# PATIENT PROFILE

## Jeff: The Endurance To Overcome Drug-induced Liver Injury


*Jeff*

Jeff is an executive at a successful furniture company, is active in his church, and volunteers with youth. In his spare time, he skis and is a competitive mountain biker—a successful one, too, with a history of winning races in his age category. Not surprisingly, he tries to take good care of his body. Aside from a couple of treatable medical conditions, he is a healthy 60-year-old. He is also accustomed to training hard for races, but there was no way he could have prepared for his encounter with drug-induced liver injury.

In 2016, eager to rid himself of a lingering and headache-inducing sinus infection, Jeff started taking a 6-week antibiotic course prescribed by his allergist. Four weeks later, he was experiencing nausea, headaches, and a low-grade fever. At that time, he was due to meet up with some friends for a 2-hour motorcycle ride from his hometown in Michigan to spend a few vacation days in a cottage at a ski resort. Despite feeling miserable, he made the trip with his wife riding on the seat behind him. At the cottage he became overwhelmed by cramps and vomiting, even briefly losing consciousness. He spent most of his remaining vacation confined to a bed. At that point, Jeff decided to stop taking the antibiotic. He wasn't fully aware of it at the time, but his liver was experiencing a severe reaction to the drug, and only after a harrowing trip to the emergency room and months of recovery would he begin to feel somewhat normal again. During that time, he would directly experience the agony and alarm that coincide with drug-induced liver injury. He would also join the NIDDK's Drug-Induced Liver Injury Network (DILIN), becoming part of a concerted, multi-site study to understand, manage, and prevent this potentially deadly disease.

### SIGNS OF A ROUGH ROAD AHEAD

Drug-induced liver injury occurs when a prescription drug, an over-the-counter drug, or a dietary or herbal supplement damages the liver. Some types of drug-induced liver injury, such as those caused by acetaminophen overdoses, are relatively easy to foresee and avoid because the type of injury tends to be similar among people and directly dependent on the amount of drug ingested. Others, such as Jeff's case, are called "idiosyncratic." They are relatively uncommon, with effects that are harder to predict and largely determined by a combination of factors unique to an individual, such as genetics and the condition being treated. This makes it difficult to know who will respond

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adversely to a given drug—even at dosages that are safe for most people.

Unsure of what was happening but knowing he needed medical treatment, Jeff decided to return home. When he and his wife got back, it was Father's Day, and his daughter and son-in-law came by for a visit. His son-in-law noticed that the whites of Jeff's eyes were tinged with yellow and his skin was darkened with a yellow-orange appearance. Jeff's daughter began to worry that there was something seriously wrong with his liver and urged him to seek treatment. He went to his family doctor, who ordered blood tests to detect markers for liver health, like bilirubin and the liver enzymes alanine aminotransferase (ALT) and alkaline phosphatase.

A high level of bilirubin, along with elevated levels of liver enzymes in the blood, are signs of liver damage, and Jeff's bilirubin level was almost six times the normal amount. Over the next few days, it continued to slowly rise, and there was seemingly nothing he could do to stop it. Jeff was starting to worry that something terrible was on the horizon. "As that was happening," he recalls, "I'm starting to wonder, how bad was this going to get?"

Jeff's doctor was beginning to suspect that drug-induced liver injury, triggered by the antibiotic, was the cause of Jeff's deteriorating health. The antibiotic that Jeff took was actually a combination of two drugs—amoxicillin and clavulanate—commonly called Augmentin®. Prescribed to treat mild-to-moderate bacterial infections, it is designed to be a double knock-out punch for bacteria: amoxicillin is an antibiotic derived from penicillin, and clavulanate targets bacteria that can degrade the amoxicillin before it can do its job. The combination is usually effective and safe and is one of the most frequently prescribed antibiotics. In a small percentage of people (about one in 2,500 people treated), it triggers an allergic response when it is broken down by the liver. The body appears to misread the breakdown products as unwelcome foreign invaders and sends powerful immune cells streaming into the liver. The resulting immune reaction wreaks havoc on the vital organ, causing jaundice and, in severe cases, acute liver failure.

Jeff's doctor thought he should see a digestive disease specialist to keep a closer eye on his liver, so Jeff went to a gastroenterologist. In the meantime, his bilirubin level continued to climb.

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## A RACE TO THE EMERGENCY ROOM

Jeff felt extremely weak and tired, but he pushed himself to continue working over the next several weeks. Then, shortly before the Fourth of July weekend, he got a call in the middle of a meeting: his test results were so alarming that his gastroenterologist urged Jeff to go to the emergency room right away. He remembers calling his wife, stopping by the house to grab some clothes, and then driving to the hospital, his mind racing. "All of a sudden, reality strikes me," he recalls. "What's going to happen here? Do I get a liver transplant? Do people die from this?"

Jeff's anxieties were not unfounded. Although most cases of idiosyncratic drug-induced liver injury resolve after the patient stops taking the drug or dietary supplement that triggered the disease, recovery is dependent upon a timely diagnosis, proper identification of the offending agent, and other factors such as genetics and the overall health of the liver. One complicating factor is that the injury from amoxicillin and clavulanate (and some other antibiotics) typically arises weeks after exposure to the drug, so symptoms may not manifest until 1-3 weeks after a short antibiotic course is completed. With rare exceptions, there are no current treatments that are effective in reversing this type of liver injury. The first and most important

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step in management is to stop taking the drug—and to not ever take it again (even if there are doses remaining in the prescribed course of antibiotics). This includes throwing away any leftover amounts of the drug and clearing it from the medicine cabinet as extra insurance that it is not used again. People who have experienced this type of liver injury should also make note of the drug so they can tell their doctors if they are ever prescribed it again. The liver has an amazing ability to heal itself and recover from damage, but if the damage is too great, liver failure occurs, and only a liver transplant will guarantee recovery. Drug-induced liver injury, although rare, is the major cause of death from acute liver failure in the United States and other developed countries of the world.

At the hospital, Jeff underwent hourly blood tests to monitor his liver. His bilirubin had soared to over 20 times the normal level—a surefire sign that his liver was under severe distress. "It was definitely a surreal feeling, realizing that I could die," he remembers. His wife was sending out alerts and prayer requests to his friends and members of his family; his son and daughter-in-law, who live in Seattle, were trying to sort out whether to catch the next flight to Michigan.

***"I just remember realizing what was important in life at that point," says Jeff when remembering his visit to the emergency room for a liver injury. "Your faith, your family, and your friends … everything else didn't matter."***

Jeff and his family spent that night in the emergency room praying and waiting anxiously for each test result. "I just remember realizing what was important in life at that point," he recalls. "Your faith, your family, and your friends … everything else didn't matter."

On the second day, to everyone's relief, Jeff's bilirubin level finally began to ease downward. He spent a few more days at the hospital, weakened to the point of barely being able to walk. After getting discharged, he sat at home on his deck, thankful, enjoying the Michigan summer weather and thinking, "I'm just happy to be here."

## THE SLOW, UPHILL PATH TO RECOVERY

Soon after Jeff left the hospital, Dr. Robert Fontana, a liver specialist and principal investigator in the NIDDK's multi-center DILIN program, contacted Jeff from the University of Michigan to see if he would be interested in joining the study. Jeff willingly agreed, even though he was still extremely fatigued from his episode in the emergency room. "I could hardly walk a hundred feet without becoming exhausted," he recalls. "That's pretty unusual for me, since I'm used to doing significant bike and ski races."

He understood that joining the study would not only contribute to advancing medical knowledge but would also provide an opportunity for his recovery to progress more quickly and smoothly because it would be closely monitored with regular checkups. "It was an opportunity to have really good care and to be monitored on a regular basis," he says. "I think that was the biggest thing, that they would be watching over me, trying to understand this better, and trying to help in the future."

The NIDDK established DILIN in 2003 to collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines, such as herbal and dietary supplements. Since that time, DILIN has collected data and specimens from more than 2,000 cases of liver toxicities due to these agents and made major contributions to understanding why certain medications and dietary supplements are more likely to damage the liver, why only some people are affected, and how the liver can heal itself after the injury. Answering these questions about the disease will continue to help researchers prevent and treat it. Genetic information from the Network's participants, for example, is providing clues into how genetics could

determine whether people react negatively to a drug or dietary supplement, even opening the possibility of screening patients before prescribing certain drugs to minimize the possibility of liver damage.

Jeff's participation in the DILIN study initially began with visiting the University of Michigan every 6 months for blood tests. At each visit he also underwent a specialized ultrasound procedure that detects the amount of scarring in the liver—a painless, noninvasive way to measure how well the liver is healing. His bilirubin level settled back into the normal range within 3 months after the trip to the emergency room, but other blood markers for liver health remained elevated, so he underwent a liver biopsy, which confirmed his liver was healing well. It was about a year after the initial injury when his liver markers came back close to the normal range—and that is where they remain 3 years after the injury, "not completely normal, but they're close to normal," Jeff says.

Jeff maintains a spreadsheet to keep track of his test results, and, with some trepidation, he still looks forward to getting his blood tested, which happens yearly now. "I want to know if I'm getting better," he says. "But at the same time, I'm very anxious about it and concerned that it's going to be moving backwards, so there's definitely still some feelings that linger, like, 'can this get worse?'"

In spite of his worries, 5 months after his liver injury Jeff was again racing in mountain bike competitions. Within a year, he was back to winning statewide races in his age group. "So, I was kind of back into full swing," he admits modestly.

## SPOTTING THE FINISH LINE: OVERCOMING DRUG-INDUCED LIVER INJURY

DILIN continues to build upon its successes. The NIDDK renewed the Network for a new project period beginning in 2018 and included provisions for pilot studies that would lay the groundwork for future clinical trials to treat severe drug-induced liver injury. The NIDDK also partners with the NIH's National Library of Medicine on an online resource called "LiverTox" (*http://livertox.nih.gov*), which features sample cases of people with drug-induced liver injury based on the Network's data, as well as a database summarizing liver injuries caused by drugs, including amoxicillin-clavulanate, and various herbal and dietary supplements. Meanwhile, Jeff continues to participate in the DILIN study and has adopted a new outlook. He admits that, like most people, he knew next to nothing about drug-induced liver injury before he was affected by it; now, after gaining firsthand knowledge, he wants to raise public awareness about it. He is thankful for everyone who supported him through his illness: his family and friends, his church, his gastroenterologist, and Dr. Fontana, who once jokingly called him "the healthiest sick person I know."

***"It was an opportunity to have really good care and to be monitored on a regular basis," Jeff says about joining the Drug-Induced Liver Injury Network study. "I think that was the biggest thing, that they would be watching over me, trying to understand this better, and trying to help in the future."***

His experience has left an indelible impression on Jeff's life, particularly with regards to his health. While there is no approved therapy for this type of liver injury, there are ways to manage it that focus on health maintenance and avoiding further injury, including stopping all medications except the most necessary, stopping alcohol consumption, paying careful attention to nutrition, and getting adequate rest. Once the injury resolves, it is possible to resume other medications and modest alcohol intake. "[The injury] is at the back of your mind," he says. "For example, I always liked a glass of wine or beer now and then, but [shortly after the injury]

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***"I'm living my life to the fullest, because you don't know what's going to happen," says Jeff of his outlook after recovering from a potentially life-threatening liver injury.***

there was no alcohol. I didn't have any of that for at least a year. When things returned to normal, I would have just a little bit. So those kinds of things are always on your mind."

He also has a renewed desire to get the most out of life. "After the injury, I was looking at things differently," he remembers. The next winter, when he and his family went on their annual skiing trip to the Canadian Rockies, he tried something new: heli-skiing. He and his son rode in a helicopter to a remote area at the top of a mountain, where they were deposited in fresh snow to ski down the untouched slope. "I said, 'OK, I'm just going to do this,' and it was great," he recalls, adding that this is an example of how liver injury affected the way he looks at things. "I'm living life to the fullest, because you don't know what's going to happen," he says. "Now I want to live life even more."