In the Limelight: January 2020

This monthly feature highlights four articles in the current print and online issue of Mayo Clinic Proceedings. These articles are also featured on the Mayo Clinic Proceedings’ YouTube Channel (https://youtu.be/vKMC5cOV3so).

VACCINATION AGAINST INFECTIOUS DISEASES: JENNER’S VITAL LEGACY

The success story of vaccination is a striking example of the time-honored adage that an ounce of prevention is worth a pound of cure. Milestones in the story of vaccination are also compelling, based as they are on astute clinical observations and clear scientific reasoning: Edward Jenner noted that dairy maids previously infected with cowpox became immune to smallpox, and then demonstrated in 1796 that inoculation with cowpox conferred resistance to smallpox (Sampathkumar P, Mayo Clin Proc. 2019;94(10):1931-1932). Smallpox not only holds a special place in the early history of vaccination, but also has the distinction of being the only infectious disease globally eradicated because of vaccination. Since Jenner’s time, vaccination has triumphed against many other infectious diseases. In October 2019, under the editorial leadership of Dr Priya Sampathkumar, Mayo Clinic Proceedings began a thematic review series on vaccination; in her editorial introducing this thematic review, Dr Sampathkumar outlined the history of vaccination, its success, and the threat posed by the anti-vaccine movement. This thematic review series thus far has discussed vaccines for health care personnel and international travel and Zika vaccine development. In the present issue of Mayo Clinic Proceedings, Hunter et al review vaccination in adults focusing on influenza, pneumococcal, hepatitis A and B, human papilloma virus, and zoster vaccines. This team of experts participates in the Advisory Committee on Immunization Practices (ACIP), the body that reviews the use of vaccines in the United States with special attention to efficacy, safety, and indications. ACIP makes recommendations to the Director of the Centers for Disease Control and Prevention (CDC) which then leads to CDC’s official position. The discussion by Hunter et al on influenza encompasses such salient considerations as epidemiology of influenza; how vaccine strains are selected; types of available vaccines and the basis for the timing of vaccination; age and other determinants of response to vaccination; and the current recommendations regarding the significance of egg allergy. In discussing pneumococcal vaccination, Hunter et al highlight the two available vaccines which are different in composition and may have age-specific and risk-specific indications. Hunter et al review recommendations for tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in general and in pregnancy in particular as this provides an effective and safe way of preventing pertussis in neonates. The indications for vaccination against hepatitis A and B, and human papilloma virus (HPV) are discussed; points of special consideration include the availability of a newer hepatitis B vaccine that requires only two doses over one month, and that vaccination for HPV is most effective at preventing HPV-associated cancers when given in early adolescence. As regards herpes zoster, the recombinant inactivated zoster vaccine, as pointed out, is preferable to the live vaccine as it is much more effective. In the second part of their article, Hunter et al emphasize the need to increase rates of vaccination in adults. An essential approach is to assess vaccination status at each clinical visit; offer needed vaccines or refer elsewhere for vaccination; and participate in state registries. Hunter et al delineate the specific challenges that impede vaccination efforts; these include patient perceptions, vaccine hesitancy, and process-related issues at clinics and health care systems. Vaccine advocacy by clinicians at regional, state, and federal levels provide an important strategy.
in increasing rates of vaccination. Hunter et al are to be applauded for their timely review on these specific vaccines and for their broader call for clinician involvement in and advocacy for strategies aimed at increasing rates of vaccination. The importance of vaccination in promoting global public health is exceeded only by a supply of clean water—safeguarding and augmenting rates of vaccination is thus a national and global imperative.


KIDNEY DISEASE AND THE USE OF ORAL ANTIHYPERGLYCEMIC AGENTS

Type 2 diabetes (T2D) is a major risk factor for chronic kidney disease (CKD), and when the latter occurs, the outcomes for patients with T2D are considerably worsened. Such adverse effects of CKD are largely imposed because CKD and uremia further augment the already increased risk for cardiovascular diseases in T2D, and diabetic CKD is often a progressive process that culminates in end-stage kidney disease. The occurrence of CKD also significantly influences glycemic control: First, CKD reduces the cellular sensitivity to insulin and impairs the catabolism of insulin by the renal proximal tubules, effects that may predispose to hyperglycemia and hypoglycemia respectively; and, second, the metabolic clearance of several oral antihyperglycemic agents (OHAs) is decreased with declining kidney function. In the present issue of Mayo Clinic Proceedings, two studies address the use of OHAs for T2D in the setting of CKD. In a retrospective cohort study undertaken in Manitoba, Canada, Whitlock et al compared the safety profiles of metformin (approximately 20,000 users) and sulfonylureas (approximately 2000 users), as first line monotherapy for T2D, in the setting of normal kidney function and varying stages of CKD. Metformin is generally regarded as the first line drug in T2D as it reduces plasma glucose concentration (by increasing the sensitivity to insulin and suppressing hepatic glucose production) without a gain in body weight or an increase in plasma insulin concentrations; metformin is generally well tolerated and relatively inexpensive; and its use may be attended by improved outcomes for cardiovascular disease in T2D. Because metformin is cleared from the body by active secretion into urine by the renal proximal tubules, there are concerns regarding the use of metformin in the setting of advanced CKD, with the rare risk of lactic acidosis; its use is proscribed in CKD when the estimated glomerular filtration rate, eGFR, is 30 ml/min/1.73 m² or less. The analysis of Whitlock et al demonstrates that metformin usage as compared with that of sulfonylurea was attended by a lower risk of major hypoglycemic episodes, cardiovascular events, and all-cause mortality. CKD modified the risk for mortality in that for an eGFR less than 60 ml/min/1.73 m², no differences in mortality were observed between these two classes of OHAs, whereas irrespective of the severity of CKD, use of metformin was still attended with a lower risk for hypoglycemic episodes and cardiovascular events. Also in this issue of Mayo Clinic Proceedings is the observational cohort study by Hong et al involving more than 80,000 adults with T2D and CKD treated with dipeptidyl peptidase-4 (DPP-4) inhibitors; this study utilized the Korean National Health Information Database, and DPP-4 inhibitors were prescribed either as monotherapy or in combination with other OHAs. The essential conclusion was that a significant number of patients on DPP-4 inhibitors received dosages that were excessive because of accompanying CKD, and that such
inappropriate dosing of DPP-4 inhibitors in patients concomitantly treated with other OHAs was associated with an increased risk for severe hypoglycemia, visits to the emergency department, and mortality. Both these studies thus underscore the common theme that underlying CKD can significantly influence outcomes in patients with T2D treated with OHAs: the study by Whitlock et al concludes in favor of the use of metformin over sulfonylureas in CKD, while the study by Hong et al calls attention to adverse outcomes in CKD with inappropriate dosing of DPP-4 inhibitors when used with other OHAs.


THE OCCURRENCE OF ACUTE MYOCARDIAL INFARCTION BEFORE THE AGE OF 55 YEARS

Traditional atherosclerotic cardiovascular risk factors and age-related multimorbidity are both less common in relatively younger individuals (less than age 55 years) as compared with older individuals. Drawing upon these observations, along with the relative cardioprotective effect of the pre- and peri-menopausal state in women, Gulati et al comprehensively and expertly discuss in this issue of Mayo Clinic Proceedings the basis for and clinical presentation and management of acute myocardial infarction (AMI) in young individuals. These authors start from the sobering premise that while AMI is significantly less common in younger individuals, it is still a significant contributor to morbidity and mortality in this age range, and has not evinced the decline in mortality from cardiovascular diseases seen in recent years in older individuals. Approximately two-thirds of AMIs in young individuals reflect, as in the older range, traditional risk factors and the occurrence of plaque rupture. Less common causes include illicit drug use (cocaine and methamphetamine); spontaneous coronary artery dissection (SCAD); myocarditis; coronary embolism; myocardial infarction (MI) due to atheromatous coronary artery disease (CAD) but without critical stenosis; and coronary vasospasm. Notable sex differences exist in young individuals with AMI. For example, while the incidence of AMI is lower in women as compared with men, women experience a longer interval before receiving medical attention for AMI; have worse outcomes when hospitalized with AMI; are much more likely to have an MI with nonobstructive CAD; and are predisposed to SCAD, a disease that may reflect underlying fibromuscular dysplasia and is more likely to occur in pregnancy. Gulati et al comprehensively discuss the management of various types of AMIs in young individuals, which range from management of AMIs where the approach is broadly agreed upon (current management guidelines for AMIs due to traditional cardiovascular risk factors) to AMIs where management is surrounded by uncertainty (SCAD). The authors conclude their article with very clear algorithms that determine the following: whether thrombus is detected in the coronary arteries and whether there are accompanying traditional cardiovascular risk factors; how to differentiate between SCAD and coronary microvascular dysfunction in patients with nonobstructive CAD; and how to home in on underlying causes for AMI in patients with nonobstructive CAD as well as a negative initial workup. As is generally underscored in medical teaching, the diagnosis of a specific disease first requires an appreciation that such a disease may occur. Awareness of the occurrence of AMIs in young individuals may be blunted because AMI in this age range is relatively uncommon, may present atypically, and may be underpinned by uncommon conditions.
diseases. This important review by Gulati et al raises the awareness of and sensitivity to this disease, discusses how it is diagnosed and its underlying cause delineated, and outlines key principles and approaches in the management of the various subtypes.


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