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This month's feature highlights three articles that appear in the current issue of *Mayo Clinic Proceedings*. These articles are also featured on the *Mayo Clinic Proceedings*' YouTube Channel (https://youtu.be/H79AfL9gByE).

ELUCIDATING FSGS BY GENETIC TESTING

Focal segmental glomerulosclerosis (FSGS), the most common primary glomerulopathy in patients with end-stage kidney disease, is a histopathologic diagnosis for sclerosing lesions involving some glomeruli (focal, not diffuse) and only a segment of the glomerular tuft (segmental, not global). This seemingly straightforward histopathologic diagnosis noticeably belies the true nature, heterogeneity, complexity, and challenge of diseases complicated by FSGS. First, these lesions of FSGS are generally diagnosed by a two-dimensional kidney biopsy section, and not from three-dimensional reconstructed images; when serial kidney sections are performed, glomeruli not involved in a given section may display segmental sclerosis in others; FSGS, in all likelihood, generally involves many more glomeruli than implied by the term "focal." Second, even with regard to the seemingly monotonous histopathologic designation itself, there are variants of FSGS that are recognized, and these are described as either cellular, tip, perihilar, collapsing, or not otherwise specified lesions. However, these histopathologic variants do not differentiate among the clinically categorized types of FSGS (primary, secondary, genetic). Third, the pathogenetic processes that culminate in FSGS, their clinical presentation and features, and how they are therapeutically managed, are quite varied. For example, primary FSGS is generally considered to arise from a circulating toxin that damages podocytes and the glomerular filtration barrier, is commonly attended by the nephrotic syndrome, and is usually treated by immunosuppression. In primary FSGS, the nephrotic syndrome generally reflects a high degree of effacement of the foot processes of podocytes (FPE), usually greater than 80% as assessed by electron microscopy. Segmental sclerosis likely involves all glomeruli at some stage in the evolution of primary FSGS. Secondary FSGS, on the other hand, does not usually cause the nephrotic syndrome, and may arise from diverse conditions that include obesity, reduced renal mass, sleep apnea, vesicoureteral reflux, drugs, viruses, sickle cell disease, among other conditions. However, there are some patients with presumed secondary FSGS in whom a known cause cannot be identified. More recently, FSGS is recognized as a consequence of genetic abnormalities that compromise podocytes and the integrity of the glomerular filtration barrier. Determining whether FSGS is primary, secondary, or genetic in origin is a key objective as there are subtype-specific considerations with regard to prognosis, therapy, and transplantation. In the present issue of *Mayo Clinic Proceedings*, the study by Miao et al addressed the utility of and the indications for genetic testing in patients with an FSGS lesion. Miao et al classified patients with FSGS into four categories: primary FSGS (the presence of nephrotic syndrome and greater than 80% FPE); secondary FSGS (absence of nephrotic syndrome and less than 80% FPE) with or

without an underlying cause; and undetermined FSGS (patients in whom the degree of FPE and the presence/absence of the nephrotic syndrome were not entirely consistent with the diagnosis of either primary or secondary FSGS). Remarkably, Miao et al found a relevant genetic abnormality in the majority of patients with undetermined FSGS (88%) and those with secondary FSGS without an underlying cause (62%). Even in patients with secondary FSGS with an underlying cause, 33% of patients exhibited a genetic abnormality, the latter uncovered in the vast majority of patients in this group with a family history of kidney disease. Indeed, for the entire patient population, a family history of kidney disease was the strongest predictor for an underlying causative genetic abnormality. The study by Miao et al is important and timely for numerous reasons. First, a monogenic basis was found in over 40% of the total patient population, thereby underscoring the importance of genetics in driving nephropathies such as FSGS. Second, undetermined FSGS may indeed be determined by a genetic cause, a finding that raises the broader issue of the potential and power of genetics to elucidate other diseases generally considered "idiopathic," "cryptogenic," "overlap," "mixed," or "undetermined." Third, this study clearly identifies patient-specific features that portend an underlying genetic abnormality, and which should lead clinicians to undertake genetic testing in such patients with an FSGS lesion. Fourth, these findings show how concomitant genetic abnormalities may account for atypical features in FSGS, such as, for example, the failure of a patient with primary FSGS to respond to immunosuppressive therapy. Finally, genetic abnormalities may not only be the principal driver of FSGS, as occurs in genetic FSGS, but in other instances they may provide a "second hit" as occurs when a relevant genetic abnormality is detected in a patient with secondary FSGS who already exhibits a known predisposing clinical cause.

Miao J, Pinto e Vairo F, Hogan MC, et al. Identification of genetic causes of focal segmental glomerulosclerosis increases with proper patient selection. *Mayo Clin Proc.* 2021;96(9):2342-2353. https://doi.org/10.1016/j.mayocp.2021.01.037.

INITIAL FLUID ADMINISTRATION IN SEPSIS: WHICH, HOW MUCH, WHEN?

Hospitalists and generalists provide the first line of care for patients admitted with sepsis to medicine services, and the central management issues they face include that of fluid resuscitation and when does such resuscitation need transfer to the intensive care unit (ICU) and the addition of vasopressors. In the present issue of *Mayo Clinic Proceedings,* Ladzinski et al provide a discerning and comprehensive overview of this topic and related considerations. At the onset, these authors emphasize a number of key considerations including the fact that while sepsis may cause both hypotension and shock, these complications are pathogenetically different: Hypotension represents a fall in systemic blood pressure below the autoregulatory capacity of major organs, but shock essentially reflects a compromise in tissue supply and availability of and/or utilization of oxygen. Additionally, while sepsis may cause all major forms of shock - hypovolemic, distributive, cardiogenic, and obstructive — septic shock is generally hypovolemic and/or distributive in nature. The former results from true volume depletion alone or in conjunction with escape of fluid from the intravascular compartment because of cytokine-induced capillary leakiness. Distributive shock reflects venodilation with increased venous capacitance and attendant venous pooling. Both types of shock in sepsis reduce ventricular preload; volume depletion is targeted by fluid resuscitation, while vasopressors reduce venous pooling. An additional consideration is that sepsis may lead to hypotension because of a reduction in arterial tone. The therapeutic implications of these considerations are that if fluid administration does not mitigate hypotension, especially when cardiac function should appropriately respond to increased preload, vasopressor therapy should be initiated to increase vascular tone and thereby combat hypotension and shock. Ladzinski et al review the evolution of guidelines

regarding fluid resuscitation leading up to the recommendations of the 2016 surviving sepsis guidelines of a 30 ml/kg fluid bolus. These authors underscore the following points: First, fluid administration to achieve a "normal" central venous pressure (CVP) of 8 to 12 mm Hg, as was done in the initial positive Early Goal-Directed therapy (EGDT) trial, may be injudicious as a CVP of 8 to 12 mm Hg may be high in these settings. Second, fluid overload is associated with increased mortality because of multiple adverse effects of edema in the cardiorespiratory systems, gastrointestinal tract, the kidney, the nervous system, and elsewhere. As regards which fluids to administer, the authors point out the lack of evidence supporting the use of colloids and that crystalloids are favored, with some studies supporting balanced crystalloids over 0.9% saline. Ladzinski et al review the resuscitation targets in sepsis, what these targets signify, their limitations and how they may respond to fluid therapy, including such targets as systemic blood pressure, serum lactate, and capillary refill time. The subsequent section addresses the basis and importance of assessing fluid responsiveness, noting that besides fluid administration, preload may be increased by passive leg raise. An increase in cardiac output, an essential index by which to evaluate the efficacy of fluid resuscitation and increased preload, may be assessed by point-of-care ultrasonography or bedside echocardiography. The authors point out that fluid responsiveness may also be assessed by carotid Doppler as carotid blood flow tends to track with that of cardiac output; the numerous challenges associated with collapsibility of the inferior vena cava in evaluating fluid responsiveness; and that measurements of CVP should play no role in assessing fluid responsiveness. In concluding, Ladzinski et al underscore the recognized adverse effects of fluid overload, emphasize the need for hemodynamically grounded fluid administration, caution against the administration of repetitive boluses of fluid, and strongly advise transfer to the ICU and the use of vasopressor therapy when hypotension is refractory to targeted fluid resuscitation in sepsis.

Ladzinski AT, Thind GS, Siuba MT. Rational fluid resuscitation in sepsis for the hospitalist: a narrative review. *Mayo Clin Proc*. 2021;96(9):2464-2473. https://doi.org/10.1016/j.mayocp.2021.05.202.

ASSESSMENT OF LONG-TERM PROGNOSIS ON ADMISSION TO THE CICU

In 2019 Jentzer et al introduced the Mayo Cardiac Intensive Care Unit Admission Risk Score (M-CARS) for risk stratification of patients admitted to the cardiac intensive care unit (CICU) and demonstrated that this model was superior to others, specifically SOFA (Sequential Organ Failure Assessment) and APACHE (Acute Physiology, Age and Chronic Health Evaluation), in predicting in-hospital mortality (Jentzer et al, *JAHA*. 2019;8: e013675). This model is based on, as assessed on admission, the following seven elements: BUN, anion gap, the Braden skin score, the RBC distribution width, and diagnosis on admission of cardiac arrest, shock, or respiratory failure. In the current issue of *Mayo Clinic Proceedings*, Breen et al assessed the accuracy of M-CARS in predicting 1-year mortality by retrospectively reviewing CICU admissions from 2007 to 2018. In this population of 12,428 patients, as M-CARS increased, 1-year survival decreased, with each of the seven elements of M-CARS significantly predicting 1-year mortality. With an M-CARS score less than 3, the 1-year survival among hospital survivors decreased as M-CARS increased, with no further decline in 1-year survival with an M-CARS of 3 or greater. Interestingly, four elements of M-CARS that associated with 1-year mortality in patients who survived the initial hospitalization included BUN, RBC distribution width, the Braden skin score, and respiratory failure. In discussing their findings, Breen et al make the following telling points, among others, regarding the attributes and greater reliability of M-CARS vis-à-vis other risk models such as SOFA and APACHE. First, M-CARS is based on data at admission, not 24 hours of data as utilized by these other scoring systems. Second, M-CARS was obtained from a more recent CICU population

and thus may more reliably disclose determinants of 1-year prognosis. Third, SOFA and APACHE were originally developed to assess in-hospital mortality and are primarily based on indices that reflect acute illness; in contrast, M-CARS incorporates markers of both acute and chronic illness. This latter consideration is especially germane, as in the study by Breen et al, markers that correlated with 1-year mortality were those that reflected chronic illness and frailty. This study is an important contribution because it complements prior findings demonstrating the validity of M-CARS in predicting mortality during hospitalization for an acute cardiac illness. Moreover, this study underscores the importance of frailty and chronic comorbidities as determinants of more distant outcomes following acute admission to the CICU. Finally, this study validates M-CARS as a reliable risk stratification model in predicting 1-year mortality when managing, decision-making, and prognosticating on acutely ill patients admitted to the CICU.

Breen TJ, Padkins M Bennett CE, et al. Predicting 1-year mortality on admission using the Mayo Intensive Care Unit Admission Risk Score. *Mayo Clin Proc.* 2021;96(9):2354-2365. https://doi.org/10.1016/j.mayocp.2021.01.031.

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