

Infective Endocarditis: Escalating Human and Health Care Burdens



Infective endocarditis (IE) is uncommon and potentially lethal. These 2 observations are not mutually exclusive, and they bespeak the need for awareness of the possibility of the diagnosis of IE in relevant clinical settings. Because IE is rarely seen by the individual primary care clinician, IE is often overlooked as a cause of illness in favor of more common maladies, some of which are noninfectious in origin. Delays in diagnosis, initiation of appropriate antimicrobial therapy, and surgical intervention in cases in which indications exist can worsen prognosis. Ultimately, hospitalization has been universal for the diagnosis and management of IE. Furthermore, an “endocarditis team” approach with multispecialty expertise is warranted in individual patient management.

“...IE may quickly become a *national epidemic* in the United States...” Alkhouli et al,^{1(p.7)} in this issue of *Mayo Clinic Proceedings*, made this statement in their evaluation of IE and its burden on hospitalizations in this country. Could this be true? After all, some of us had previous concerns for a national IE epidemic over the past 2 decades. In 1997, Connolly et al² described valvular disease associated with an appetite suppressant, fenfluramine-phentermine (“fen-phen”), in 24 women who had no history of valvular disease before taking fen-phen. We watched to see if epidemic levels of IE would develop because of an underlying valvulopathy caused by these agents, coupled with the knowledge that millions of people had taken fen-phen or other related appetite suppressants.^{3,4} Moreover, valvular regurgitation was a result of unusual valvular morphology, and in some cases, either valve repair or replacement was required, which would also increase the risk of IE. Fortunately, no national IE epidemic was declared. The

improvement in valvulopathy over time after discontinuation of these drugs likely reduced the risk of an IE epidemic.

Because we have no clinical trial data to define the efficacy, if any, of antibiotic prophylaxis (AP) in preventing IE due to invasive dental procedures, changes in guidelines used in this country and abroad during the first decade of this century—which, parenthetically, was addressed by Alkhouli et al—have prompted serious concerns that these changes would result in an “endocarditis epidemic.”⁵⁻⁷ The changes, which greatly restricted or eliminated AP in the setting of invasive dental procedures, have prompted a cascade of investigations that have included at least 19 international “before and after guidelines” studies to determine whether IE incidence has increased after the publication of guidelines. Three of them included a cohort with IE from the National (Nationwide) Inpatient Sample, a large US database that was used by Alkhouli et al.⁸⁻¹⁰ In one investigation, there was no increase in IE hospitalization rate, although the “after” period extended only until 2009.⁸ No increase in IE incidence due to viridans group streptococci was found in the second investigation.⁹ The remaining investigation reported an increase in IE incidence due to streptococci for the “after” period, but enterococci were included as streptococci, which seriously compromises the interpretation of the data.¹⁰⁻¹²

It is important to remember that there are multiple factors active at any time point and can influence IE incidence in either a positive or a negative fashion. Some examples include an aging population, prevalence of rheumatic heart disease, implantation rates of a panoply of cardiovascular devices, appropriate use of surgical site infection AP, and prevalence of chronic hemodialysis with specific types of vascular access

See also page 858

(arteriovenous fistula, vascular graft, or indwelling catheter).

Injection drug use is another factor that has markedly influenced all aspects of IE in the United States. Alkhouli et al noted the effect of injection drug use on the National (Nationwide) Inpatient Sample population, which had tripled in patients with IE. Not surprisingly, the proportion of patients with IE who were younger than 30 years doubled during the study period. Although not included in their investigation, one would anticipate that *Staphylococcus aureus* was the primary pathogen in this cohort that was characterized by multiple IE complications, which generally are associated with increased mortality risks. However, Alkhouli et al found a declining in-hospital mortality rate during the study period, and factors responsible for this were speculative but remain undefined. It could be related to limitations of variables available for analysis from the database or calculations limited to short-term follow-up.

Expenditures on IE-related hospitalizations increased overall. This is particularly worrisome for several reasons for patients who inject drugs. First, they are generally healthy, albeit with a high rate of underlying (and underdiagnosed) hepatitis C virus infection.¹³ This is a population that should be characterized by a low economic burden of health care, on the basis of age, instead of what was described in Alkhouli's article. Moreover, these patients frequently either have no health care insurance or receive Medicaid support, which further affects the burden on health care systems. Second, it is tragic that younger patients who survive an initial bout of IE continue to harbor a life-long high risk for subsequent bouts of IE, regardless of whether they continue injection drug use.

Also accompanying Alkhouli's article, an excellent review of IE by Hubers et al¹⁴ was included in this issue. The focus was on diagnosis and management, and there was limited overlap between the 2 publications. Hubers et al detailed contemporary diagnostic strategies that included echocardiography, cardiac computed tomography, and nuclear

scanning. They reviewed antibiotic therapy for the 3 most common causes of IE: streptococci, staphylococci, and enterococci. A decision tree for the surgical management of IE and an algorithm to manage cardiovascular implantable electronic device infections were also provided. The "Knowledge Gaps" section was also helpful as we look forward to improving outcomes in IE.

In summary, both articles in this issue provide complementary information that will be useful to clinicians. Whether we are witnessing an IE epidemic, creative management strategies by an endocarditis team are required for every patient. Moreover, these strategies may have to dramatically change from one day to the next, depending on the clinical course of the patient.

Larry M. Baddour, MD, FIDSA, FAHA

Division of Infectious Diseases
Department of Medicine
and Department of Cardiovascular Diseases
Mayo Clinic College of Medicine and Science
Rochester, MN

Potential Competing Interests: The author reports no competing interests.

Correspondence: Address to Larry M. Baddour, MD, FIDSA, FAHA, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (baddour.larry@mayo.edu; Twitter: @LBaddour1).

ORCID

Larry M. Baddour:  <https://orcid.org/0000-0002-4473-7077>

REFERENCES

1. Alkhouli M, Alqahtani F, Alhajji M, Berzingi CO, Sohail MR. Clinical and economic burden of hospitalizations for infective endocarditis in the United States [published online ahead of print January 3, 2020]. *Mayo Clin Proc*. <https://doi.org/10.1016/j.mayocp.2019.08.023>.
2. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine [published online ahead of print *N Engl J Med*. 1997;337(24):1783]. *N Engl J Med*. 1997;337(9):581-588.
3. Teramae CY, Connolly HM, Grogan M, Miller FA Jr. Diet drug-related cardiac valve disease: the Mayo Clinic echocardiographic laboratory experience. *Mayo Clin Proc*. 2000;75(5):456-461.
4. Connolly HM, McGoon MD. Obesity drugs and the heart. *Curr Probl Cardiol*. 1999;24(12):745-792.
5. Wilson W, Taubert KA, Gewitz M, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Cardiovascular Surgery and Anesthesia; Quality of Care and Outcomes Research Interdisciplinary Working Group. Prevention of infective endocarditis: guidelines from

- the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736-1754.
6. National Institute for Health and Care Excellence (NICE). Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. NICE Clinical Guideline No 64. <https://www.nice.org.uk/guidance/cg64/chapter/Recommendations>. Published March 2008. Accessed February 20, 2020.
 7. Habib G, Hoen B, Tornos P, et al; ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009); the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J*. 2009;30(19):2369-2413.
 8. Bor DH, Woolhandler S, Nardin R, Bruschi J, Himmelstein DU. Infective endocarditis in the U.S., 1998-2009: a nationwide study. *PLoS One*. 2013;8(3):e60033.
 9. DeSimone DC, Tleyjeh IM, Correa de Sa DD, et al; Mayo Cardiovascular Infections Study Group. Incidence of infective endocarditis due to viridans group streptococci before and after the 2007 American Heart Association's prevention guidelines: an extended evaluation of the Olmsted County, Minnesota, population and Nationwide Inpatient Sample. *Mayo Clin Proc*. 2015;90(7):874-881.
 10. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 2015;65(19):2070-2076.
 11. DeSimone DC, Wilson WR, Baddour LM. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011: the devil is in the details. *J Am Coll Cardiol*. 2015;66(10):1201-1202.
 12. Pericas JM, Falces C, Moreno A, Marco F, Mestres CA, Miro JM; Hospital Clínic Endocarditis Study Group. Neglecting enterococci may lead to a misinterpretation of the consequences of last changes in endocarditis prophylaxis American Heart Association guidelines. *J Am Coll Cardiol*. 2015;66(19):2156.
 13. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med*. 2019;170(1):31-40.
 14. Hubers SA, DeSimone DC, Gersh BJ, Anavekar NS. Infective endocarditis: a contemporary review. *Mayo Clin Proc*. 2020;95(5):982-997.