Appoint a transplant recipient representative to contribute to ASP guidelines at the hospital and national levels. The best way to involve patients is to show that you welcome and value their experience and voice. Giving patients the opportunity to have meaningful input is the first step.

Like asking a patient to write the kick-off piece in an infectious disease journal.

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