



INSANE IN THE BRAIN: SUBSTANCE USE AND THE RISKS OF ENDOCARDITIS



STROKE CARE NETWORK

Jessica Lee, MD

Professor and Vice Chair for Quality, Dept of Neurology
University of Kentucky College of Medicine

OBJECTIVES

Upon completion of this activity, participants will be able to:

- Discuss substance use and the risk for endocarditis
- Understand the neurological complications of infective endocarditis



DISCLOSURES

- I have received honoraria for activities as a question writer for the Neuro Self-Assessment Examination for the American Academy of Neurology
- I have received honoraria for activities as a speaker for Christiana Health and Hospitals



CASE PRESENTATION

- 24-year-old male presented to a rural community hospital from jail
 - By report he was non-verbal, with jaw clenching prior to transport
 - On arrival, he was febrile to 103.8, tachycardic at 135 bpm, and hypertensive with BP 169/72
 - White blood cell count was 17.9k
 - Serum sodium was 120mg/dl
 - COVID rapid test was negative
 - A non-contrasted CT head showed a large right frontal hemorrhage



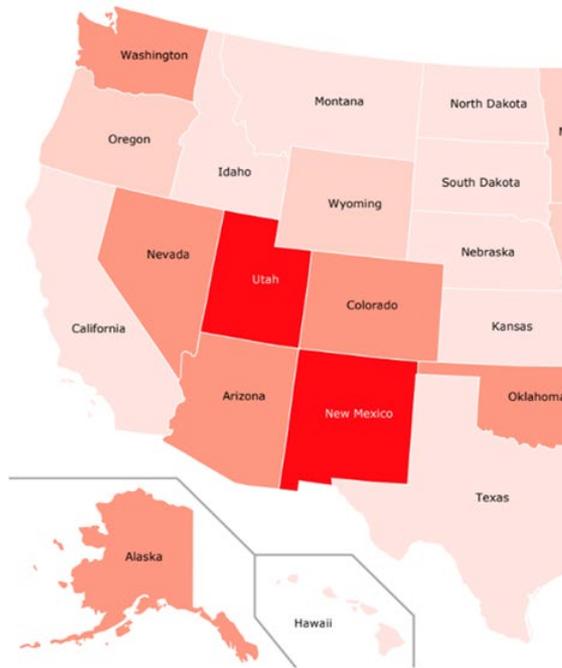
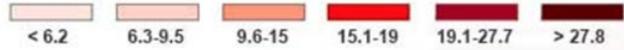
BACKGROUND ON SUBSTANCE USE AND STROKE

- Stroke is the fifth leading cause of death and a leading cause of long-term disability in the US
- Kentucky has one of the highest rates of stroke hospitalization in the US
- In the US, an estimated 20 million people are suffering from substance use disorders (SUD)
- Substance abuse may cause stroke through multiple mechanisms:
 - Vasoconstriction
 - Endothelial dysfunction
 - Drug-induced vasculopathies
 - Advanced rates of atherosclerotic plaques
 - Infective endocarditis



BACKGROUND ON SUBSTANCE USE AND STROKE

2017 Opioid-Related Overdose Death Rates (per 100,000 peop



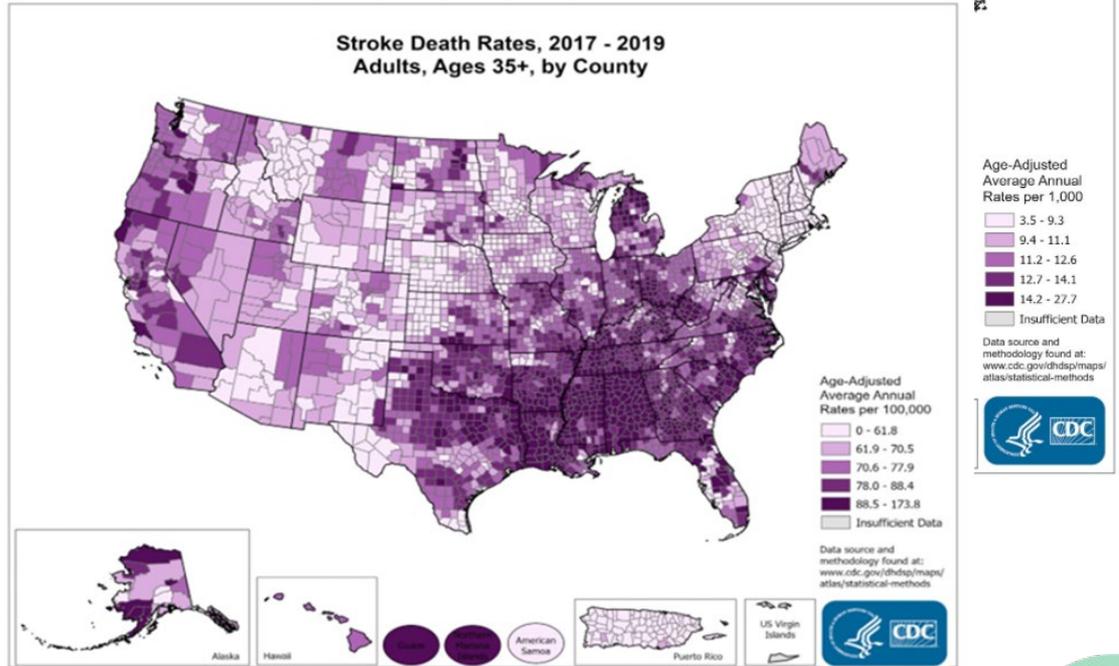
Stroke Hospitalization Rates, Total Population Ages 65+

Stroke Hospitalization Rates, 2017 - 2019
All Medicare Beneficiaries, Ages 65+, by County



Stroke Death Rates, Total Population 35+

Stroke Death Rates, 2017 - 2019
Adults, Ages 35+, by County



BACKGROUND ON SUBSTANCE USE AND STROKE

- Among people aged 12 or older in 2019
 - 60.1 percent (or 165.4 million people) used a substance (i.e., tobacco, alcohol, kratom, or an illicit drug) in the past month
 - 50.8 percent (or 139.7 million people) drank alcohol
 - 21.1 percent (or 58.1 million people) used a tobacco product
 - 13.0 percent (or 35.8 million people) used an illicit drug in the past month



SUBSTANCE USE DISORDER: BACKGROUND AND EPIDEMIOLOGY

- What is a Substance Use Disorder?
 - **recurrent use of alcohol and/or drugs causes clinically significant impairment**, including health problems, disability, and failure to meet major responsibilities at work, school, or home
 - 20.4 million people aged 12 or older with a past year SUD
 - nearly 1 million adults aged 65 and older live with a substance use disorder (SUD), as reported in 2018 data



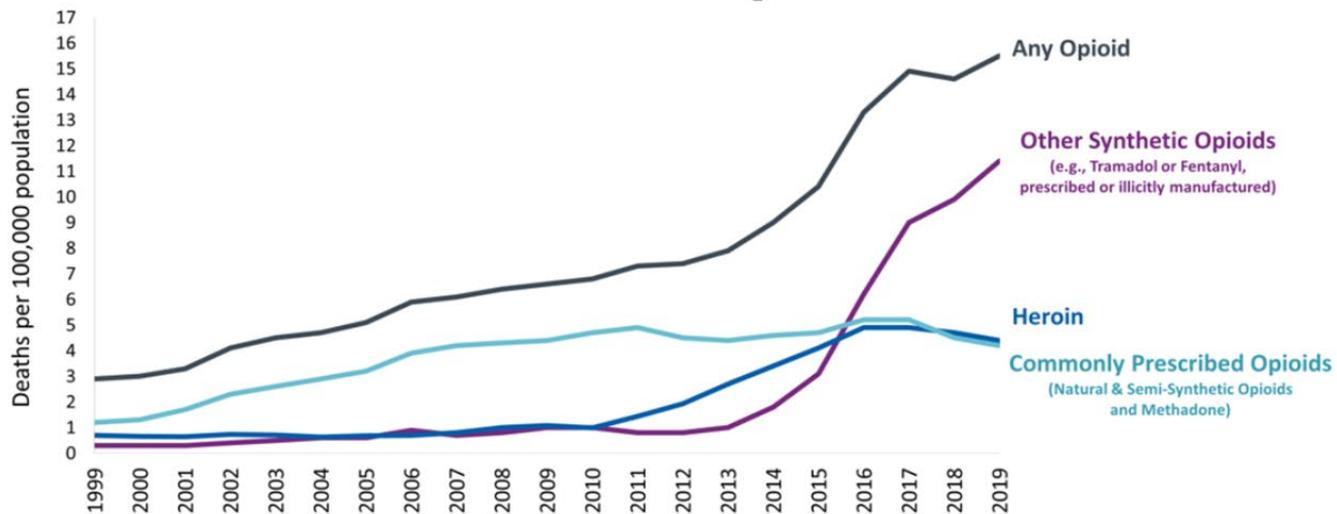
UNDERSTANDING THE DRUG EPIDEMIC

- Number of drug overdose deaths increased by nearly 5% from 2018 to 2019 and has quadrupled since 1999
 - Over 70% of the 70,630 deaths in 2019 involved an opioid
- From 2018 to 2019, there were significant changes in opioid-involved death rates:
 - [Opioid-involved death rates](#) increased by over 6%
 - [Prescription opioid-involved death rates](#) decreased by nearly 7%
 - [Heroin-involved death rates](#) decreased by over 6%
 - [Synthetic opioid-involved death rates](#) (excluding methadone) increased by over 15%



UNDERSTANDING THE DRUG EPIDEMIC

Three Waves of the Rise in Opioid Overdose Deaths



Wave 1: Rise in Prescription Opioid Overdose Deaths Started in 1999

Wave 2: Rise in Heroin Overdose Deaths Started in 2010

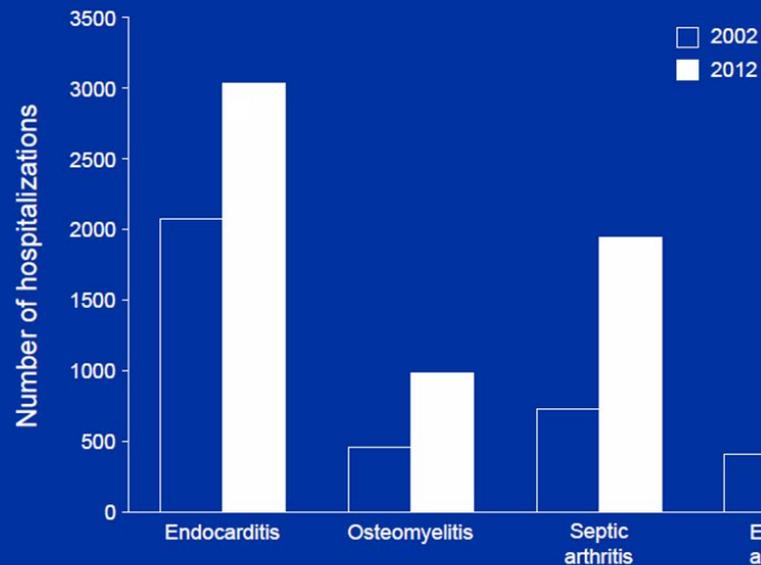
Wave 3: Rise in Synthetic Opioid Overdose Deaths Started in 2013

SOURCE: National Vital Statistics System Mortality File.



UNDERSTANDING THE DRUG EPIDEMIC

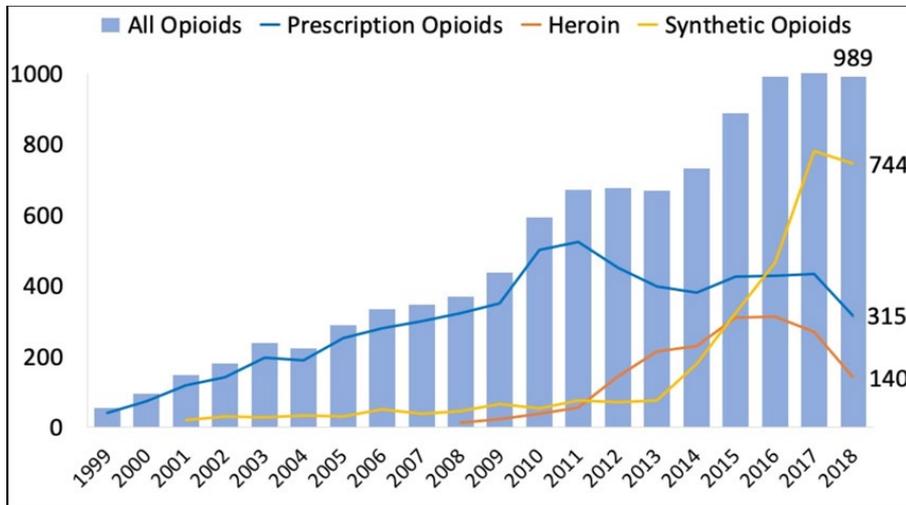
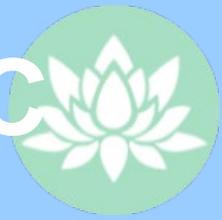
US Hospitalizations for Opioid Use Disorder and Associated Infections



Health Affairs. 2016; 35(5):832-837



KENTUCKY'S OPIOID EPIDEMIC



- In Kentucky, there were 989 (a rate of 23.4) drug overdose deaths involving opioids in 2018—a decrease from the 1,160 deaths (a rate of 27.9 per 100,000) in 2017
- Deaths involving synthetic opioids other than methadone (mainly fentanyl and fentanyl analogs) remained stable, but high, with 744 in 2018 (a rate of 17.9)

KENTUCKY'S OPIOID EPIDEMIC

Lexington, KY – 2012-2015	Boston, MA – 2004-2014
108 inpatients injection-related infections	102 inpatients infective endocarditis
Mean age: 32	67% < 39 years old
OUD by ICD-9: 57%	OUD in discharge summary: 56%
Discharge plan for MAT: 4.6%	Discharge plan for MAT: 7.8%
Mortality: 7.4%	Mortality: 25.5% (median age 40.9)

Liebschutz JAMA Int Med. 2014, 174(8):1369-1376;
Jicha JAM. 2018.



HOW DOES SUBSTANCE USE INCREASE STROKE RISK?

- Substance abuse may cause stroke through multiple mechanisms:
 - Vasoconstriction
 - Endothelial dysfunction
 - Drug-induced vasculopathies
 - Advanced rates of atherosclerotic plaques
 - **Infective endocarditis**





POLLING QUESTION

- True or False?
 - Prescription opioid related deaths have increased over the last 15 years.



Infective Endocarditis



INFECTIVE ENDOCARDITIS: BACKGROUND AND EPIDEMIOLOGY

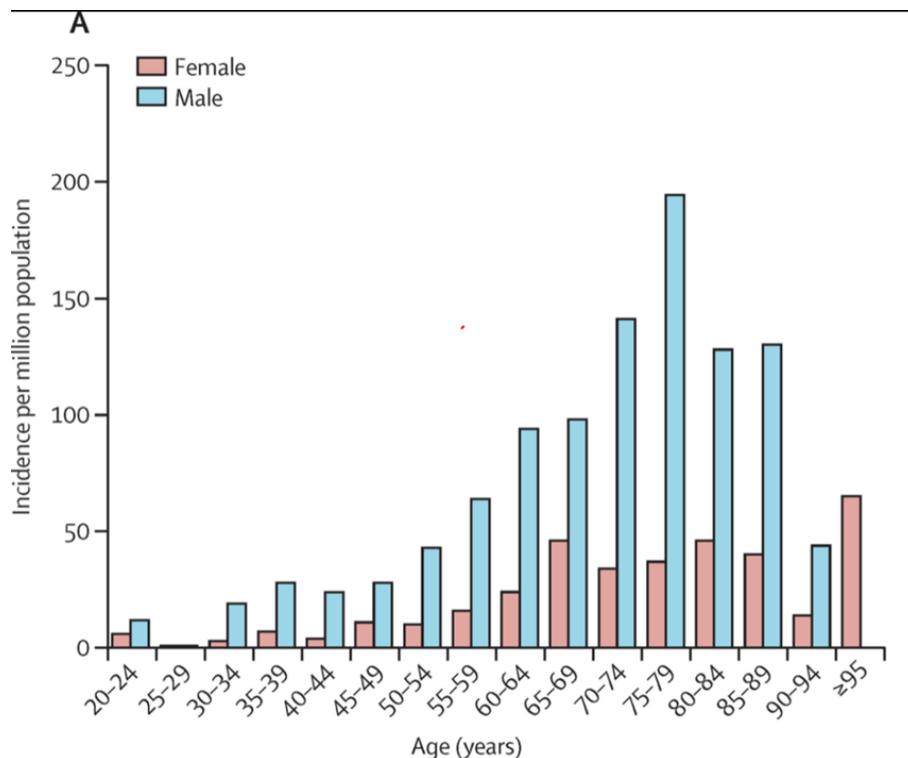
- Normal heart is relatively resistant to infection as bacteria and fungi do not typically adhere easily to the endocardial surface.
- Disruption of the normal structure of the heart can create turbulence
 - Allows virulent microorganisms to settle and adhere to the endocardium
 - May lead to systemic bacteremia infection of the heart valves.
- The first widely published descriptions of this disease came from Sir William Osler in the Gulstonian lectures to the Royal College of Physicians in the late 1800s, then referred to as “ulcerative” or “malignant endocarditis”.



INFECTIVE ENDOCARDITIS: BACKGROUND AND EPIDEMIOLOGY



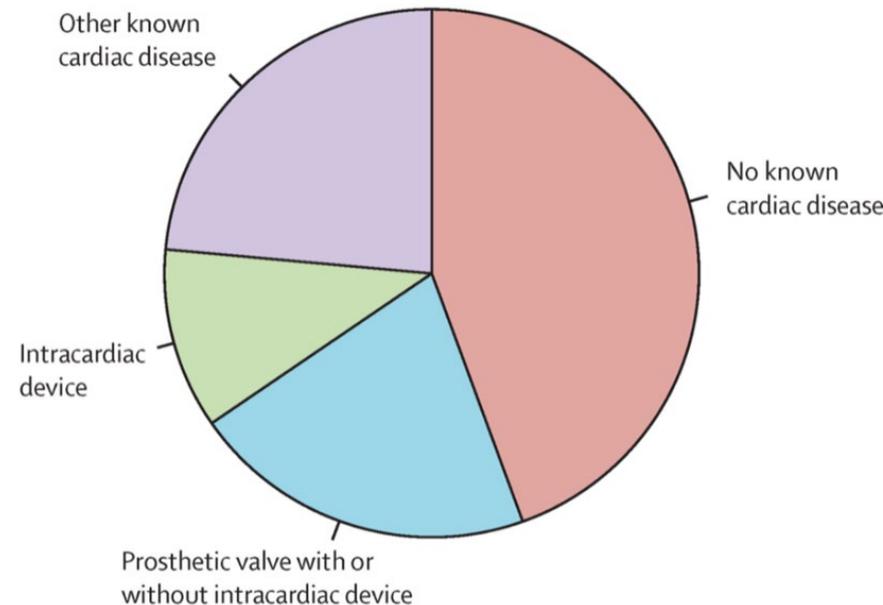
- Patients affected are older and sicker than in the past, often with many comorbidities
 - Greater than half of all patients now diagnosed with IE are older than 50 years of age
- incidence of about 3–10 per 100,000



Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016

INFECTIVE ENDOCARDITIS: BACKGROUND AND EPIDEMIOLOGY

- Degenerative valve disease, diabetes, cancer, intravenous drug use, and congenital heart disease have replaced rheumatic heart disease as the major risk factors for infective endocarditis
- Virulent staphylococci have eclipsed penicillin-sensitive streptococci most common cause in many high-income countries



INFECTIVE ENDOCARDITIS: EPIDEMIOLOGY

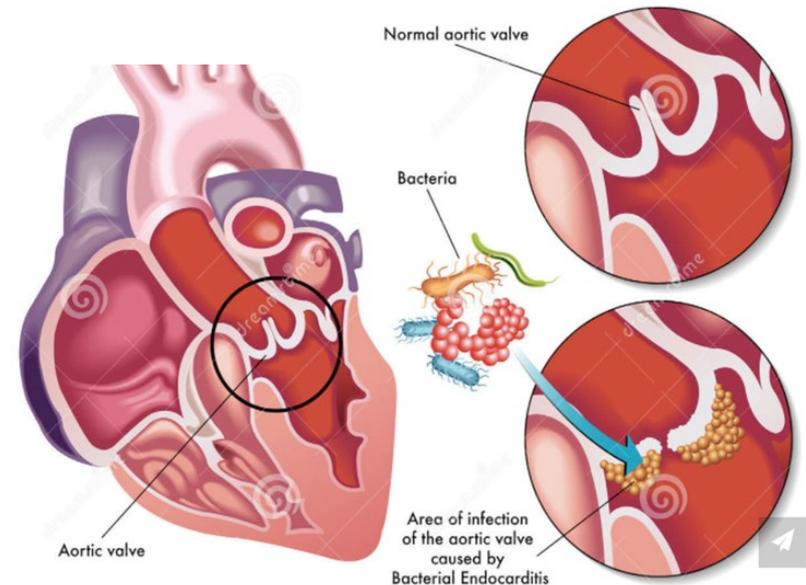
- Infective Endocarditis (IE) may be divided into subcategories
 - Native valve IE
 - Prosthetic valve IE
 - Intravenous drug abuse associated IE.
- In one study (ICE-PCS), more than 70 % of the enrolled patients had native valve endocarditis. IV drug abuse occurred in only 9.8 % while 22.2 % of patients with definite IE had a prosthetic valve.
- History of rheumatic heart disease was quite uncommon, with only 3.3 % of the study population having underlying rheumatic mitral valve disease.



INFECTIVE ENDOCARDITIS: PATHOPHYSIOLOGY



- Several events need to occur for endocarditis to develop
 - Damage to cardiac valves occurs, altering the surface of the
 - Valve surface changes result in the deposit of fibrin, fibronectin, platelets and other serum proteins to create a sterile vegetation, or thrombus.
 - Exposure of the sterile thrombus to bacteria or other microorganisms and adherence of the microorganism to the thrombus
 - Accumulation of additional fibrin/platelets provides protection for the organism, allowing replication



INFECTIVE ENDOCARDITIS: PATHOPHYSIOLOGY

- Certain types of bacteria adhere more readily to the endocardial surface than others
- Animal studies conducted by Gould et al - found organisms commonly associated with IE adhered more readily to aortic valve leaflets
 - *Streptococcus viridans*
 - *Staphylococcus aureus*
 - *Staphylococcus epidermidis*
 - *Pseudomonas aeruginosa*
- French study of 497 cases of IE
 - Staph aureus 26.6%
 - Staph epidermidies 9.7%
 - Oral streptococci 18.7%
 - Enterococcus 10.5%
 - HACEK 1.2%
 - No identified organism 5.2%



CLASSIFICATION OF IE



• Acute IE

- Develops over days
- Evidence of a source of infection or site of entry.
- Presents with high fever, systemic toxicity, leukocytosis, and death within days to 6 weeks if untreated.
- Causative organisms of acute IE usually are *S.aureus*, group A hemolytic streptococci, pneumococci, or gonococci.

• Subacute IE

- Clinical course occurs over weeks to months
- Characterized by low grade fever, night sweats, weight loss, fatigue, and vague systemic complaints.
- Usually no source of infection or site of entry is apparent.
- Causative organisms for subacute IE are mainly streptococci (viridians, microaerophilic, anaerobic, and non-enterococcal group D streptococci and enterococci).

POTENTIAL COMPLICATIONS OF IE

- Cardiac
 - Valvular abscess (42-85%)
 - Valvular regurgitation
 - Congestive heart failure
- Pulmonary- right heart endocarditis
- Renal
- Musculoskeletal
- Neurological
 - Ischemic stroke
 - Hemorrhagic stroke
 - Mycotic aneurysm
 - Abscess



INFECTIVE ENDOCARDITIS: DIAGNOSTIC EVALUATION

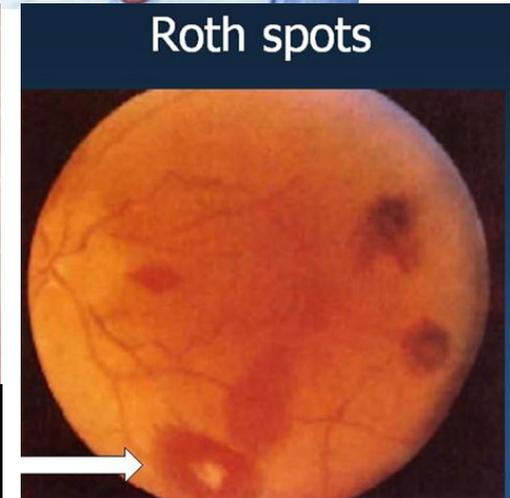
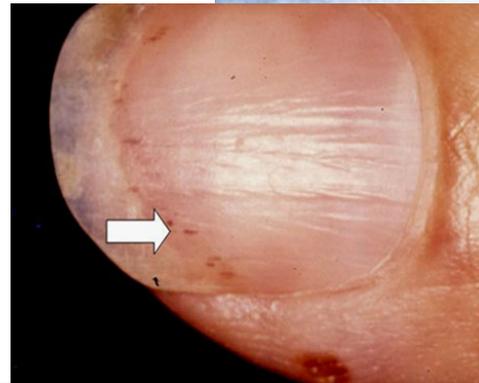
- Endocarditis should be suspected in patients with persistent fever of unexplained origin, especially when there is an associated heart murmur.
- IE should further be suspected in patients who have a known underlying valvular disorder, a prosthetic heart valve, a recent invasive procedure, and in those patients who are IV drug abusers



INFECTIVE ENDOCARDITIS: CLINICAL FINDINGS



- Classic physical exam findings in patients with suspected IE
 - **Splinter hemorrhages (nail beds)**
 - **Osler nodes (painful or sore lesions on the hands and feet)**
 - **Janeway lesions (macular or hemorrhagic lesions on the palms and soles)**
 - **Roth spots (retinal hemorrhage)**



DIAGNOSIS: MODIFIED DUKE CRITERIA

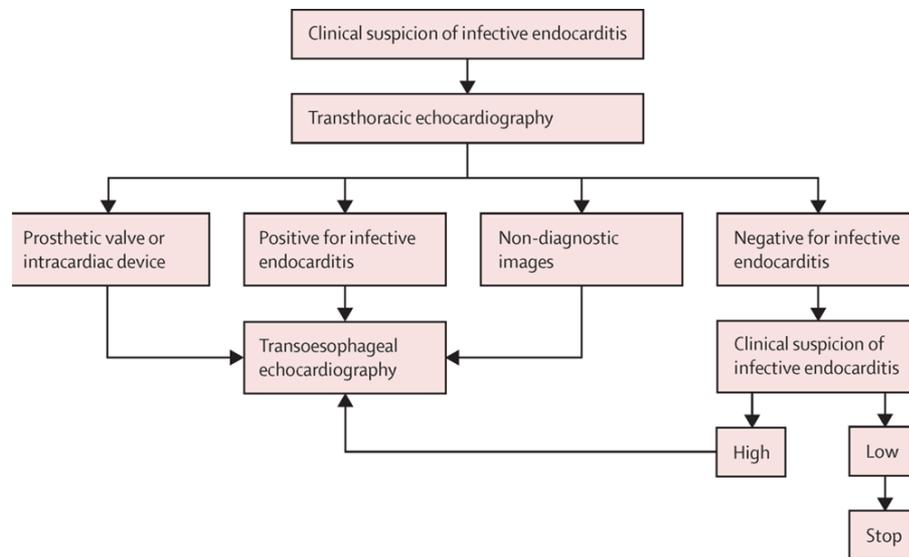
Pathological Criteria	Major Clinical Criteria	Minor Clinical Criteria
<ul style="list-style-type: none"> Microorganisms on histology or culture of a vegetation or intracardiac abscess 	<ul style="list-style-type: none"> Blood cultures positive for infective endocarditis (Staph, Strep, HACEK) on two separate blood cultures 	<ul style="list-style-type: none"> Predisposing heart condition, intravenous drug use
<ul style="list-style-type: none"> Vegetation or intracardiac abscess showing active endocarditis on histology 	<ul style="list-style-type: none"> Single positive blood culture for <i>Coxiella burnetii</i>, or phase 1 IgG antibody titre >1:800 	<ul style="list-style-type: none"> Fever: temperature >38°C
	<ul style="list-style-type: none"> Evidence of endocardial involvement 	<ul style="list-style-type: none"> Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, conjunctival haemorrhages, Janeway lesions
		<ul style="list-style-type: none"> Immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
		<ul style="list-style-type: none"> Positive blood culture that does not meet a major criterion or serological evidence of active infection with organism consistent with infective endocarditis



DIAGNOSTIC EVALUATION:



- Blood cultures
- Transthoracic echocardiogram
 - Native valve– sensitivity 75%
 - Prosthetic valve– sensitivity 46-69%
- Ophthalmologic funduscopic evaluation
- CT angiogram of the head

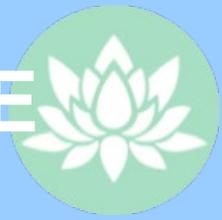


INFECTIVE ENDOCARDITIS AND IV DRUG USE

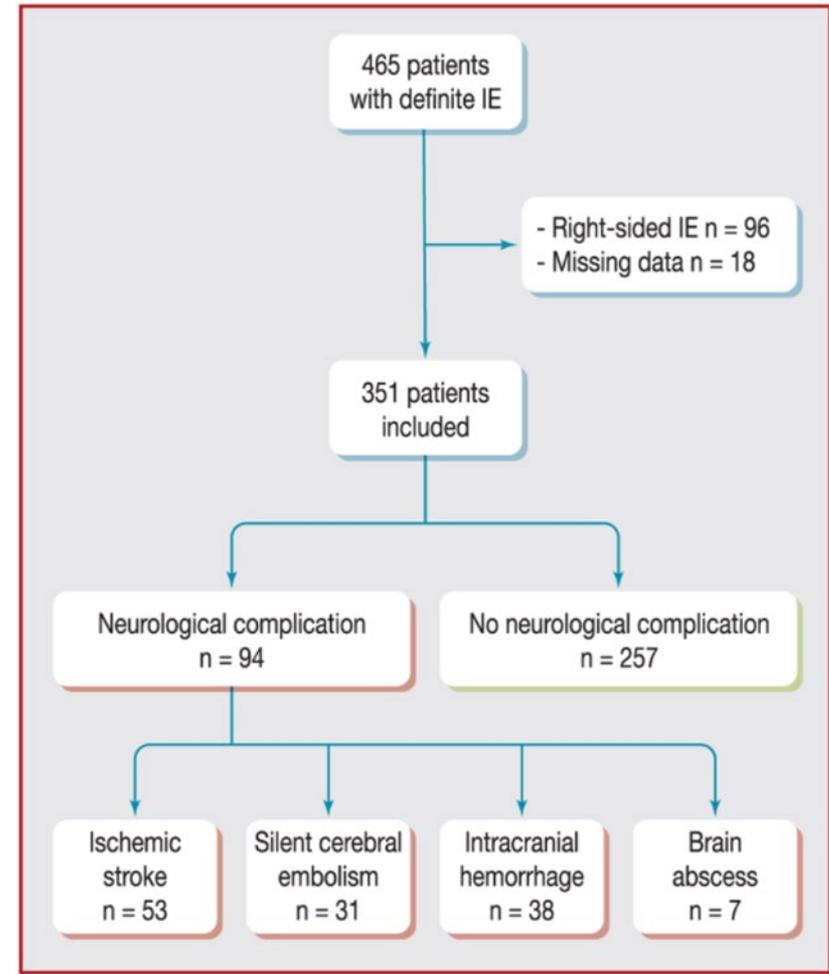
- Study published in 2018 utilizing National Readmissions Database (NRD) for IE cases between January 2010 and September 2015
- survey-weighted sample contained 96,344 (77.8%) non-IVDU related cases and 27,432 (22.2%) IVDU related cases
- IVDU related infective endocarditis increased from 15.3% to 29.1% of IE cases between 2010 and 2015 ($p < 0.001$)
 - Overall IVDU-IE had increased lengths of stay, cost of care, and readmission compared to those with non-IVDU-IE, whether surgically or medically managed



NEUROLOGIC COMPLICATIONS OF IE



- Neurologic complications are one of most common extra-cardiac complications of IE
- Affect between 25-70% of patients
 - Ischemic events - cerebral infarcts /TIA
 - Cerebral abscess
 - 1-20%
 - Intracerebral hemorrhages (ICH)
 - 12-30%
 - Mycotic aneurysms
 - 2-4%
 - Meningitis
- More than two-thirds of patients admitted to the ICU with neurologic manifestations of IE either die or have residual neurologic sequelae



NEUROLOGICAL COMPLICATIONS OF IE: PATHOPHYSIOLOGY

- Widely accepted that most CNS complications are caused by septic emboli
- Other hypothesis
 - small-vessel vasculitis, mediated by autoimmune complexes
 - radiological brain lesion pattern in IE patients is similar to those observed in cerebral vasculitis
 - coexistence of cortical microbleeds, microabscesses, and small ischemic lesions, located in multiple vascular territories and of different ages
 - *vasa vasorum* embolic processes occurring after the systemic embolic phase



NEUROLOGIC COMPLICATIONS OF IE: ISCHEMIC STROKE: DIAGNOSIS

- Studies of imaging modalities reveal MRI (magnetic resonance imaging) to be superior compared with computed tomography (CT) in determining areas of infarction due to septic embolization
 - Several studies have shown that systematic cerebral imaging diagnoses silent cerebral embolism in 60—80% of patients
- Ruttman et al (n=65)-showed 43 % had complete or partial middle cerebral artery infarctions
- Staphylococcus species tend to promote earlier septic embolization when compared with other bacterial agent



NEUROLOGIC COMPLICATIONS OF IE: ISCHEMIC STROKE

- Cerebral infarctions in patients with IE is the result of septic embolization from endocardial vegetations.
- Most common neurological complication of IE
 - ~40 % of patients with IE will develop a cerebral infarction.
- Embolization from mitral valve vegetations were the most common source of cerebral infarcts, with the aortic valve being second most common source



STROKE AND INFECTIVE ENDOCARDITIS AND SUD

- From 1993 to 2015, there were 14,429,338 hospitalizations involving stroke, 12,169,131 involving opioid use, and 815,482 involving IE
 - 5283 hospitalizations with stroke associated with IE and opioid use (mean age, 41.2 years; female, 34.2%)
 - non-Hispanic white, 57.6%
 - Ischemic stroke accounted for 71.5% of hospitalizations
 - Hemorrhagic stroke accounted for 28.5%
- Between 1993 and 2015, hospitalizations for stroke associated with IE and opioid use increased from 2.4 (95% CI, 0.5–4.3) to **18.8** (95% CI, 14.4–23.3) per 10 million US residents per year



NEUROLOGIC COMPLICATIONS OF IE: ISCHEMIC STROKE--TREATMENT

- Thrombolytic therapy (IV rt-PA) contraindicated if known or suspected endocarditis
 - *Possibly* candidates for mechanical thrombectomy if LVO
 - Based on 34 case reports and 3 single center studies, patients with thrombolysis more likely to experience hemorrhagic complications
- Acute antithrombotic therapy is generally not recommended in these patients, due to the increase risk of hemorrhagic conversion of the infarcted sites
- Management of cerebral infarcts secondary to septic embolization includes supportive care and most importantly tailored antibiotic therapy



NEUROLOGIC COMPLICATIONS OF IE: HEMORRHAGIC STROKE

- Intracerebral hemorrhage (ICH) has a poor outcome compared with the other neurologic complications of IE.
- Incidence of ICH due to IE varies by report from as low as 2% to as high as 30%
- The pathological mechanisms of ICH due to IE can vary.
 - hemorrhagic conversion of an infarcted cerebral artery secondary to septic embolization
 - Rupture of mycotic aneurysms



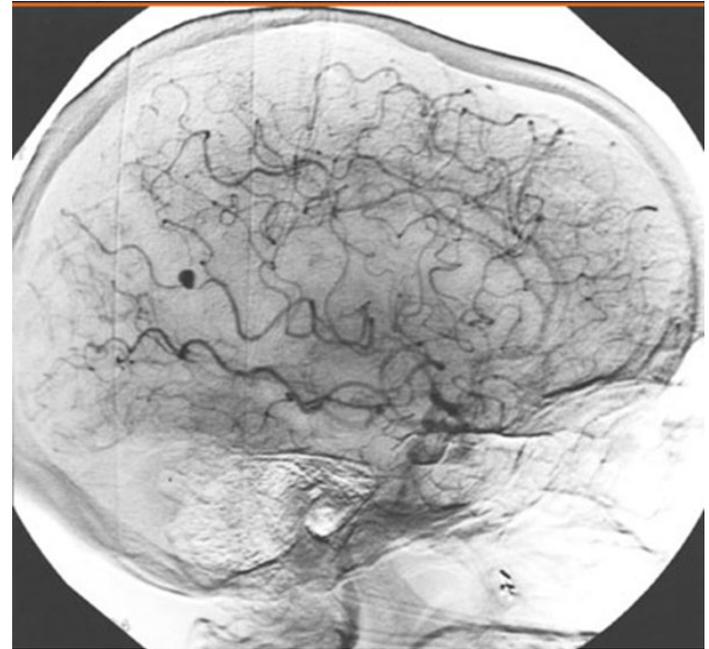
NEUROLOGIC COMPLICATIONS OF IE: HEMORRHAGIC STROKE

- Management of these patients involves supportive care
- May require surgical evacuation of hematoma or hemicraniectomy for edema management
- Antiplatelet or anticoagulation therapy should be discontinued and only re-started at the appropriate time especially in those patients with prosthetic valve



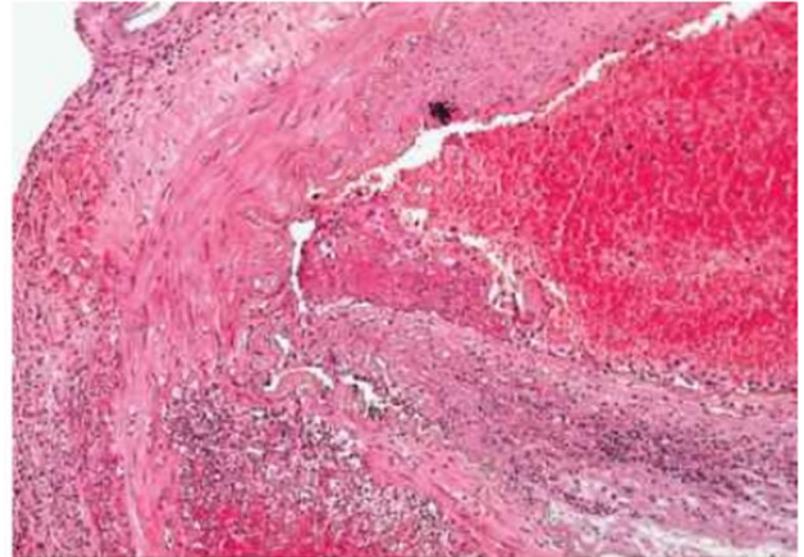
NEUROLOGIC COMPLICATIONS: MYCOTIC ANEURYSM

- Cerebral mycotic aneurysm represents less than 5 % of all intracranial aneurysms
 - Location of mycotic aneurysms usually favors branching points of cerebral arteries
- Studies show occurrence from 10 to 15 % in patients with IE.
- Most patients with unruptured mycotic aneurysms will clinically present with fevers, followed by headaches, seizures, and focal findings such as hemiparesis.



NEUROLOGIC COMPLICATIONS: MYCOTIC ANEURYSM

- Mechanism of mycotic aneurysm formation is believed to be initiated by septic embolization of the vasa vasorum of the cerebral vessel
 - theorized that inflammation from the infectious emboli causes destruction and weakening of the vessel wall starting from the adventitia to the intima of the vessel
- With ruptured mycotic aneurysms, symptoms can vary from focal neurologic findings to alterations of consciousness



NEUROLOGIC COMPLICATION: MYCOTIC ANEURYSM

- Conventional cerebral angiography is regarded as the gold standard in diagnosing mycotic aneurysms.
- Other imaging modalities employed in diagnosing these aneurysms include CT angiography and MR angiography
 - Lower sensitivity, especially MRA
 - If negative CTA and high suspicion, consider repeat study in 7-10 days
- Treatment largely supportive
 - Antibiotics
 - Possible Coiling if unruptured aneurysms not resolved with appropriate course of antibiotics



NEUROLOGIC COMPLICATIONS: CEREBRAL ABSCESS

- Up to 5 % of patients with IE will develop a cerebral abscess due to hematogenous spread
 - most cases associated with *S. aureus*
- Symptoms of cerebral abscess include fever (most common), headache, alterations of consciousness, hemiparesis, and seizures.
- Treatment of cerebral abscesses includes targeted antibiotics and possible neurosurgical intervention if the abscess is large



SHARING OUR EXPERIENCE

- large academic medical center in Kentucky between January 1, 2013 and December 31, 2016
- There were 2,100 cases of IE during the study period. The mean (SD) age was 53 years (21).
 - 440 also had an SUD.
 - Mean age of these patients was 41 years +/-11.
 - Patients in both the IE and IE/SUD categories were primarily male (54% and 55%) and white (94% and 94%).
 - Number of cases of IE increased from 190 in 2013 to 430 in 2016 ($R^2 = 0.9877$).
 - Number of IE/SUD cases increased from 30 (16% of all IE cases) in 2013 to 130 (30% of all IE cases) in 2016 ($R^2 = 0.7352$ for the trend).
 - Corresponds to a 333% increase in the number of cases of IE with SUD.



DEVELOPMENT OF MULTIDISCIPLINARY ENDOCARDITIS TEAM (MDET)

- Recent formation of a Team approach at University of Kentucky
- Meets weekly to review cases and make treatment recommendations
- Representatives from
 - Cardiology
 - Cardiothoracic Surgery
 - Infectious Disease
 - Addiction Consult and Education Services (ACES)
 - Neurology
 - Neurosurgery
 - Ophthalmology





POLLING QUESTIONS

- True or False:
 - Cerebral abscess formation is the most common neurological complication of infective endocarditis.

- True or False:
 - Use of intravenous thrombolysis (rt-PA) is safe and effective in the setting of ischemic stroke and infective endocarditis.



CONCLUSIONS

- Substance use continues to be on the rise
- Complications of IV drug abuse, including infective endocarditis, carries high morbidity and mortality
- High costs of care
- Early recognition and treatment is vital
- Management of IE is multidisciplinary and requires high level coordination of care



QUESTIONS?



REFERENCES

- Cahill TJ, Prendergast BD. Infective endocarditis. Lancet. 2016 Feb 27;387(10021):882-93.
- Salehi Omran S, Chatterjee A, Chen ML, Lerario MP, Merkler AE, Kamel H. National Trends in Hospitalizations for Stroke Associated With Infective Endocarditis and Opioid Use Between 1993 and 2015. Stroke. 2019 Mar;50(3):577-582.
- DD Correa de Sa, IM Tleyjeh, NS Anavekar, *et al.* Epidemiological trends of infective endocarditis: a population-based study in Olmsted County, Minnesota Mayo Clin Proc, 85 (2010), pp. 422-426
- DR Murdoch, GR Corey, B Hoen, *et al.*, the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med, 169 (2009), pp. 463-473
- Mocchegian R, Nataloni M. Complications of Infective Endocarditis, Cardiovascular & Hematological Disorders-Drug Targets 2009; 9(4).
- JS Li, DJ Sexton, N Mick, *et al.* Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis, 30 (2000), pp. 633-638
- F Victor, C De Place, C Camus, *et al.* Pacemaker lead infection: echocardiographic features, management, and outcome. Heart, 81 (1999), pp. 82-87
- C Selton-Suty, M Célard, V Le Moing, *et al.*, the AEPEI Study Group **Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey.** Clin Infect Dis, 54 (2012), pp. 1230-1239



REFERENCES

- G Habib, L Badano, C Tribouilloy, *et al.* Recommendations for the practice of echocardiography in infective endocarditis. *Eur J Echocardiogr*, 11 (2010), pp. 202-219
- S De Castro, D Cartoni, G d'Amati, *et al.* Diagnostic accuracy of transthoracic and multiplane transesophageal echocardiography for valvular perforation in acute infective endocarditis: correlation with anatomic findings. *Clin Infect Dis*, 30 (2000), pp. 825-826
- Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health.
<https://www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRPDFWHTML/2019NSDUHFFR1PDFW090120.pdf>
- Bettencourt S, Ferro JM. Acute Ischemic Stroke Treatment in Infective Endocarditis: Systematic Review. *J Stroke Cerebrovasc Dis*. 2020 Apr;29(4)
- Hess A., Klein I., lung B., Lavallee P., Ilic-Habensus E., Dornic Q., *et. al.*: Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. *AJNR Am J Neuroradiol* 2013; 34: pp. 1579-1584.
- Cantier M, Mazighi M, Klein I, Desilles JP, Wolff M, Timsit JF, Sonnevile R. Neurologic Complications of Infective Endocarditis: Recent Findings. *Curr Infect Dis Rep*. 2017 Sep 19;19(11):41

