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ABSTRACT & COMMENTARY

Risk of Endocarditis Revisited

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Dr. Crawford reports no financial relationships relevant to this field of study.

SYNOPSIS: The authors of a population-wide study of hospitalizations and deaths from infective endocarditis (IE) in England confirmed the high risk of IE in certain cardiac conditions, but showed that other conditions thought to be low risk also are at higher risk and found new higher-risk categories not previously identified.

SOURCES: Thornhill MH, Jones S, Prendergast B, et al. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *Eur Heart J* 2018;39:586-595.

Sun YP, O'Gara PT. Cardiovascular conditions predisposing to infective endocarditis: Time to reconsider the current risk classification system? *Eur Heart J* 2018;39:596-598.

Data on the relative risks of developing infective endocarditis (IE) or dying from IE with different predisposing cardiac conditions in a large population cohort are lacking. Thus, investigators from England surveyed all patients admitted to English hospitals between 2000 and 2013 with a condition associated with an increased risk of IE and followed them for five years to assess subsequent admissions for IE. This information was compared to a reference group of the entire population of England (> 51 million).

The incidence of IE in the whole English population was 36.2 cases/million/year with an admission-related mortality of 6.3 cases/million/year. The incidence was highest in those with a previous history of IE and prosthetic valves or repaired valves (14,359, 4,637, and 4,710 cases/million/year, respectively). IE admission deaths also were highest in these groups (2,940, 1,092, and 907 cases/million/year, respectively). Admissions for IE and subsequent deaths were high in patients with congenital heart conditions (CHC) with a

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shunt or conduit, but lower in those with unrepaired cyanotic CHC and considerably lower in those post repair using prosthetic material. In fact, the incidence of IE or death on admission for IE was higher in those with rheumatic fever or nonrheumatic valve disease compared to those with cyanotic CHC repaired with prosthetic material.

Among conditions in which the risk of IE has not been characterized, hypertrophic cardiomyopathy had a significantly higher risk of IE than the controls (odds ratio [OR], 33; 95% confidence interval [CI], 23-45; $P < 0.0001$) but an insignificant risk of IE death (OR, 4; 95% CI, 0.2-18; $P = 0.17$). However, implanted electrophysiology (EP) devices had a relatively high incidence of IE (OR, 10; 95% CI, 9-11; $P < 0.0001$) and a higher risk of IE death (OR, 10; 95% CI, 9-12; $P < 0.001$) compared to controls.

The authors concluded that some conditions considered at moderate risk of IE and not candidates for antibiotic prophylaxis should be re-evaluated.

■ COMMENTARY

After consideration of the lack of quality data and with pressure from the dental industry, the guidelines were changed in 2007 to state that the use of prophylactic antibiotics for traumatic procedures in areas of the body not amenable to sterilization should be restricted to a few very high-risk conditions. Subsequent studies on the effect of these changes on the incidence of IE have shown conflicting results. This study was designed to use the National Health Service data from England to establish the incidence of IE and hospital death from IE in the English population from 2000 until 2013 with a minimum five-year follow-up and to relate these data to the patients' cardiac conditions that put them at risk for IE.

The results confirm the high-risk status of prior IE, valve surgery (replacement, repair), or CHC with shunts or conduits, but not unrepaired cyanotic CHC and repaired CHC with prosthetic material. There were too few heart transplant patients to accurately assess IE incidence (considered high risk if they have valve regurgitation). Unrepaired cyanotic CHC had a risk of IE similar to rheumatic fever, non-rheumatic valve disease, and congenital valve abnormalities (e.g., bicuspid valve). Repaired CHC with prosthetic material had a lower risk than these valve diseases. The surprise was the moderate risk of IE in hypertrophic cardiomyopathy (HCM). However, many patients with HCM have mitral valve regurgitation. Not surprising was the moderate risk of IE with implanted EP devices.

There were limitations to this study. The authors used ICD-10 codes to categorize the patients rather than the actual medical records. There are no data on comorbidities, the infecting organisms, therapy, or surgery. Also, nonrheumatic valve disease is a broad category that could have subgroups with different results. Finally, the authors only examined hospital admissions and deaths, so the incidence estimates probably are underestimated.

There always has been a proviso that the antibiotic prophylaxis guidelines were just that, and clinical judgment regarding individual patients should be employed. These data from England will help inform which patient considerations outside the restrictive guidelines would be appropriate.

Clearly, high-risk patients (OR, > 76) are those with prior IE, valve replacement/repair, and CHC with shunts/conduits. Intermediate-risk patients (OR, 10-66) would include (in decreasing order by OR): congenital valve abnormalities, unrepaired cyanotic CHC, rheumatic fever, nonrheumatic valve disease, HCM, CHC repaired with prosthetic material, and EP devices.

Whether the next edition of the antibiotic prophylaxis guidelines will alter the recommendations based on these data is unknown, but clinicians should be aware that many believe we have been too restrictive and the patient categories requiring prophylaxis should be revised. ■

ABSTRACT & COMMENTARY

Planes, Pathogens, and Passengers: Infection Risk During Commercial Air Travel

By Philip R. Fischer, MD, DTM&H

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Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: Although air travel has been linked to transmission of respiratory infections, the actual risk of becoming infected during air travel is low. The risk is greatest, though, when seated within about two seats/rows of a contagious individual. Walking around the cabin increases the risk.

SOURCE: Hertzberg VS, Weiss H, Elon L, et al; FlyHealthy Research Team. Behaviors, movements, and transmission of droplet-mediated respiratory diseases during transcontinental airline flights. *Proc Natl Acad Sci U S A* 2018;115:3623-3627.

Commercial airline passengers take billions of trips each year, and it is well-documented that air travel can serve as a conduit for the spread of infections. Researchers have studied pathogens and aircraft to better understand the risks for infection, but no one had carefully observed the actual behaviors of crew members and airline passengers. Thus, Hertzberg et al documented careful observations of the behaviors during flight that could enhance the spread of infection.

The researchers made observations on 10 separate transcontinental flights in the United States involving single-aisle aircraft (three seats on each side of the aisle). Flight durations varied between 211 and 313 minutes. Seven of the 10 flights were full, and the others had two, three, and 17 empty seats. Observations involved 1,540 passengers and 41 crew members in economy class seating.

Overall, 38% of passengers remained in their seats for the entire flight, another 38% left their seats once, 13% left their seats twice, and 11% left their seats more than twice. For those who left their seats, they were up for a median of 5.4 minutes. Seat location was linked to movement away from the seat, with 80% of people seated at the aisle moving, 62% of those in middle seats moving, and only 43% of those in window seats getting up to move around. Only half the passengers used a lavatory during the flight. The average crew member spent about one-third of the flight in contact with passengers and two-thirds of the flight in the galley area.

Moving around the aircraft increased contact with other passengers. Those who left their seats had a median of 44 other contacts with people and a total of 47 person-minutes of contact with someone not seated near them. Crew members had 206 person-minutes of contact with other crew members and 1,149 person-minutes of contact with passengers. Passengers in aisle seats had much more contact with other passengers (64 contacts with other people) than passengers seated in window seats (12 contacts with others).

Based on this information about passenger and crew behavior and knowing that respiratory pathogens are transmitted via droplets over distances less than one meter by cough, sneeze, and breathing, Hertzberg et al constructed a

dynamic network model simulating transmission of influenza. Assuming a high rate of influenza transmission and an index case seated mid-plane in an aisle seat, up to 11 passengers likely would become infected, with the rest of the passengers having less than a 3% chance of coming in close contact with the index case. An infected coughing crew member likely would share the infection with four or five passengers.

Finally, the investigators gathered 228 air and surface (such as seat belt buckle) samples during the flights they studied. Eight of the 10 studied flights occurred during influenza season, and samples were tested by polymerase chain reaction for 18 common respiratory viruses. No sample showed evidence of harboring a respiratory pathogen.

The authors noted the extremely low risk of infection transmitted on the 10 flights they observed. By their modeling, even with a highly contagious individual moving around from an aisle seat in the middle of the plane, less than 10% of fellow passengers would risk contracting an infection.

However, there are reports of higher infection rates with air travel. Astutely, Hertzberg et al noted that transmission of infection also can occur in waiting areas and during the boarding and deplaning processes. Additionally, pathogens that spread via aerosol might reach passengers more than a meter away from an infected index case. Some of the reported outbreaks were associated with flights of longer duration than the three- to six-hour flights in this study.

■ COMMENTARY

These new data remind us that passenger behaviors influence the risk of becoming infected during air travel. Although most infections don't extend more than two seats beyond an infected index passenger, movement around the aircraft can expand the risk of spread.

Anecdotally, I reviewed this paper during a trans-Atlantic flight; I did not notice anyone coughing or sneezing within two seats or two rows of me. However, standing 6'4", I tend to move from my aisle seat much more than the typical passenger reported by Hertzberg et al, and I tend to spend more time out of my seat stretching my legs than did the average studied passenger.

These new data offer clues as to how my mobility exposed me to more potentially infected co-travelers and might explain why I developed a viral upper respiratory infection shortly after arriving at my destination.

Passenger movement during flight increases contact with different passengers. Modeling data also suggest that passenger movement alters the displacement of aerosolized particles in ways that might increase the spread of aerosolized pathogens.[1]

Beyond passenger behavior, other factors also influence whether a passenger will become infected during a long flight. Cabin ventilation systems on commercial aircraft use particulate filters and fully exchange cabin air approximately 15 times per hour.[2] This is effective in decreasing the risk of transmission of infection and explains why most cases are from passengers sitting in close proximity to contagious individuals or related to passenger movement around the cabin. However, ventilation systems are not always activated during flight delays prior to takeoff, and spread of influenza has been reported with a three-hour on-ground delay when a plane's ventilation system was not activated.[3]

The Hertzberg et al data suggest that it is relatively uncommon for sick people to travel. However, with approximately 3 billion air passengers each year (averaging one flight for each two people on the planet each year), there will be times when germs are flying with airplane passengers. What should be done when someone with a respiratory infection is traveling? "Cover the cough" always is good advice, and the use of surgical-type face masks is relatively more common in Asia than elsewhere for protection against both air pollution and infection.

As noted by Hertzberg et al, aircraft cabin hard surfaces are disinfected at least daily; it is not clear that wiping down seats and trays by passengers alters the transmission of infection. Since most transmission occurs within a meter of an infected person, asymptomatic passengers might try to move away from coughing travelers when other seats are available. ■

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ABSTRACT & COMMENTARY

Differences Between Type 1 and Type 2 Diabetic Neuropathy

By Russell L. Chin, MD

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Dr. Chin reports no financial relationships relevant to this field of study.

SYNOPSIS: Microstructural nerve damage in distal symmetric diabetic neuropathy differs between subjects with type 1 diabetes (T1D) and type 2 diabetes (T2D). The predominant nerve lesions in T1D correlated with hyperglycemia and nerve conduction impairment, while the predominant lesions in T2D correlated with dyslipidemia.

SOURCE: Jende JME, Groener JB, Oikonomou D, et al. Diabetic neuropathy differs between type 1 and type 2 diabetes: Insights from magnetic resonance neurography. *Ann Neurol* 2018;83:588-598.

Diabetes mellitus, specifically type 2 diabetes (T2D), is the most common cause of neuropathy in the United States and Europe. Approximately half of all diabetic patients will develop some form of neuropathy during their lifetime. More than 20 million Americans currently have neuropathy secondary to either prediabetes, type 1 diabetes (T1D), or T2D, and the worldwide prevalence is expected to increase, particularly in countries adopting a more Western diet.[1] Distal symmetric diabetic neuropathy (DPN) accounts for about 75% of diabetic neuropathies and is characterized by bilateral, symmetric damage to nerves of the feet in a "stocking" distribution with later involvement of hands and mild distal motor weakness. Neuropathic pain is a disabling consequence of DPN, affecting 25-50% of patients. Sensory symptoms include positive symptoms of pain, tingling, prickling sensations, altered sensation (such as allodynia or hyperalgesia), and negative symptoms of numbness.

The pathogenesis of DPN remains elusive, and, consequently, there are no approved disease-modifying therapies that unequivocally prevent or reverse the neuropathy. Vigilance about foot care and neuropathy development, lifestyle changes, and strict glycemic control are counseled. Symptoms are managed, often suboptimally, with pregabalin, duloxetine, and gabapentin. Medications that target ion channels that are more selectively expressed in nociceptors (e.g., Nav 1.7, 1.8, and 1.9) are under investigation.[1]

Research into the pathophysiology of DPN has evolved from a "glucocentric" viewpoint to a broader understanding that the DPN is a complex disorder secondary to multiple linked and cascading reactions. Inflammation, endothelial dysfunction, deposition of advanced glycation end products (AGE), microvascular-induced ischemia, increased aldose reductase activity, and oxidative stress are implicated in nerve damage. Research into whole nerve metabolism and insulin sensitivity and resistance (potentially at the level of the nervous system) also provide clues about the mechanism behind DPN in T2D.[2] Rigorous glycemic control, while reducing the incidence of DPN in T1D, has little to no effect in the more common T2D, indicating different mechanisms underlying the DPN in each disorder. It is likely that components of the metabolic syndrome promote the onset and progression of DPN in T2D, as evidenced by the higher rates of dyslipidemia and obesity in T2D compared with T1D.[3,4]

In this study, 120 patients (35 with T1D and 85 with T2D), of whom 84 had DPN, were evaluated. Detailed medical history, clinical and electrodiagnostic findings, blood studies, and objective and subjective scoring data were obtained. High-resolution MR neurography of the right leg in a 3.0T magnetic resonance scanner was obtained. The earliest and most prominent nerve lesions in DPN have been reported to occur at the level of the distal sciatic nerve, so calculation of the T2-weighted hyperintense and hypointense lesions was performed for the sciatic nerve at the mid-thigh level. Both kinds of lesions were found more commonly in DPN and associated with an increased severity of clinical symptoms.

T2-weighted hypointense lesions appeared hyperintense on T1-weighted images, strongly suggesting a high lipid content. The lipid volume in these lesions was higher in T2D compared to T1D patients with and without DPN, and there was a positive correlation with neuropathy symptoms and triglyceride levels and a negative correlation with serum HDL levels. The authors hypothesized that

these lesions might represent an imaging correlate of intraneural aggregates of lipids or microvascular lipid deposits inside the wall of perineural blood vessels. However, T2-weighted hyperintense lesion load was higher in T1D compared with T2D, and there was a positive correlation with hemoglobin A1c level and impairment of nerve conductions. The authors hypothesized that these lesions represent an imaging correlate of AGEs in the extracellular matrix of myelinating cells.

■ COMMENTARY

MR neurography allows unprecedented in vivo evaluation of DPN, offsetting the limitations of human nerve accessibility and rodent models of DPN. The differing patterns of nerve damage described in this article provide additional evidence of the unique pathophysiologic mechanisms behind the two types of DPN and help explain the limited benefit of glycemic control in T2D DPN. An improved basic understanding of the disease process is crucial to clinical trials, which have been disappointing to date. Mechanism-based treatments are desperately needed for this global epidemic. ■

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PHARMACOLOGY UPDATE

Erenumab-aooe Injection (Aimovig)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

A new class of drug has been approved for the preventive treatment of migraine in adults. Erenumab-aooe is a fully human monoclonal antibody and is the first-in-class calcitonin gene-related peptide (CGRP) receptor antagonist. It is marketed as Aimovig.

INDICATIONS

Erenumab-aooe is indicated for the preventive treatment of migraine in adults.[1]

DOSAGE

The recommended dose is 70 mg given subcutaneously once monthly.[1] Some patients may need 140 mg (two injections of 70 mg) once monthly. Erenumab-aooe is available as a 70 mg single-dose prefilled syringe or autoinjector (SureClick).

POTENTIAL ADVANTAGES

Erenumab-aooe, with a novel mechanism of action, is the first drug approved specifically for the preventive treatment of migraine.

POTENTIAL DISADVANTAGES

Erenumab-aooe must be administered by injection. Injection site reactions and constipation are the most common side effects (3-5%). The long-term safety of erenumab-aooe remains to be established.

COMMENTS

CGRP is believed to be a key mediator in migraine headaches, suggesting that targeting the CGRP receptor may be an effective approach in preventing migraine.[2] The efficacy of erenumab-aooe was evaluated in three randomized, double-blind, placebo-controlled studies.[1,3,4] Two were in subjects with episodic migraine (four to 14 migraine days per month) and one in subjects with chronic migraine (≥ 15 headache days and ≥ 8 migraine days per month).

In the first six-month study, subjects were randomized to erenumab-aooe 70 mg (n = 317), 140 mg (n = 319), or placebo (n = 319).[1,3] Migraine-specific medications such as triptans, ergotamine derivative, and nonsteroidal anti-inflammatory drugs were allowed during the study. The primary efficacy endpoint was change from baseline in mean monthly migraine days (MMD) over months four to six. A migraine day was defined as any calendar day that the patient had onset, continuation, or recurrence of a migraine lasting at least 30 minutes and

manifesting with at least two pain features, at least one associated nonpain feature, or both.[3] Secondary endpoints included the percentage of subjects achieving ≥ 50% reduction from baseline in mean monthly migraine days (% responders) and change from baseline in mean monthly acute migraine-specific medications over months 4 to 6. At baseline, the mean migraine frequency was about eight days per month, and approximately 39% had a history of preventive treatment failure due to lack of effectiveness or intolerance.

Erenumab-aooe 70 mg reduced MMD by a mean of 3.2 days, while 140 mg reduced MMD by 3.7 days, compared to -1.8 days for placebo, a difference from placebo of -1.4 and -1.9, respectively (both $P < 0.001$). Response was achieved at the first efficacy time point of one month. Percent responders were 43.3% and 50% for erenumab-aooe compared to 26.6% for placebo. Difference in monthly acute migraine-specific medication days were -0.9 and -1.4 ($P < 0.001$). Physical impairment and everyday activity scores also improved significantly with both doses of erenumab-aooe.

The second study was a three-month investigation of erenumab-aooe 70 mg (n = 286) and placebo (n = 291) in subjects with episodic migraine (approximately eight migraine days per month).[1,4] At month 3, the difference between drug and placebo was -1.0 MMD ($P < 0.001$). The percent responders were 39.7% vs. 29.5% ($P = 0.01$). The difference in monthly migraine-specific medication days was -0.6 ($P = 0.002$). However, erenumab-aooe did not significantly improve everyday activity or physical impairment scores.

In subjects with chronic migraine (mean of 18 MMD at baseline), erenumab-aooe 70 mg and 140 mg both reduced MMD by 2.5 days compared to placebo. Percent responders were 40-41% compared to 23.5% for placebo. The difference in monthly medication days were -1.9 and -2.6 ($P < 0.001$). Recently, Novartis released results from a study assessing the effectiveness of erenumab-aooe in subjects who experienced two to four previous preventive treatment failures.[5] Thirty percent responded to erenumab-aooe compared to 14% for placebo. Erenumab-aooe appears to be well tolerated. Less than 3% of subjects withdrew from the six-month trial because of adverse reactions.[2] Anti-erenumab-aooe antibodies developed in about 5% of subjects and < 0.1% exhibited in vitro neutralizing activity. However, this may be underestimated because of the limitation of the assay.[1]

CLINICAL IMPLICATIONS

It is estimated that close to 40% of migraineurs need preventive therapy.[6] Current evidence-based guidelines of the American Academy of Neurology and the American Headache Society list antiepileptics (divalproex sodium, sodium valproate, topiramate) and beta-blockers (propranolol, timolol, metoprolol) as pharmacologic migraine prophylaxis with established efficacy.[6] Erenumab-aooe provides a novel drug for preventing migraine headaches. The list price is $575 for one month. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. **A population-based study in England showed that which of the following conditions was associated with a low risk of infective endocarditis?**
   a. Congenital heart disease with a shunt or conduit
   b. Repair of congenital heart disease with prosthetic material
   c. Unrepaired cyanotic congenital heart disease
   d. Prosthetic heart valve

2. **Risk factors for becoming infected by a respiratory pathogen during air travel include which of the following?**
   a. Sitting within 3 m of a coughing passenger
   b. Remaining seated throughout the flight
   c. Failing to sanitize tray tables
   d. Sitting in the plane during pre-takeoff delays

3. **Which of the following statements about distal symmetric diabetic neuropathy (DPN) is *false*?**
   a. MR neurography findings in DPN in type 1 diabetes were associated with elevated hemoglobin A1c and impaired nerve conduction studies.
   b. MR neurography findings in DPN in type 2 diabetes were associated with low HDL and high triglycerides.
   c. Approximately 50% of all diabetic patients will develop neuropathy during their lifetime.
   d. Strict glycemic control has a similar effect on the incidence of DPN in type 1 diabetes and type 2 diabetes.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Fish Consumption and Disease Activity in Rheumatoid Arthritis

As-needed Budesonide-Formoterol vs. Maintenance Budesonide in Mild Asthma