THeartsick: Medical and Ethical Challenges of Infective Endocarditis in the Opioid Epidemic

Laura Gerik, MS

HOUSTON METHODIST DEBAKEY HEART & VASCULAR CENTER, HOUSTON, TEXAS

"Excerpta" columns are editorials to supplement reviews in each journal issue with author interviews and a look at the practical aspects of the science reviewed in the Journal. Any opinions stated are the author's own. Quotations reflect the ideas of the persons interviewed and do not represent their respective institutions.

Published online August 2, 2018; Updated June 11, 2021

The patient was a young man in his twenties, lying in a coma in the intensive care unit (ICU) of the Cleveland Clinic. Mark was in the late stages of infective endocarditis—a heart valve infection that, until recently, was associated with a much older population. He had contracted the infection via an unsterile injection of intravenous (IV) drugs, and now his life was hanging in the balance, with nobody but his younger sister to speak for him.*

Bryn Esplin, JD, was in the first month of her clinical ethics fellowship when she approached Mark's sister to get a sense of what he would have wanted next. Esplin wanted to establish what a good day looked like for the patient; this was a routine inquiry to gauge the patient's values and was usually answered with something cheerfully mundane, like a day spent with friends or getting to walk the dog before work. So when she asked Mark's sister, "Tell me a little bit about your brother. What does he enjoy doing?"

"Well," the sister answered, "he just liked to get high. He liked to check out."

In hospitals across the United States, physicians are seeing a new type of epidemic: young men and women, usually in their 20s to 40s, presenting with infective endocarditis (Figure 1) secondary to IV drug use. The rise of IV drug use-related infective endocarditis (IVDU-IE) is one of the many tragedies of the opioid epidemic currently sweeping the nation. Its young victims have disproportionately negative outcomes, higher rates of repeat infection, and costlier treatment.[1] As the medical community grapples for solutions, IVDU-IE is forcing physicians to confront heart-wrenching medical and ethical dilemmas and exposing the flaws of a system ill-prepared to treat and rehabilitate people with complex drug addictions.

RISING TIDE OF ADDICTION

According to the Centers for Disease Control and Prevention, the opioid epidemic has flooded the United States in three distinct waves. The first began around 1999 with the rise of overdose deaths from opioid prescriptions. Second, around 11 years later, deaths from heroin began to skyrocket, heroin being a cheaper—and more dangerous—alternative to illicitly obtained prescription opioids. Synthetic opioids, especially fentanyl, caused the third wave of deaths, which have been rising exponentially since 2013 (Figure 2).[2]

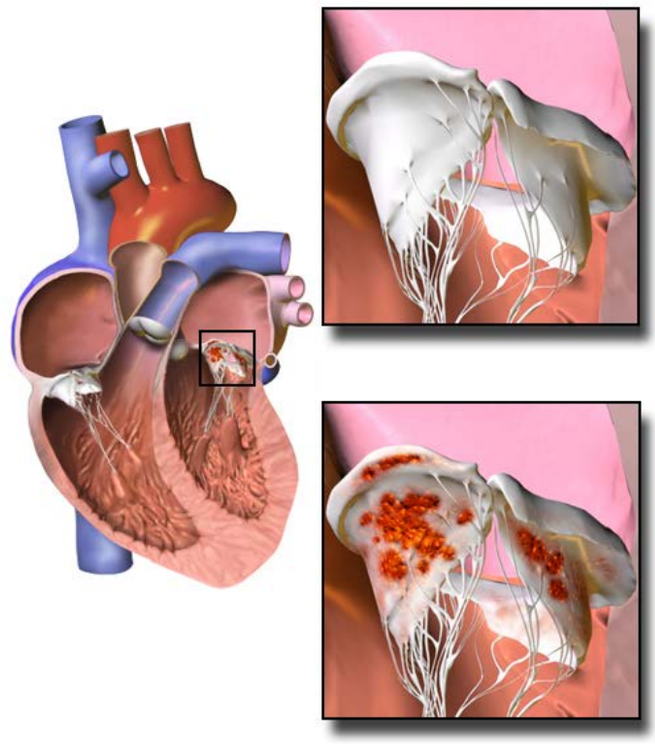

Figure 1.
Drawing of endocarditis of affecting the mitral valve. The top image shows a healthy valve; on the bottom, the valve is infected with endocarditis. Source: Bruce Blausen, Wikipedia commons.

As the epidemic progressed, physicians and public health officials noticed a corresponding increase in infective endocarditis. To date, there is relatively little research on this

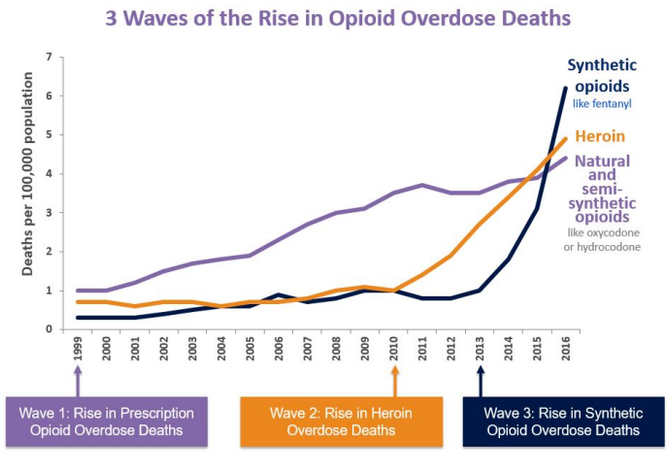

Figure 2.
The opioid epidemic in the U.S. has arrived in three waves: first prescription opioid abuse, then heroin, and now synthetic opioids. Source: Centers for Disease Control and Prevention

emerging public health crisis, but retrospective studies from around the country show an alarming trend. In North Carolina, IVDU-IE discharges increased 12-fold from 2010 to 2015 (with an 18-fold increase in hospital costs).[3] A Massachusetts hospital saw the proportion of IVDU-IE double from 2004 to 2014.4 As the IVDU crisis spreads into the suburbs and rural areas, similar patterns are being reported around the country in places like rural Ohio and West Virginia, where opioids weren't a problem before.[5,6] These patients are young, white, and usually male,[1,2,3] although female admissions are rising.[1]

Thanks to unsafe injection behaviors that introduce bacteria directly into the blood stream—from crushing or dissolving pills to licking, sharing, or reusing syringes[5,8]—IV drug users contract IE at 50 to 100 times the rate of the general population.[4] Adding addiction into the mix compounds the challenges of an already deadly disease. In-hospital mortality rates for IE, drug-related or otherwise, range from 11% to 26%, with 5-year mortality estimated at 12% to 50%.[1]

SURGICAL CHALLENGES

The standard treatment for IE is aggressive antibiotic therapy and, for 60% to 70% of patients,[4] valve replacement surgery.

"Valve replacement surgery for an infection is always more complicated and high-risk than it would be for non-infectious reasons," says Ravi Ghanta, M.D., chief of cardiac surgery at Ben Taub Hospital in Houston, Texas. He points out that patients with IE often have more extensive damage than those with a routine valve blockage; the infection can spread to the surrounding tissue or cause an abscess requiring debridement. If the infection reaches the aortic root, an aortic root replacement may be necessary. Moreover, the infection

Left.
Ravi Ghanta, MD, now chief of cardiac surgery at Ben Taub Hospital in Houston, first observed the rise in IVDU-IE cases while working in the Appalachian region of Virginia

Right.
Vanessa Medrano, MD, has seen an increase in cases of IVDU-IE at Ben Taub Hospital in Houston.

can affect other organs, and IE patients are more prone to having strokes, all of which frequently leads to longer stays in the hospital and ICU.

Furthermore, valve replacement surgery raises a patient's risk for repeat endocarditis. Man-made replacement valves, whether bioprosthetic (crafted from pig or cow valves) or mechanical, are more prone to infection; although the procedure can save the patient's life, it also could land them right back in the operating room with repeat IE. Ghanta calls it a "catch-22," and it is particularly problematic for IV drug users. Patients with IVDU-IE have a significantly higher rate of repeat infection than non–IVDU-IE patients,[1,6,7] with recorded readmission rates as high as 50%.[9]

EIGHING TREATMENT O TIONS

For physicians treating IVDU-IE, the treatment is essentially the same as it would be for non-IVDU-IE—until the decision of whether or not to perform surgery. Then things get complicated.

"I definitely look at things differently whenever I have a known opioid addict coming in and possibly needing surgery," says Vanessa Medrano, MD, cardiologist at Ben Taub. "You have to consider whether surgery is in the patient's best interests, physically or mentally. Physically, would they recover? Would they survive? Then you have to consider the psychosocial aspects. Do they have the mental capacity to understand what is happening? Are they willing and able to quit using drugs? If they need a mechanical valve, will they take their anticoagulation medications?"

It's a multifaceted problem, and for now, there are no guidelines specific to treating IVDU-IE. Medically, IV drug users tend to have different comorbidities than the usual IE patient population. They are less likely to present with diabetes, hypertension, end-stage renal disease, or coronary artery disease. However, they are more likely to be smokers and have pulmonary embolism, large vegetations, tricuspid valve disease, multiple infected valves, and hepatitis C virus. IV drug users also more likely to have been infected with antibiotic-resistant Staphylococcus aureus.[4,6] Any of these comorbidities can make medical or surgical treatment more difficult.

That being said, overall survival of IVDU-IE patients isn't significantly worse than that of non–IVDU-IE patients, at least in terms of recovery from IE.[4,6,7] That may have something to do with their age: the typical IVDU-IE patient is between 20 to 40 years old compared to typical IE patients in their 50s and 60s.

"In some ways, they're more resilient because young people can tolerate more insults to the body," says Mahesh Ramchandani, MD, cardiac surgeon at Houston Methodist Hospital. "That's the only thing going in their favor: their youth."

HERE TO DRA THE LINE

The biggest obstacle for IVDU-IE patients is addiction itself, particularly when it comes to reinfection. Repeat valve surgery is inherently more challenging and riskier than the initial intervention, and it is an expensive use of money, time, and hospital resources. But even patients who do well after the original valve replacement are at a high risk of repeat IE if they continue injecting drugs. The potential cycle of injection-infection-surgery to injection-reinfection-surgery has led many surgeons to decline to operate on repeat IVDU-IE patients. This cycle has spurred heated debate in the surgical community over when—or if—surgeons should refuse to operate. Ghanta explains:

"Repeat heart operations are sometimes necessary, but whenever a person's behavior is dictating the repeated interventions, we have to make tough ethical decisions. When I operate on a patient who has endocarditis that we believe is secondary to IV drug abuse, I explain to them the gravity of this operation and that if they continue to use drugs and get a repeat infection, there is no guarantee there will be another operation. I am hesitant to offer repeat valve surgery to a patient who has recurrent endocarditis and laboratory evidence of active IV drug use, and I think it comes down to a judgment call. Addiction is a disease that is very difficult to treat, so if the patient does have a relapse, we have to weigh whether it's reasonable to do this high-risk repeat operation and give the patient another opportunity to abstain from the drugs. But where do we draw that line? Is it one time, two times, three times? I don't have the answer."

REFERENCES

1. Intensive Care Unit Physician Staffing. The Leapfrog Group. http://www.leapfroggroup.org/sites/default/files/Files/Castlight-Leapfrog-ICU-Physician-Staffing-Report-2016.pdf. Published July 14, 2016. Accessed November 27, 2018.
2. Udeh C, Udeh B, Rahman N, Canfield C, Campbell J, Hata JS. Telemedicine/Virtual ICU: Where Are We and Where Are We Going? Methodist DeBakey Cardiovasc J. 2018;14(2):126-133.
3. Peckham C. Medscape National Physician Burnout & Depression Report 2018. Medscape Log In. https://www.medscape.com/slideshow/2018-lifestyle-burnout-depression-6009235. Published January 17, 2018. Accessed November 7, 2018.
4. Working day for night using international remote medical care. Emory News Center. http://news.emory.edu/stories/2016/11/hspub_hsupdate_day_for_night/. Published November 16, 2016. Accessed November 7, 2018.
5. Shahpori R, Hebert M, Kushniruk A, Zuege D. Telemedicine in the intensive care unit environment— A survey of the attitudes and perspectives of critical care clinicians. Journal of Critical Care. doi:10.1016/j.jcrc.2010.07.013.
6. Young LB, Chan PS, Cram P. Staff acceptance of tele-ICU coverage: a systematic review. Chest. 2010;139(2):279-288.
7. Moeckli J, Cram P, Cunningham C, Reisinger HS. Staff acceptance of a telemedicine intensive care unit program: a qualitative study. J Crit Care. 2013 Dec;28(6):890–901.

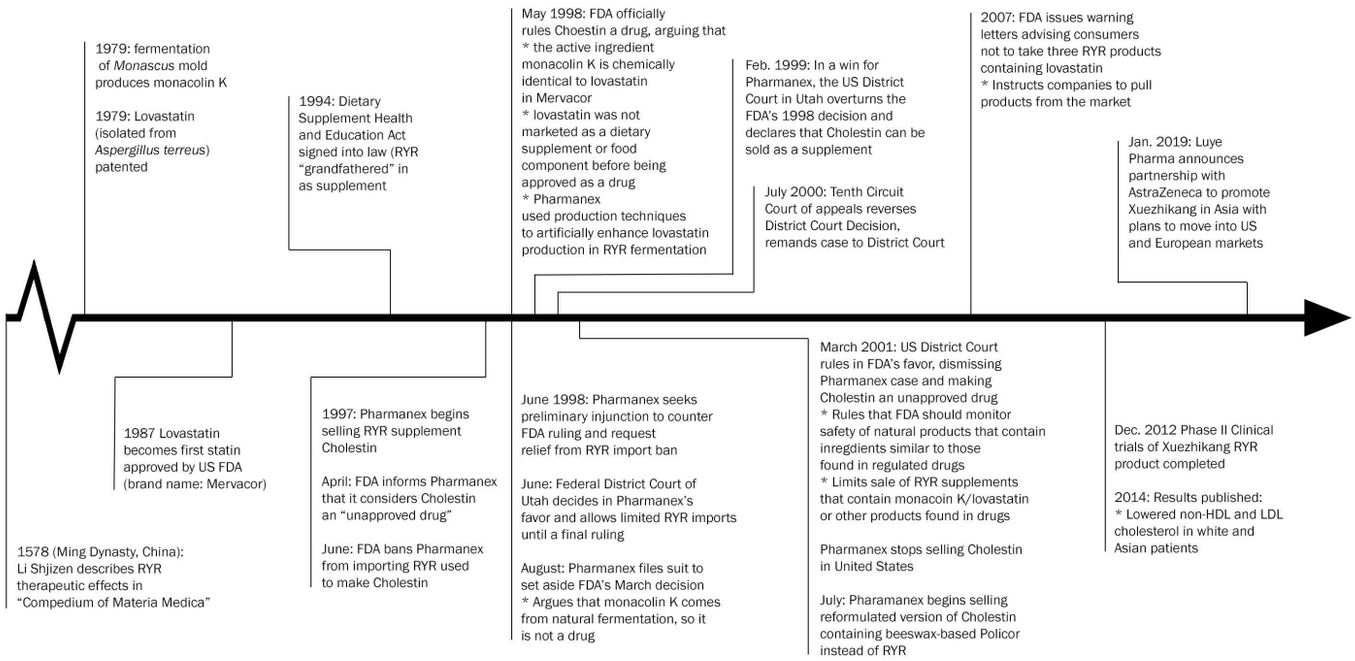

Figure 1.
Molecular Microscope Diagnostic System report. The yellow arrow shows the biopsy. AMBR: antibody-mediated rejection; NR: normal; TCMR: T-cell-mediated rejection; PC: principal component

"Sometimes I'm flabbergasted by the improvement in cholesterol levels that some patients have by taking red yeast rice," he said. "But the other side of the coin is that I've seen patients that did not have success. I don't view it as a substitute for a prescribed statin, but I do see it as an alternative if somebody has tried several statins and doesn't tolerate them. The problem always comes down to: What dose do you prescribe? What specific product to you prescribe? It's unclear. I think the inconsistency is why red yeast rice has not become a first- or even second-line recommendation for physicians.""

RED YEAST RICE GOES TO COURT

Making things more complicated, the FDA considers any RYR product with more than trace levels of monacolin K an unapproved new drug,[7] subject to FDA drug regulations and testing. Considering that the recommended daily dose of monacolin K needed to lower cholesterol is 10 mg, this rule makes it technically illegal to sell a RYR supplement that contains enough of the active ingredient to be useful. Of course, since the FDA has limited oversight over supplement manufacturers, the standard is difficult to enforce and, as illustrated in the aforementioned studies, choosing a RYR supplement remains a gamble.

On occasion, the FDA has taken action against RYR supplements that contained substantial levels of monacolin K. Notably, in the late 1990s, the FDA won a four-year legal with Pharmanex, Inc., to reclassify their RYR product Cholestin from supplement to unapproved drug and remove it from the US market (Figure 1). The FDA argued that Pharmanex used manufacturing practices that increased the concentration of monacolin K above that which is found in traditionally fermented RYR products.[8] Indeed, 2.4 g of Cholestin contained approximately 10 mg of monacolin K, meaning it contained doses of lovastatin comparable to lovastatin in the prescription drug Mervacor, which was already on the market at that time.[9] Under an exclusion clause in the definition of supplements under the DSHEA, a product that contains an ingredient already approved as a drug cannot be classified as a supplement, making Cholestin legally an unapproved drug. Ultimately, the FDA prevailed, and Cholestin disappeared from US store shelves.[8]

NE ROADS TO THE US MARKET

Two decades later, it appears that the RYR market might be in store for another shakeup, with a major pharmaceutical company betting on a RYR product, and seemingly inching toward drug status. In January 2019, UK-based pharmaceutical giant AstraZeneca and China-based Luye Pharma announced a strategic partnership giving AstraZeneca exclusive rights to promote Xuezhikang—a RYR "natural drug"—in China. (Xuezhikang is the RYR formulation used in some of the well-known Chinese studies showing the cholesterol-lowering effects of RYR.) In press releases, the

companies declared their long-term goal to introduce Xuezhikang to international markets, including the United States and Europe.[10] Like Cholestin, Xuezhikang is manufactured to produce enhanced quantities of monacolin K, so presumably it would have to be approved as a drug by the FDA. Indeed, Xuezhikang completed a phase II clinical trial, in compliance with FDA regulations (biospace PR, clinical trial). The trial showed that Xuezhikang treatment significantly lowered non-HDL and LDL cholesterol in white and Asian patients.[11]

Although this announcement raises the possibility that someday a FDA-approved and regulated RYR drug could be available in the United States, for now, consumers are left in the dark. Compounding the problem, RYR supplements are often significantly more costly than generic statins, so picking a product that actually contains monacolin K can be an expensive game of trial and error. Until something changes in supplement law or RYR legal status, promising results in RYR studies have limited utility when choosing a product that actually contains the active ingredient remains a medical and financial gamble.

Corresponding Author:
lgerik@houstonmethodist.org

Conflict of Interest Disclosure:
Laura Gerik is Assistant Managing Editor of the *Methodist DeBakey Cardiovascular Journal.*

Keywords:
red yeast rice, monacolin K, Dietary Supplement Health & Education Act, DSHEA

REFERENCES

1. Cicero AFG, Fogacci F, Banach M. Red Yeast Rice for Hypercholesterolemia. Methodist DeBakey Cardivasc J; 15(3):132-9.
2. Red yeast rice. Penn State Hershey Health Information Library website. http://pennstatehershey.adam.com/content.aspx?productid=107&pid=33&gid=000323 Accessed September 17, 2019.
3. Binns CS, Lee MK, Lee AH. Problems and Prospects: Public Health Regulation of Dietary Supplements. Annu Rev Public Health. 2018 Apr 1;39:403-20.
4. Childress L, Gay A, Zargar A, Ito MK. Review of red yeast rice content and current Food and Drug Administration oversight. J Clin Lipidol. 2013 Mar-Apr;7(2):117-22.
5. Cohen PA, Avula B, Khan IA. Variability in strength of red yeast rice supplements purchased from mainstream retailers. Eur J Prev Cardiol. 2017 Sep;24(13):1431-4.
6. Lachenmeier D, Monakhova Yulia, Kuballa T, et al. Regulatory evaluation of red yeast rice (Monascus spp.) food supplements sold via the Internet. Deutsche Lebensmittel-Rundschau: Zeitschrift für Lebensmittelkunde und Lebensmittelrecht. 2012;108:357-60.
7. Thompson D. 'Red Yeast Rice' Statin Alternative Not Harmless. WebMD website. https://www.webmd.com/cholesterol-management/news/20170124/red-yeast-rice-statin-alternative-not-harmless-either-study-says. January 24, 2017. Accessed September 10, 2019.
8. Wheeler CD, Woodlee JW, Young AL. Lessons from Red Yeast Rice: Factors to Consider Regarding FDA's Position on CBD Supplements. Kleinfeld Kaplan & Becker LLP website. http://www.kkblaw.com/lessons-from-red-yeast-rice-factors-to-consider-regarding-fdas-position-on-cbd-supplements/. Accessed September 18, 2019.
9. Havel RJ. Dietary supplement or drug? The case of cholestin [Editorial]. Am J Clin Nutr. 1999 Feb;69(2):175-6.
10. Luye Pharma Reaches Strategic Partnership with AstraZeneca, Strengthens Commitment to Cardiovascular Therapeutic Field [press release]. Shanghai, China: Luye January 16, 2019. https://www.biospace.com/article/releases/luye-pharma-reaches-strategic-partnership-with-astrazeneca-strengthens-commitment-to-cardiovascular-therapeutic-field/. Accessed September 19, 2019.
11. Moriarty PM, Roth EM, Karns A, et al. Effects of Xuezhikang in patients with dyslipidemia: A multicenter, randomized, placebo-controlled study. J Clin Lipidol. 2014 Nov;8(6):568-75.