INCREASED INCIDENCE OF INFECTIVE ENDOCARDITIS RELATED TO THE OPIOID EPIDEMIC

Introduction

Infective endocarditis (IE) is a life-threatening bacterial infection affecting the cardiac valves. There are several origins of the disease, such as aging and predisposing cardiac legions, however, an increasing amount of infective endocarditis is attributed to injection of illicit drugs [1,2]. In this paper, the correlation between the rising opioid epidemic and the increasing incidences of intravenous drug user infective endocarditis (IDU-IE) will be discussed.

Infective Endocarditis Pathogenesis

Pathogenesis of infective endocarditis is caused by bacteria entering the bloodstream at the site of injection and adhering to damaged valvular endothelium [2]. The bacteria then colonizes, causing vegetation and infection of the valve (See Figure 1) [2]. The bacteria most attributed to infective endocarditis is *Staphyococcus aureus*, accounting for 15-40% of all IE, and the majority of intravenous drug user associated infective endocarditis. Additionally, in IE resulting from intravenous drug use, it is hypothesized that solid particles are injected within the drugs, and thus cause further endothelial injury [2]. Further, the more unhygienic the injection site is, the more likely additional bacteria is to enter the blood stream. Infective endocarditis is associated with organ failure, prolonged hospitalizations, high costs and death in about a quarter of all IE patients [3].

Alyssa Ruman

MSOE Masters of Cardiovascular Perfusion Program

Milwaukee, WI

Class of 2020

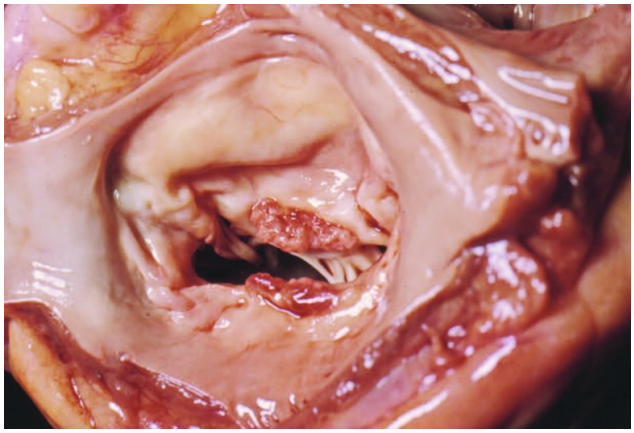


Figure 1. *Native mitral valve affected by infective endocarditis resulting in vegetation on both leaflets [4].*

Opioid Epidemic

Over the past two decades, the United States has seen a sharp increase in the amount of prescription and illicit opioid abuse, resulting in an increase of intravenous drug user infective endocarditis, overdoses, and even deaths. More than 4% of the adult American population, which equals more than 10 million Americans, misuses prescription opioids. Paired with illicit opioid use, the number

of opioid overdose deaths can be used as a measure of tracking the opioid epidemic (Figure 2) [5].

The opioid epidemic has been attributed to two seemingly unrelated events that occurred in the 1990's: the recognition of pain as the fifth vital sign and the approval of the sustained-release formulation of Oxycodone (OxyContinÒ) [6]. The American Pain Society introduced pain as the fifth vital sign, which was quickly embraced by both the Veterans Health Administration and the Joint Commission on Accreditation of Healthcare Organizations in 2000 [6]. Although the efforts of these organizations were one of well-intention, intended to stress a patients right to assessment and management of pain, it resulted in the abundance of prescriptions of opioids to chronic pain patients [6]. In 1996, the sustained-release formulation of Oxycodone (OxyContinÒ) was approved and hit the market, earning $48 million in sales the first year and rising to $3.1 billion in 2010 [6]. The establishment of pain as the fifth vital sign drastically increased the prescription of the highly addictive opioid and between 1997 and 2002, OxyContin prescriptions increased 10-fold [6]. Patients who subsequently developed an opioid-tolerance then began crushing and snorting or injecting the drug to result in a more rapid response from the medication [6]. However, with the reformulation of OxyContin, in efforts to decrease the addictiveness, and the increased difficulty for physicians to prescribe the medication, addicted individuals have started to turn to heroin, a more readily available and cheaper option that activates the same receptors (mu receptors) and produces the same desired effect [6].

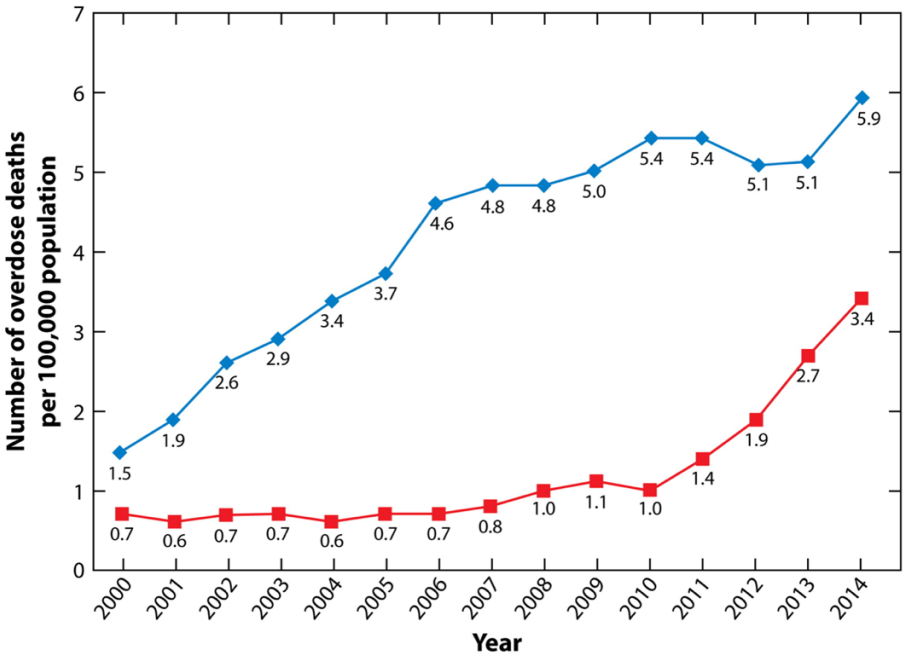


Figure 2. *Rate of prescription opioid (blue triangles) and heroin (red squares) overdose deaths in the United States from 2000-2014 [6].*

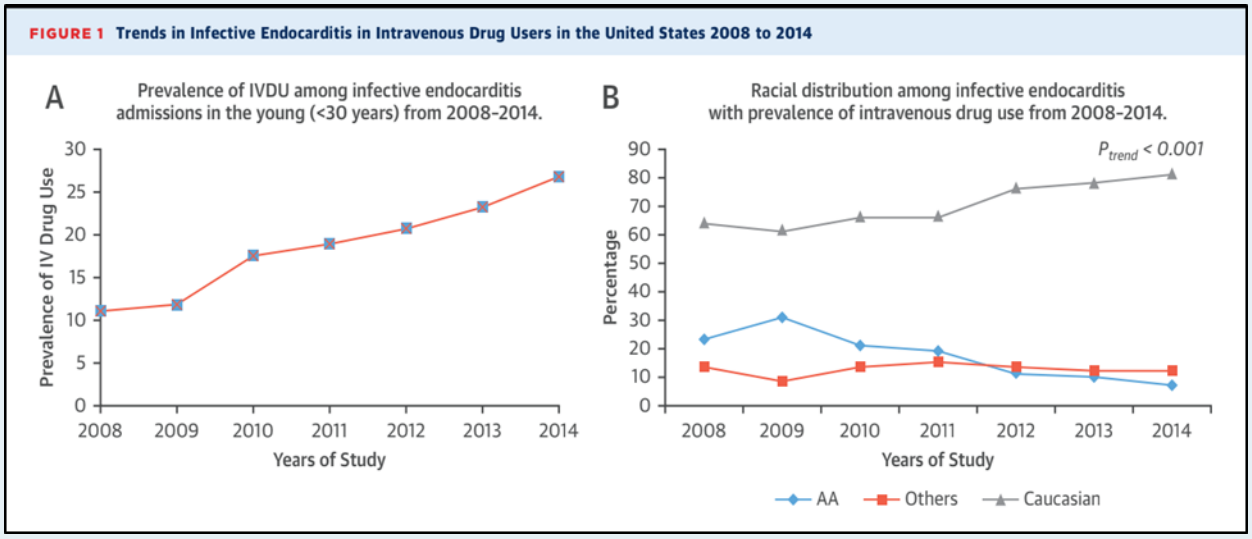
Infective Endocarditis and IV Drug Use

In North Carolina, Asher J Schranz, MD and his colleagues performed an analysis of North Carolina's hospital discharge database from 2007 to 2017 to determine statewide trends for drug use associated infective endocarditis (DUA-IE) hospitalizations [6]. The researchers determined that out of 22,825 infective endocarditis patients, who were 18 or older, 11% (n=2,602) were DUA-IE patients [6]. Additionally, out of those hospitalized for IE, 1,655 of them require valve surgery and 17% of

those requiring valve surgery were DUA-IE patients [6]. Over the period studied, Dr. Schranz and his colleagues found a 12-fold annual increase in DUA-IE hospitalizations from 0.92 to 10.95 per 100,000 persons [6]. Moreover, there was a 13-fold annual increase in DUA-IE patients requiring valve surgery from 0.1 to 1.38 per 100,000 persons [6]. These increases were not observed in patients with infective endocarditis that did not stem from intravenous drug use [6].

Salil V. Deo, MD and colleagues performed a different study analyzing admissions for infective endocarditis from the National Inpatient Sample (NIS) database from 2008 to 2014 [7]. Admission for IE increased from 33,073 (2008) to 39,805 (2014) [7]. Prevalence of drug user associated infective endocarditis increased from 4.3 ± 0.4% in 2008 to 10.0 0.3% ± in 2014 ($p < 0.1$) [7]. Figure 3 summarizes the breakdown of the DUA-IE patient demographics, including the significant difference between races and ages regarding the admitted drug user associated infective endocarditis. Overall, Deo et al. concluded that DUA-IE hospital admissions have doubled in the last few years in the United States. They also concluded that the increased admission, coupled with the high post-operative morbidity and increased resource utilization on these patients, represents a growing health care crisis; one that needs to be addressed at the source before it becomes an epidemic itself.

Figure 3. Infective Endocarditis in Intravenous Drug Users in the United States from 2008 to 2014. *(A) For young adults admitted for infective endocarditis, the prevalence of DUA-IE increased significantly during the period studied (from 11% to 27% ($p<0.001$)). (B) The proportion of Caucasian patients admitted for DUA-IE increased significantly during the study period (from 63% to 73%, $p<0.001$).*



Mechanisms for Dealing with Opioid Abusers

Both of these studies indicate a large increase of drug user associated infective endocarditis in the recent few years. This can be directly correlated with the opioid epidemic that has been occurring since the early 2000's. Multiple controversial solutions to decrease the incidence of infective endocarditis, overdoses, and deaths have been proposed and put into place, such as supervised injection sites, medication-assisted therapies, and Naloxone distribution.

The idea behind supervised injection sites is to supply the drug user with clean needles and supplies to prepare and inject their drugs, while simultaneously having staff nearby to prevent overdoses and offer information about drug treatment and other services. Studies have suggested that safe injection sites are associated with lower overdose mortality (88 fewer overdose deaths per

100,000 person-years), 67% less ambulance calls for treating overdoses, and a decrease in HIV infections [8].

There are several different medication-assisted therapies such as Methadone, and Buprenorphine therapy. Methadone is a full agonist to heroin, meaning that it continues to produce effects on the mu receptors until they are fully saturated, or the maximum effect has been achieved [9]. Buprenorphine, on the other hand, is a partial agonist and does not activate the mu receptors to the same extent as methadone [9]. Its effects increase until a plateau is reached. Methadone has a long half-life of about 8 to 59 hours, Buprenorphine has a half-life of 24 to 60 hours, while heroin has a very short half-life [9]. Medication-assisted therapies are extremely controversial in the sense that one opioid is just being replaced with another, however, for patients who are dependent on prescription opioids, studies have shown that this long-term therapy decreases prescription opioid use and causes better adherence to medication and psychological therapies than opioid tapering or psychological therapy alone [10].

Naloxone is a potent opioid mu receptor antagonist that is FDA approved for emergency treatment of both know and suspected opioid overdoses with respiratory and/or central nervous system depression [11]. Distribution of naloxone paired with education of individuals exposed to opioid use can significantly decrease opioid overdose deaths. A study involving 19 Massachusetts communities found that opioid overdoses were decreased significantly in communities where opioid education and naloxone distribution were implemented [12].

Conclusion

Infective endocarditis is a serious life-threatening condition and its incidences have significantly increased over the past few years in correlation to the rising opioid epidemic. In order to prevent a health care epidemic, society must address the problem at its source and create more resources for individuals who have an opioid abuse problem. Furthermore, the healthcare system must try and prevent any more individuals from becoming addicted to opioid prescription medications by reducing the amounts that they are prescribed, and by reformulating the medications to be less addictive.

References

[1] A. G. Wurcel *et al.*, "Increasing Infectious Endocarditis Admissions Among Young People Who Inject Drugs," *Open Forum Infect. Dis.*, vol. 3, no. 3, Jul. 2016.

[2] A. Wright, O. Otome, C. Harvey, S. Bowe, and E. Athan, "The Current Epidemiology of Injecting Drug Use-Associated Infective Endocarditis in Victoria, Australia in the Midst of Increasing Crystal Methamphetamine Use," *Heart Lung Circ.*, vol. 27, no. 4, pp. 484–488, Apr. 2018.

[3] L. Hartman, E. Barnes, L. Bachmann, K. Schafer, J. Lovato, and D. C. Files, "Opiate Injection-associated Infective Endocarditis in the Southeastern United States," *Am. J. Med. Sci.*, vol. 352, no. 6, pp. 603–608, Dec. 2016.

[4] "INFECTIVE ENDOCARDITIS," *CThSurgery.com*. [Online]. Available: http://www.CThSurgery.com/infective-endocarditis.html. [Accessed: 28-Jan-2019].

[5] P. Skolnick, "The Opioid Epidemic: Crisis and Solutions," *Annu. Rev. Pharmacol. Toxicol.*, vol. 9^2, no. 5, pp. 587–159, 2018.

[6] S. AJ, et al A. I. M. 2018;doi:10 7326/M18-2124 December 3, and 2018, "Opioid epidemic causes surge in infective endocarditis." [Online]. Available: https://www.healio.com/internal-medicine/cardiology/news/online/%7bb2a5af82-f5f1-409d-8be2-d7dc668f6a9e%7d/opioid-epidemic-causes-surge-in-infective-endocarditis. [Accessed: 28-Jan-2019].

[7] S. V. Deo *et al.*, "Admissions for Infective Endocarditis in Intravenous Drug Users," *J. Am. Coll. Cardiol.*, vol. ^{1}5, no. 58, pp. 59^{30}–1597, Apr. 2018.

[8] J. Ng, C. Sutherland, and M. R. Kolber, "Does evidence support supervised injection sites?," *Can. Fam. Physician*, vol. 63, no. 11, p. 866, Nov. 2017.

[9] "Buprenorphine vs. Methadone – Addiction Treatment Forum." [Online]. Available: http://atforum.com/2013/02/buprenorphine-vs-methadone/. [Accessed: 29-Jan-2019].

[10] S. Nielsen, B. Larance, and N. Lintzeris, "Opioid Agonist Treatment for Patients With Dependence on Prescription Opioids," *JAMA*, vol. 317, no. 9, pp. 967–968, 07 2017.

[11] T. Kerensky and A. Y. Walley, "Opioid overdose prevention and naloxone rescue kits: what we know and what we don't know," *Addict. Sci. Clin. Pract.*, vol. 12, no. 1, p. 4, Jan. 2017.

[12] A. Y. Walley *et al.*, "Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis," *BMJ*, vol. 346, p. f174, Jan. 2013.