WHAT'S NEW IN UPTODATE

DECEMBER 2023

KOSAR LIBRARY HOSPITAL

JANUARY 2024

PRACTICE CHANGING UPDATES

- **Thyroid hormone administration in deceased organ donors**

- ●For hemodynamically unstable, brain-dead organ donors, we suggest **against** the use of thyroid hormone (Grade 2C). Thyroid hormone supplementation has little to no effect on organ procurement or graft outcomes, but it increases the rates of hypertension and tachycardia in deceased donors.

- Thyroid hormone administration has been a longstanding component of some organ procurement protocols due to concern that acute hypothyroidism might contribute to hemodynamic instability and left ventricular dysfunction, reducing heart and other organ procurement; however, evidence for the practice has been inconsistent. In a recent trial of 838 hemodynamically unstable, brain-dead donors assigned to receive a levothyroxine infusion or saline placebo, there was little to no difference in number of hearts transplanted or 30-day cardiac graft survival [1]. Recovery of other organs was similarly unaffected. More cases of severe hypertension or tachycardia occurred in the levothyroxine group than in the saline group. Based on these data, we suggest avoiding thyroid hormone administration in deceased organ donors. (See "Management of the deceased organ donor", section on 'Thyroid hormone'.)

WHAT'S NEW IN
PULMONARY AND CRITICAL CARE MEDICINE

- **Tapering inhaled corticosteroids in asthma patients responding to biologics (December 2023)**

- Strategies for tapering other asthma therapies, such as inhaled corticosteroids (ICS), for patients who achieve good asthma control with biologics has not been well studied. In an open-label, randomized trial of 168 adults with a history of severe eosinophilic asthma and good control on benralizumab and high-dose ICS, 43 patients were assigned to an ongoing high-dose ICS-formoterol regimen and 125 patients were assigned to a 32-week taper protocol (medium-, low-, and as-needed dosing of ICS-formoterol) [1]. In the tapering arm, 92 percent of patients achieved lower doses of ICS, with only 9 percent experiencing exacerbations. However, significant decreases in FEV_1 and increases in fraction of exhaled nitric oxide occurred in patients using the least amount of as-needed ICS-formoterol after their taper. These data suggest that most patients well-controlled on biologics may be successfully tapered to regimens containing medium- or low-dose ICS with long-acting bronchodilators. However, the safety and efficacy of tapering to as-needed ICS-formoterol requires further study. (See "Treatment of severe asthma in adolescents and adults", section on 'Tapering therapy'.)

- **Sighs during mechanical ventilation (December 2023)**

- A ventilatory sigh refers to the administration of a deep breath every few minutes, which in prior studies was proven to maintain lung volume and to avoid atelectasis. However, sighs subsequently fell out of favor when high lung volumes were shown to be harmful. In a recent trial of over 500 ventilated trauma patients, compared with usual care, intermittent sigh volumes delivered every six minutes (plateau pressure 35 cm H20) did not increase the number of ventilator-free days or 28-day mortality [10]. There were few adverse events, but sigh-related hypotension was seen in 2 percent. While encouraging, further data are needed before sighs can be routinely applied during mechanical ventilation. (See "Overview of initiating invasive mechanical ventilation in adults in the intensive care unit", section on 'Intermittent sigh'.)

- **Extracorporeal cardiopulmonary resuscitation (December 2023)**

- Extracorporeal cardiopulmonary resuscitation (ECPR) is being increasingly used, but data are limited and the benefits are uncertain. In a recent meta-analysis of 11 studies (10,000 patients) who underwent CPR, compared with standard CPR, ECPR was associated with decreased in-hospital mortality and increased long-term favorable neurologic outcome and survival at one year [9]. The benefit of ECPR was confined to patients with in-hospital cardiac arrest. These data support the growing practice of ECPR in select patients likely to benefit. (See "Extracorporeal life support in adults: Management of venoarterial extracorporeal membrane oxygenation (V-A ECMO)", section on 'Sudden cardiac arrest (extracorporeal cardiopulmonary resuscitation)'.)

- **Heart rate control in septic shock (December 2023)**

- Beta blockade has the potential to limit harm from the adrenergic overdrive that occurs in septic shock. However, data to support heart rate control in patients with septic shock are limited. In a recent, unblinded randomized trial of 126 patients with septic shock-related tachycardia (heart rate ≥95/min) who were receiving norepinephrine, the beta blocker landiolol did not reduce organ failure as measured by the sequential organ failure assessment score [11]. Furthermore, landiolol was associated with increased 28-day mortality compared with standard care (37 versus 25 percent). We continue to avoid the routine use of beta blockers in patients with septic shock. (See "Investigational and ineffective pharmacologic therapies for sepsis", section on 'Heart rate control'.)

- **No benefit to tight glucose control in critically ill patients (December 2023)**

- In earlier studies that showed benefit from tight glucose control in critically ill patients, early parenteral nutrition was a potential variable that influenced the outcome. In a recent study of over 9000 patients in whom parenteral nutrition was withheld for a week, 90-day mortality, duration of intensive care unit care, and several other outcomes (eg, infections) were similar when liberal glucose control was compared with tight glucose control [12]. These results are consistent with more recent studies that support the use of liberal rather than tight targets for glucose control in critically ill patients. (See "Glycemic control in critically ill adult and pediatric patients", section on 'Adults'.)

- **Liberal transfusion strategy for acute myocardial infarction (December 2023)**

- Restrictive transfusion (transfusing at a lower hemoglobin, typically <7 or 8 g/dL) is appropriate for most patients based on evidence from randomized trials, but trial data for patients with acute myocardial infarction (MI) have been slower to accumulate. In the MINT trial, which randomly assigned 3504 patients with acute MI and anemia to a restrictive or liberal (transfusing for hemoglobin <10 g/dL) strategy, there was a trend toward better outcomes with the liberal strategy without an increased risk of adverse events [13]. We now suggest a liberal strategy for acute MI. A slightly lower hemoglobin may be reasonable for stable, asymptomatic patients, and patients with hemodynamic instability may require a higher hemoglobin. (See "Indications and hemoglobin thresholds for RBC transfusion in adults", section on 'Acute MI'.)

WHAT'S NEW IN
SURGERY

- ENDOCRINE SURGERY
- **Cardiometabolic features of adrenal incidentaloma with mild autonomous cortisol secretion (December 2023)**

- In some individuals with adrenal incidentaloma, mild autonomous cortisol secretion (MACS) is evident in the absence of clinical features of Cushing syndrome. The long-term risks of MACS and optimal management strategies are not well defined. In a meta-analysis of 47 observational studies in 17,156 patients with adrenal incidentaloma, individuals with MACS (defined as serum cortisol 1.8 mcg/dL after a 1 mg overnight dexamethasone suppression test) exhibited a higher prevalence of diabetes, hypertension, and dyslipidemia compared with individuals with nonfunctioning adrenal adenomas [6]. Further, patients with MACS who underwent adrenalectomy showed greater improvement in cardiometabolic parameters than those who did not undergo surgery. These findings demonstrate the potential cardiometabolic risks of MACS and support our preference for adrenalectomy in patients with MACS and younger age or evidence of cardiometabolic dysregulation. (See "Evaluation and management of the adrenal incidentaloma", section on 'Clinical manifestations'.)

- **Tranexamic acid to reduce bleeding after percutaneous nephrolithotomy (December 2023)**
- Postoperative bleeding can occur after percutaneous nephrolithotomy (PNL) for kidney stone removal; most bleeding is venous in origin and can be managed with conservative measures. A recent meta-analysis of 10 randomized trials found that use of tranexamic acid (TXA), an antifibrinolytic agent used to reduce bleeding in other clinical settings, may reduce the risk of blood transfusion after PNL [17]. Most trials were conducted in low- to middle-income settings in populations that were younger than those in higher-income settings; whether these findings are generalizable to practice in higher-income settings is uncertain. Pending additional data, we do not routinely use TXA after PNL. (See "Kidney stones in adults: Surgical management of kidney and ureteral stones", section on 'Bleeding'.)

WHAT'S NEW IN NEPHROLOGY AND HYPERTENSION

- **DIALYSIS**
- **Taurolidine catheter locks for the prevention of hemodialysis catheter-related bloodstream infections (December 2023)**

- Catheter-related bloodstream infections (CRBSIs) are an important cause of morbidity and mortality in patients on hemodialysis. In a randomized trial of nearly 800 patients on maintenance hemodialysis via a tunneled central venous catheter, a catheter lock solution containing taurolidine, an antimicrobial agent, plus heparin reduced the incidence of CRBSI compared with a heparin control lock solution (2 versus 8 percent) over a mean of 200 days [3]. No trial participants used chlorhexidine-coated catheter caps, which are commonly used to reduce the risk of CRBSI. Based on these results, taurolidine lock solutions are a reasonable alternative to chlorhexidine-coated catheter caps to help prevent CRBSIs in select patients. (See "Tunneled hemodialysis catheter-related bloodstream infection (CRBSI): Management and prevention", section on 'Methods we use'.)

- GLOMERULAR DISEASE AND VASCULITIS

Sibeprenlimab for IgA nephropathy (December 2023)

- A Proliferation-Inducing Ligand (APRIL) is critical for mucosal B cell survival, maturation, and proliferation and has been implicated in the pathogenesis of IgA nephropathy (IgAN). The efficacy and safety of sibeprenlimab, an investigational monoclonal antibody against APRIL, were evaluated in a phase II trial in which over 150 patients with IgAN and persistent proteinuria despite optimized supportive care were randomly assigned to intravenous sibeprenlimab (2, 4, or 8 mg/kg body weight) or placebo once monthly for 12 months [7]. At 12 months, patients receiving sibeprenlimab had a greater, dose-dependent reduction in proteinuria; rates of serious adverse events were similar among the treatment groups. A larger phase III trial is in progress. (See "IgA nephropathy: Treatment and prognosis", section on 'Investigational agents'.)

- **Sparsentan in patients with IgA nephropathy (December 2023)**

- Patients with IgA nephropathy (IgAN) generally receive a renin-angiotensin system (RAS) inhibitor to reduce proteinuria, but proteinuria may persist despite maximally tolerated therapy. The efficacy and safety of sparsentan, a dual angiotensin II receptor and endothelin-1 receptor antagonist, were evaluated in a phase 3 trial in which over 400 adults with IgAN and persistent proteinuria despite three months of optimized supportive care were randomly assigned to sparsentan or irbesartan once daily [8,9]. At week 110, patients receiving sparsentan had a greater reduction in proteinuria and a smaller decline in two-year estimated glomerular filtration rate (eGFR) chronic slope; while rates of serious adverse events were similar between the groups, hypotension, dizziness, and acute kidney injury were more frequent with sparsentan. We consider sparsentan as an alternative option to reduce proteinuria in patients with IgAN and persistent proteinuria ≥1 g/day despite optimal treatment with an RAS inhibitor and a sodium-glucose cotransporter 2 (SGLT2) inhibitor for at least three to six months. (See "IgA nephropathy: Treatment and prognosis", section on 'Dual endothelin angiotensin receptor antagonists'.)

- **Trial of sparsentan in focal segmental glomerulosclerosis (December 2023)**

- Patients with focal segmental glomerulosclerosis (FSGS) are commonly treated with renin-angiotensin system (RAS) inhibitors to reduce proteinuria and stabilize kidney function. In a phase 3 trial in which over 370 patients with an FSGS lesion on kidney biopsy or a genetic variant associated with FSGS were randomly assigned to sparsentan, a dual endothelin receptor and angiotensin II receptor antagonist, or to the angiotensin II receptor antagonist irbesartan, sparsentan-treated patients had a greater reduction in proteinuria at 36 and 108 weeks, but there was no significant difference between the groups in estimated glomerular filtration rate (eGFR) slope at 108 weeks [10]. The discrepancy between sparsentan's effects on proteinuria and eGFR may reflect the enrollment of a heterogeneous mix of patients with primary, secondary, and genetic FSGS, who have a fundamentally different pathogenesis and disease course. Based on these findings, we do not use sparsentan in patients with an FSGS lesion. (See "Focal segmental glomerulosclerosis: Treatment and prognosis", section on 'Investigational therapies'.)

WHAT'S NEW IN
ENDOCRINOLOGY AND DIABETES MELLITUS

- **Prenatal genetic testing for monogenic diabetes due to glucokinase deficiency (December 2023)**

- In pregnant individuals with monogenic diabetes due to glucokinase (GCK) deficiency, management depends on the fetal genotype. If the fetus inherits the maternal *GCK* variant, maternal hyperglycemia will not cause fetal hyperinsulinemia and excessive growth, and maternal hyperglycemia does not require treatment. However, if the fetus does not inherit the pathogenic variant, maternal insulin therapy is indicated to prevent excessive fetal growth. Fetal ultrasound has been used to predict fetal genotype but has limited diagnostic utility. In a cohort of 38 pregnant individuals with GCK deficiency, fetal genetic testing using cell-free DNA in maternal blood had higher sensitivity (100 versus 53 percent) and specificity (96 versus 61 percent) for prenatal diagnosis of GCK deficiency compared with ultrasound measurement of fetal abdominal circumference [4]. When available, noninvasive prenatal genotyping should be used to guide management of GCK deficiency during pregnancy. (See "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'Glucokinase'.)

- **No benefit to tight glucose control in critically ill patients (December 2023)**

- In earlier studies that showed benefit from tight glucose control in critically ill patients, early parenteral nutrition was a potential variable that influenced the outcome. In a recent study of over 9000 patients in whom parenteral nutrition was withheld for a week, 90-day mortality, duration of intensive care unit care, and several other outcomes (eg, infections) were similar when liberal glucose control was compared with tight glucose control [20]. These results are consistent with more recent studies that support the use of liberal rather than tight targets for glucose control in critically ill patients. (See "Glycemic control in critically ill adult and pediatric patients", section on 'Adults'.)

WHAT'S NEW IN
HEMATOLOGY

- **CHRONIC LEUKEMIAS AND MYELOPROLIFERATIVE NEOPLASMS**
- **Ibrutinib plus venetoclax in previously untreated CLL/SLL (December 2023)**
- In two recent studies in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), ibrutinib plus venetoclax improved progression-free and overall survival compared with chemoimmunotherapy, with acceptable toxicity [2,3]. In one, all patients received 15 months of ibrutinib plus venetoclax, while in the other the duration of therapy was guided by measurable residual disease assessments. The two approaches have not been directly compared. These data support ibrutinib plus venetoclax as an effective initial option for CLL/SLL; fixed-duration ibrutinib plus venetoclax is approved for this indication in Europe but not the United States. (See "Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia/small lymphocytic lymphoma", section on 'Efficacy and toxicity'.)

- **Pirtobrutinib in relapsed CLL/SLL (July 2023, Modified December 2023)**

- Noncovalent Bruton tyrosine kinase (BTK) inhibitors such as pirtobrutinib are active in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with progression on a prior covalent BTK inhibitor (eg, ibrutinib, acalabrutinib, zanubrutinib). In a phase 1/2 trial including 247 such patients, pirtobrutinib was associated with an overall response rate of 82 percent and median progression-free survival of 19.6 months [4]. Response rates were similar irrespective of prior exposure to venetoclax or presence of BTK C481 mutations, which frequently arise upon progression on a covalent BTK inhibitor. Based on these results, the US Food and Drug Administration granted accelerated approval for pirtobrutinib in adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor. We consider pirtobrutinib an option in this setting. (See "Treatment of relapsed or refractory chronic lymphocytic leukemia", section on 'Pirtobrutinib'.)

- **Rare secondary T cell lymphomas after chimeric antigen receptor (CAR)-T cell therapy (December 2023)**

- Chimeric antigen receptor (CAR)-T cell therapy is effective for treatment of relapsed or refractory B cell lymphomas, multiple myeloma, and other disorders, but it may be associated with severe and potentially fatal adverse effects (AEs). Reports are now emerging of secondary T cell lymphomas in patients treated with CD19- and B cell maturation antigen (BCMA)-directed CAR-T cell therapy, some of which have CAR-positive malignant cells [7]. Although rare, the actual incidence is not well defined and it is uncertain if they are associated with all CAR-T cell products. US Food and Drug Administration (FDA)-approved CAR-T cell products include warnings about potential secondary malignancies, but at present, no regulatory action has been taken and no product has been recalled. Patients receiving CAR-T cell therapy should be monitored for development of new malignancies, and any such events should be reported to the manufacturer and to the FDA AE Reporting System (FAERS) [8]. The overall benefits of CAR-T cell products continue to outweigh potential risks for approved uses, but patients should be monitored and events reported. (See "Diffuse large B cell lymphoma (DLBCL): Suspected first relapse or refractory disease in patients who are medically fit", section on 'Relapse <12 months or primary refractory DLBCL'.)

Gene therapy and gene editing in sickle cell disease (September 2023, Modified December 2023)

- Several strategies are under study for individuals with sickle cell disease (SCD) who are seeking curative therapy. In December 2023, the US Food and Drug Administration approved two autologous cell-based therapies [17-19]:
- ●Lovotibeglogene autotemcel (lovo-cel) uses lentivirus-based gene therapy to introduce the antisickling beta globin variant T87Q and produce hemoglobin A with antisickling properties.
- ●Exagamglogene autotemcel (exa-cel) uses gene editing to disrupt the *BCL11A* gene and reverse the gamma globin to beta globin switch.
- In a previous study, three individuals with SCD who were treated with a different gene editing approach (disrupting the gamma globin promotor) had marked reduction in vaso-occlusive complications and transfusion requirements [20,21]. All current gene therapy and gene editing approaches for SCD require autologous hematopoietic cell transplantation with myeloablative conditioning. (See "Investigational therapies for sickle cell disease", section on 'Gene therapy and gene editing'.)

WHAT'S NEW IN GASTROENTEROLOGY AND HEPATOLOGY

- **Model for End-stage Liver Disease (MELD) 3.0 for liver transplantation (October 2023, Modified December 2023)**

- The Model for End-stage Liver Disease (MELD) score is used to allocate livers for transplantation. Recently, the Organ Procurement and Transplantation Network implemented an updated score, MELD 3.0, for prioritizing liver transplantation candidates who are ages 12 and older [4]. MELD 3.0 includes variables from the original model (ie, serum bilirubin, serum creatinine, and international normalized ratio) in addition to other inputs (ie, serum sodium, patient sex, and serum albumin) and a lower creatinine ceiling. Goals of using MELD 3.0 include reducing overall waitlist mortality and improving access for female liver transplant candidates. (See "Model for End-stage Liver Disease (MELD)", section on 'MELD 3.0'. and "Liver transplantation for hepatocellular carcinoma", section on 'MELD 3.0'.)

- **Clinical practice update on risk stratification for colorectal cancer screening and postpolypectomy surveillance (December 2023)**

- The American Gastroenterological Association (AGA) recently published nine statements of best practice advice on risk stratification for colorectal cancer (CRC) screening and postpolypectomy surveillance [11]. They advise basing risk stratification on an individual's age, a known or suspected predisposing hereditary CRC syndrome, other CRC predisposing conditions (eg, inflammatory bowel disease), and/or a family history of CRC. They also suggest that the decision to continue postpolypectomy surveillance for individuals older than 75 years should be individualized. Shared decision-making discussions should include an assessment of the risks of incident CRC, procedure-related risks, comorbidities, and life expectancy (>5 years). Our approach is consistent with this guidance. (See "Overview of colon polyps", section on 'Risk assessment for subsequent colorectal cancer'.)

WHAT'S NEW IN
NEUROLOGY

- **Adult-onset ADHD and dementia (December 2023)**

- Individuals with adult-onset attention deficit hyperactivity disorder (ADHD) may have difficulties compensating for deficits from neurodegenerative or cerebrovascular processes, but any association with dementia has been inconsistent. In a prospective study including over 100,000 adults without ADHD or dementia at baseline, those who were subsequently diagnosed with adult-onset ADHD were more likely to receive a diagnosis of dementia (adjusted relative risk 2.8) [6]. Whether symptoms that resulted in the ADHD diagnosis were early or prodromal dementia symptoms is uncertain; nevertheless, these findings suggest that caregivers be alert for signs of dementia in individuals with adult-onset ADHD. (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Comorbidity'.)

- **Vamorolone for Duchenne muscular dystrophy (December 2023)**

- Glucocorticoid treatment with prednisone or deflazacort for Duchenne muscular dystrophy (DMD) is associated with improved motor function, but adverse effects include weight gain, slowing of growth, and bone loss. Vamorolone, a novel steroid, was designed to reduce adverse effects of glucocorticoid therapy for DMD. In the VISION-DMD trial, vamorolone treatment led to improvement on several motor outcomes compared with placebo, while efficacy was similar compared with prednisone [22]. Prednisone treatment (but not vamorolone) led to growth deceleration and bone biomarker abnormalities. Based on these findings, the US Food and Drug Administration approved vamorolone for children age ≥2 years with DMD [23]. We suggest glucocorticoid treatment for children with DMD and anticipate using vamorolone as an alternative to prednisone and deflazacort. (See "Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment", section on 'Benefits of glucocorticoid therapy'.)

- **Intraoperative techniques for glioblastoma resection (December 2023)**

- Several intraoperative neurosurgical techniques are available to improve the extent of glioblastoma resection while minimizing damage to normal brain, but little comparative data exist. In a multicenter parallel-group trial that included over 300 patients undergoing resection of a newly diagnosed glioblastoma, rates of complete resection were comparable with use of either intraoperative magnetic resonance imaging (iMRI) or 5-aminolevulinic acid (ALA; 81 and 78 percent, respectively) [31]. In both groups, absence of any enhancing tumor postoperatively was associated with improved progression-free and overall survival. These results further support use of adjunctive tools like iMRI and ALA to facilitate maximal safe resection; selection of a specific operative plan is individualized based on neurosurgeon preference, tumor location, and availability of various technologies. (See "Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas", section on 'Intraoperative techniques'.)

WHAT'S NEW IN CARDIOVASCULAR MEDICINE

- **Thyroid hormone administration in deceased organ donors (December 2023)**
- Thyroid hormone administration has been a longstanding component of some organ procurement protocols due to concern that acute hypothyroidism might contribute to hemodynamic instability and left ventricular dysfunction, reducing heart and other organ procurement; however, evidence for the practice has been inconsistent. In a recent trial of 838 hemodynamically unstable, brain-dead donors assigned to receive a levothyroxine infusion or saline placebo, there was little to no difference in number of hearts transplanted or 30-day cardiac graft survival [19]. Recovery of other organs was similarly unaffected. More cases of severe hypertension or tachycardia occurred in the levothyroxine group than in the saline group. Based on these data, we suggest avoiding thyroid hormone administration in deceased organ donors. (See "Management of the deceased organ donor", section on 'Thyroid hormone'.)

- **Extracorporeal cardiopulmonary resuscitation (December 2023)**

- Extracorporeal cardiopulmonary resuscitation (ECPR) is being increasingly used, but data are limited and the benefits are uncertain. In a recent meta-analysis of 11 studies (10,000 patients) who underwent CPR, compared with standard CPR, ECPR was associated with decreased in-hospital mortality and increased long-term favorable neurologic outcome and survival at one year [1]. The benefit of ECPR was confined to patients with in-hospital cardiac arrest. These data support the growing practice of ECPR in select patients likely to benefit. (See "Extracorporeal life support in adults: Management of venoarterial extracorporeal membrane oxygenation (V-A ECMO)", section on 'Sudden cardiac arrest (extracorporeal cardiopulmonary resuscitation)'.)

- **Heart rate control in septic shock (December 2023)**

- Beta blockade has the potential to limit harm from the adrenergic overdrive that occurs in septic shock. However, data to support heart rate control in patients with septic shock are limited. In a recent, unblinded randomized trial of 126 patients with septic shock-related tachycardia (heart rate ≥95/min) who were receiving norepinephrine, the beta blocker landiolol did not reduce organ failure as measured by the sequential organ failure assessment score [2]. Furthermore, landiolol was associated with increased 28-day mortality compared with standard care (37 versus 25 percent). We continue to avoid the routine use of beta blockers in patients with septic shock. (See "Investigational and ineffective pharmacologic therapies for sepsis", section on 'Heart rate control'.)

WHAT'S NEW IN
EMERGENCY MEDICINE

- **Guidelines for primary spontaneous pneumothorax (December 2023)**

- The British Thoracic Society (BTS) has recently issued new guidelines for the management of primary spontaneous pneumothorax (PSP) [6]. Major changes since 2010 include a symptom- rather than size-based approach. For patients with mild symptoms who are stable following adequate analgesia, monitored observation is preferred, while those with significant dyspnea should undergo a drainage procedure (eg, aspiration or catheter/chest tube thoracostomy). Also promoted was ambulatory management in select patients with adequate outpatient support. We agree with these recommendations. (See "Treatment of primary spontaneous pneumothorax in adults", section on 'Initial evaluation and management'.)

- **Avoiding intubation in acutely poisoned but stable, unresponsive adults (December 2023)**

- In unresponsive patients with trauma or undifferentiated coma, tracheal intubation is generally recommended to protect the airway and prevent aspiration. However, the benefit of intubation is unclear in stable poisoned patients who have decreased level of consciousness but are oxygenating and ventilating adequately. In a randomized trial of 225 adults with acute poisoning and coma (GCS score ≤8), compared with airway management at the physician's discretion, individuals not intubated unless hypoxia, seizure, vomiting, or hypotension developed had a lower likelihood of mechanical ventilation (18 versus 60 percent), intensive care unit admission (40 versus 66 percent), or adverse events from intubation (6 versus 15 percent); they also had a lower risk of pneumonia [23]. These findings support avoiding intubation solely for a GCS score ≤8 in stable, unresponsive poisoned patients who are expected not to deteriorate based upon the suspected poison (eg, ingestion of a short-acting sedative such as ethanol). (See "Initial management of the critically ill adult with an unknown overdose", section on '"A": Airway stabilization'.)

WHAT'S NEW IN
PSYCHIATRY

- **Adult-onset ADHD and dementia (December 2023)**

- Individuals with adult-onset attention deficit hyperactivity disorder (ADHD) may have difficulties compensating for deficits from neurodegenerative or cerebrovascular processes, but any association with dementia has been inconsistent. In a prospective study including over 100,000 adults without ADHD or dementia at baseline, those who were subsequently diagnosed with adult-onset ADHD were more likely to receive a diagnosis of dementia (adjusted relative risk 2.8) [3]. Whether symptoms that resulted in the ADHD diagnosis were early or prodromal dementia symptoms is uncertain; nevertheless, these findings suggest that caregivers be alert for signs of dementia in individuals with adult-onset ADHD. (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Comorbidity'.)

- **Esketamine for treatment-resistant depression (December 2023)**

- Although esketamine has established efficacy for treatment-resistant depression, direct comparisons with other agents are limited. In a recent open label randomized trial in 676 adults with treatment-resistant major depression receiving baseline antidepressant therapy, addition of esketamine nasal spray for 32 weeks led to higher remission rates than addition of quetiapine extended release (XR, 49 versus 33 percent) [4]. Rates of discontinuation for adverse events were nearly three times lower with esketamine then quetiapine XR (4 versus 11 percent). Nevertheless, clinicians and patients considering esketamine need to weigh its benefits and disadvantages, including the need to administer it in a certified medical clinic. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Initial approach'.)

- **Cannabinoids and mental health in adolescents (December 2023)**

- Cannabis use is associated with an increased risk of mental health disorders. However, little is known about the effects of cannabidiol (CBD), a nonpsychoactive component of cannabis used for anorexia and childhood epilepsy, or of recreational synthetic cannabinoids. In a school-based survey from the United Kingdom that included over 6500 adolescents ages 13 to 14 years, reported use of cannabis, CBD, or synthetic cannabinoids were each associated with probable depression, anxiety disorder, or conduct disorder, as well as with auditory hallucinations [12]. For each disorder, the risk appeared greatest with synthetic cannabinoids. This study highlights the need for further investigation into the association between mental health effects in youth and the different types of cannabinoids. We advise adolescents (and younger children) to avoid cannabis consumption, including CBD. (See "Substance use disorder in adolescents: Epidemiology, clinical features, assessment, and diagnosis", section on 'Cannabis, cannabidiol, and synthetic cannabinoids'.)

WHAT'S NEW IN
ANESTHESIOLOGY

- **Labor epidural analgesia and risk of emergency delivery (December 2023)**

- It is well established that contemporary neuraxial labor analgesia does not increase the overall risk of cesarean or instrument-assisted vaginal delivery. However, a new retrospective database study of over 600,000 deliveries in the Netherlands reported that epidural labor analgesia was associated with an increased risk of emergency delivery (cesarean or instrument-assisted vaginal) compared with alternative analgesia (13 versus 7 percent) [2]. Because of potential confounders and lack of detail on epidural and obstetric management, we consider these data insufficient to avoid neuraxial analgesia or change the practice of early labor epidural placement to reduce the potential need for general anesthesia in patients at high risk for cesarean delivery. (See "Adverse effects of neuraxial analgesia and anesthesia for obstetrics", section on 'Effects on the progress and outcome of labor'.)

- **Thyroid hormone administration in deceased organ donors (December 2023)**

- Thyroid hormone administration has been a longstanding component of some organ procurement protocols due to concern that acute hypothyroidism might contribute to hemodynamic instability and left ventricular dysfunction, reducing heart and other organ procurement; however, evidence for the practice has been inconsistent. In a recent trial of 838 hemodynamically unstable, brain-dead donors assigned to receive a levothyroxine infusion or saline placebo, there was little to no difference in number of hearts transplanted or 30-day cardiac graft survival [7]. Recovery of other organs was similarly unaffected. More cases of severe hypertension or tachycardia occurred in the levothyroxine group than in the saline group. Based on these data, we suggest avoiding thyroid hormone administration in deceased organ donors. (See "Management of the deceased organ donor", section on 'Thyroid hormone'.)

WHAT'S NEW IN
ALLERGY AND IMMUNOLOGY

- **Tapering inhaled corticosteroids in asthma patients responding to biologics (December 2023)**
- Strategies for tapering other asthma therapies, such as inhaled corticosteroids (ICS), for patients who achieve good asthma control with biologics has not been well studied. In an open-label, randomized trial of 168 adults with a history of severe eosinophilic asthma and good control on benralizumab and high-dose ICS, 43 patients were assigned to an ongoing high-dose ICS-formoterol regimen and 125 patients were assigned to a 32-week taper protocol (medium-, low-, and as-needed dosing of ICS-formoterol) [1]. In the tapering arm, 92 percent of patients achieved lower doses of ICS, with only 9 percent experiencing exacerbations. However, significant decreases in FEV_1 and increases in fraction of exhaled nitric oxide occurred in patients using the least amount of as-needed ICS-formoterol after their taper. These data suggest that most patients well-controlled on biologics may be successfully tapered to regimens containing medium- or low-dose ICS with long-acting bronchodilators. However, the safety and efficacy of tapering to as-needed ICS-formoterol requires further study. (See "Treatment of severe asthma in adolescents and adults", section on 'Tapering therapy'.)

WHAT'S NEW IN
ONCOLOGY

- **Novel treatment approaches for metastatic urothelial carcinoma (December 2023)**

- For patients with metastatic urothelial carcinoma (UC), randomized trials are evaluating treatments that improve upon the efficacy and/or tolerability of platinum-based chemotherapy:

- ●Among 900 patients with previously untreated locally advanced or metastatic UC eligible for platinum-based chemotherapy, enfortumab vedotin (an antibody-drug conjugate) plus pembrolizumab improved overall survival (median 31 versus 16 months) versus platinum-based chemotherapy with less grade ≥3 toxicity (56 versus 70 percent) [21].

- ●Among 600 cisplatin-eligible patients with advanced or metastatic UC, the addition of nivolumab to gemcitabine and cisplatin improved overall survival (median 22 versus 19 months) [22].

- Based on these data, for patients with metastatic UC, we now offer initial treatment with enfortumab vedotin plus pembrolizumab but consider nivolumab plus gemcitabine and cisplatin to be a reasonable alternative. (See "Treatment of metastatic urothelial carcinoma of the bladder and urinary tract", section on 'Enfortumab vedotin plus pembrolizumab' and "Treatment of metastatic urothelial carcinoma of the bladder and urinary tract", section on 'Nivolumab plus gemcitabine plus cisplatin'.)

- **Mirvetuximab soravtansine in folate receptor alpha-positive ovarian cancer (December 2023)**

- Mirvetuximab soravtansine (MIRV) is a folate receptor (FR) alpha-directed antibody and microtubule inhibitor conjugate that is being evaluated for platinum-resistant, FR alpha-positive epithelial ovarian cancer (EOC). In a randomized trial of MIRV versus investigator's choice chemotherapy in 453 patients with such cancers, MIRV improved objective response rates (42 versus 16 percent), progression-free survival (5.6 versus 4.0 months), and overall survival (16.5 versus 12.8 months) [28]. Grade ≥3 adverse events were less common in the MIRV group (42 versus 54 percent). Based on these results, MIRV has regulatory approval in the United States for FR alpha-positive, platinum-resistant EOC that has been treated with one to three prior systemic treatment regimens. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease", section on 'Mirvetuximab soravtansine'.)

- **Intraoperative techniques for glioblastoma resection (December 2023)**

- Several intraoperative neurosurgical techniques are available to improve the extent of glioblastoma resection while minimizing damage to normal brain, but little comparative data exist. In a multicenter parallel-group trial that included over 300 patients undergoing resection of a newly diagnosed glioblastoma, rates of complete resection were comparable with use of either intraoperative magnetic resonance imaging (iMRI) or 5-aminolevulinic acid (ALA; 81 and 78 percent, respectively) [38]. In both groups, absence of any enhancing tumor postoperatively was associated with improved progression-free and overall survival. These results further support use of adjunctive tools like iMRI and ALA to facilitate maximal safe resection; selection of a specific operative plan is individualized based on neurosurgeon preference, tumor location, and availability of various technologies. (See "Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas", section on 'Intraoperative techniques'.)

- **Tarlatamab in small cell lung cancer (December 2023)**

- Delta-like ligand 3 is overexpressed in approximately 90 percent of small cell lung cancer (SCLC). In a phase II study in 220 patients with a median of two prior treatments for SCLC, tarlatamab, an investigational bispecific T cell engager immunotherapy directed against delta-like ligand 3, was associated with response rates of 32 percent among those receiving 10 mg daily and 40 percent among those receiving 100 mg daily [49]. Overall survival rates at 9 months were 66 and 68 percent, respectively. The most common adverse events were cytokine-release syndrome (mostly grade 1 to 2), decreased appetite, and pyrexia. Tarlatamab is under regulatory review in the United States and is not yet available outside of a clinical trial. (See "Treatment of refractory and relapsed small cell lung cancer", section on 'Other options'.)

- **Stereotactic body radiation therapy in oligometastatic NSCLC (December 2023)**

- For patients with oligometastatic non-small cell lung cancer (NSCLC), studies are evaluating whether local treatment of metastatic lesions, when used in conjunction with standard systemic therapy, can improve outcomes. In an open-label trial including patients with either oligometastatic breast or NSCLC, among the 59 patients with lung cancer, the addition of stereotactic body radiation therapy to standard of care systemic treatment improved median progression-free survival (PFS, 10.0 versus 2.2 months) but failed to improve overall survival (OS) [50]. PFS benefit was not observed among breast cancer patients. For patients with NSCLC and one to three metastases, we suggest using both local therapy and systemic therapy, while recognizing the need for larger studies to clarify the effect on OS. (See "Oligometastatic non-small cell lung cancer", section on 'Overall'.)

- **Pemetrexed-cisplatin as adjuvant chemotherapy for nonsquamous NSCLC (December 2023)**

- Although platinum-based doublet chemotherapy is a standard adjuvant regimen for resected non-small cell lung cancer (NSCLC), trials are investigating the optimal chemotherapy agent to pair with the platinum agent. In a randomized trial including 783 patients with stage II to IIIA nonsquamous NSCLC, there was a nonsignificant trend in recurrence-free survival favoring pemetrexed-cisplatin compared with vinorelbine-cisplatin (43 versus 38 months) [51]; overall survival rates were comparable. Previous data suggest lower rates of neutropenia with pemetrexed-based therapy. For those receiving adjuvant chemotherapy for resected nonsquamous histology NSCLC, we suggest pemetrexed to partner with the platinum agent. (See "Systemic therapy in resectable non-small cell lung cancer", section on 'Cisplatin-based doublets'.)