MAY 2018

MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

UPDATED *CLOSTRIDIUM DIFFICILE* GUIDELINES

Clostridium difficile (C. difficile) is the most commonly recognized cause of infectious diarrhea in healthcare settings, with over 450,000 cases of *C. difficile* infections (CDI) in the United States (US) annually. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published updated consensus guidelines on CDI. The guidelines emphasize the importance of good diagnostic practices and antibiotic stewardship to control CDI.

The IDSA/SHEA prefers *C. difficile* testing in patients with new-onset, unexplained, and clinically significant (e.g., ≥ 3 unformed stools in a 24-hour period) diarrhea (weak recommendation). Providers should start empiric antibiotic therapy for CDI if laboratory confirmation is delayed or for fulminant cases (weak recommendation). A 10-day oral course of vancomycin or fidaxomicin is recommended for initial episodes in adults (strong recommendation). Metronidazole may be considered for nonsevere CDI only if access to vancomycin or fidaxomicin is limited (weak recommendation). For fulminant cases, oral vancomycin is recommended and should be used in combination with intravenous (IV) metronidazole (strong recommendation), particularly if ileus is present. Vancomycin per rectum may be prescribed in cases with ileus. For the first recurrence of CDI, a tapered and pulsed regimen of oral vancomycin or a 10-day course of oral fidaxomicin is preferred over a second 10-day standard regimen of vancomycin (weak recommendations). In patients with multiple recurrences, IDSA/SHEA weakly recommends a tapered or pulsed regimen of oral vancomycin, a standard course of oral vancomycin followed by rifaximin, or a course of fidaxomicin. Fecal microbiota transplantation (FMT) is strongly recommended in patients with multiple recurrences after failure of proper antibiotic therapy. In children, metronidazole or vancomycin is recommended for an initial episode and first recurrence of nonsevere CDI (weak recommendation). Oral vancomycin is preferred for severe initial episodes (strong recommendation) or following ≥ 2 CDI recurrences (weak recommendation). FMT may be considered in children who experience multiple recurrences (weak recommendation).

Antibiotic exposure is the most important modifiable risk factor for CDI. While CDI has been associated with nearly all antibiotics, a high risk has been noted with third and fourth generation cephalosporins, clindamycin, fluoroquinolones, and carbapenems. The IDSA/SHEA advises to minimize use of antibiotics to treat non-CDI infections as clinically appropriate and affirms that stewardship strategies should target antibiotics based on local epidemiologic data. While there is a suggested association between proton pump inhibitors (PPIs) and CDI, and IDSA/SHEA discourages unnecessary PPI use, they do not recommend PPI discontinuation to prevent CDI. Data are limited to support the use of probiotics for primary prevention.

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Since the completion of the updated guidelines, bezlotoxumab (Zinplava®), a *C. difficile* toxin B-binding monoclonal antibody indicated as adjunct to antibiotics in patients who are at risk for CDI recurrence, became available. Its use is not addressed in the guidelines.

AUA GUIDELINES ON TESTOSTERONE DEFICIENCY

The American Urological Association (AUA) published guidelines on the Evaluation and Management of Testosterone Deficiency that focuses on proper diagnosis, on-treatment monitoring, and risks and benefits of therapy.

The AUA states assessment of serum total testosterone (T) levels should be considered in men with a history of unexplained anemia, decreased bone mineral density (BMD), diabetes, chemotherapy or testicular radiation exposure, human immunodeficiency virus (HIV) infection, infertility, pituitary dysfunction, or chronic corticosteroid or narcotic use (moderate recommendation). Total T should be drawn on 2 separate early morning occasions (strong recommendation). Diagnosis of testosterone deficiency is determined only in men with signs and/or symptoms of low testosterone and who also have a total T < 300 ng/dL (moderate recommendations). The AUA also strongly recommends evaluation of serum luteinizing hormone, prolactin, hemoglobin, and hematocrit in patients with low testosterone. Measuring serum estradiol may be considered in select patients. Prior to beginning exogenous testosterone, prostate cancer should be ruled out based on PSA testing in men over age 40 years.

Regarding treatment, the AUA recommends commercially-manufactured testosterone agents over compounded testosterone preparations and states alkylated oral testosterone should not be used. Total T should be measured every 6 to 12 months during therapy, and testosterone dose should be adjusted to maintain a total T level in the mid-normal range. Discontinuation of therapy should be considered if signs and symptoms fail to improve within 3 to 6 months of beginning treatment, even if the desired total T level is achieved. Additionally, patients should be instructed on the risk of transference of topical testosterone preparations.

Patients should be aware that low testosterone is a risk factor for cardiovascular (CV) disease; however, it is unknown if testosterone therapy will increase or decrease the risk of CV events. Moreover, exogenous testosterone should not be prescribed for 3 to 6 months after a CV event. Testosterone therapy may improve erectile function, libido, anemia, BMD, mean body mass, and mood. Data are insufficient to conclude that therapy will increase the risk of prostate cancer or thrombotic events. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with men interested in future fertility; its use is not recommended in men who are currently trying to conceive.

BEHAVIORAL HEALTH CORNER

ADVICE ON ADOLESCENT DEPRESSION FOR PRIMARY CARE (PC) CLINICIANS

The American Academy of Pediatrics (AAP) published part 2 of the updated Guidelines for Adolescent Depression in Primary Care (GLAD-PC). After initial diagnosis of mild depression, the AAP recommends a 6- to 8-week period of active support and monitoring (weekly or biweekly). If symptoms persist, evidence-based treatment with an antidepressant (e.g., selective serotonin reuptake inhibitor [SSRI]) or psychotherapy (e.g., cognitive behavioral therapy [CBT], interpersonal psychotherapy for adolescents [IPT-A]) should be offered. For patients with moderate or severe depression or complicating factors, such as substance abuse or psychosis, consultation with a mental health specialist should be considered.

An individualized treatment plan should be based on disease severity, risk of suicide, and comorbid conditions. Fluoxetine and escitalopram are approved to treat depression in adolescent patients; the effective dose may be lower than required in adults.

According to the AAP, systematic monitoring, beginning within 1 week of therapy initiation, should encompass functional improvement, symptom resolution, treatment-related adverse effects (e.g., suicidality, mania), treatment adherence, and environmental stressors. If no improvement is seen after 6 to 8 weeks of starting therapy, the diagnosis should be reassessed and a mental health specialist consult may be considered. If a partial improvement is seen, review adherence and/or consider additional therapy, such as medication or psychotherapy, that has not already been instituted. If the patient is already on pharmacotherapy, an increase to a maximum tolerated dose and/or mental health specialist consult can also be considered. Antidepressant therapy should be continued for 6 to 12 months after remission of symptoms, and monitoring should continue monthly for 6 to 12 months following full resolution (up to 24 months if episode is a recurrence).

DRUG INFORMATION **HIGHLIGHTS**

- The Alzheimer's Association (AA) and the National Institute on Aging (NIA) proposed a new Alzheimer's disease (AD) framework to better distinguish it from other causes of dementia. The new framework will help researchers develop AD treatments based on biomarkers rather than clinical symptoms and allow medications to be tested in asymptomatic subjects. The AA/NIA identifies beta-amyloid and tau proteins and neurodegeneration as biomarkers that can be detected via brain imaging or cerebral spinal fluid tests in live subjects. In AD, beta-amyloid and tau proteins can clump or tangle in the brain and block neurotransmission. If a person is beta-amyloid-positive, they are considered to be on the AD continuum. If they are also tau-positive, they are considered to have AD. Neurodegeneration indicates pathologic stages of AD symptoms. Subjects who are beta-amyloid-negative and tau- or neurodegeneration-positive are considered to have non-AD pathology.
- The Centers for Disease Control and Prevention (CDC) reported that opioid overdoses increased by 30% between July 2016 and September 2017. The US Surgeon General urges more individuals, including family, friends, and those who are at risk for an opioid overdose, to keep naloxone (Narcan®) readily available. States have passed laws to increase access to naloxone. Local public health programs and retailer and manufacturer discounts may also allow for access to naloxone at low or no cost to individuals without insurance coverage.
- It is estimated that people living with HIV (PLWH) have about a 50% higher risk of cancer than the general population. However, studies indicate that PLWH with cancer are treated at significantly lower rates than people with cancer who are HIV-negative. In their new Clinical Practice Guidelines in Oncology, the National Comprehensive Cancer Network (NCCN) advises that most PLWH with cancer should be offered the same cancer treatments as HIV-negative individuals. Also, HIV status should not be the only factor used as a basis for treatment modifications. An oncologist and HIV specialist should jointly oversee the patient's care; HIV and oncology pharmacists, if available, should review proposed cancer therapy and antiretroviral medications for possible drug-drug interactions and overlapping toxicity concerns prior to initiation of therapy.
- The CDC published hepatitis B virus (HBV) vaccination recommendations for use of Heplisav-B™ (HepB-CpG) for adults at risk for acquiring HBV, including risks due to sexual transmission, incarceration, HIV, injection drug use, and household contacts with HBV-infected people. The Heplisav-B 2-dose regimen is appropriate when both doses in the series consist of HepB-CpG and are administered at least 4 weeks apart. The CDC advises that an alternative HBV vaccine should be used in pregnant females since Heplisav-B has not been tested during pregnancy.

PIPELINE NEWS: UPCOMING PRESCRIPTION DRUG/BIOSIMILAR USER FEE ACT (PDUFA/BsUFA) DATES

- **May 2018:** filgrastim (biosimilar to Amgen's Neupogen®); IV/subcutaneous (SC) colony stimulating factor (CSF); neutropenia/leukopenia; Adello.
- **May 2018:** rituximab (biosimilar to Genentech's Rituxan®); IV anti-CD20 antibody; rheumatoid arthritis, chronic lymphocytic leukemia/small lymphocytic lymphoma, non-Hodgkin lymphoma (indolent), and antineutrophil cytoplasmic antibodies associated vasculitis; Novartis/Sandoz.
- **May 4, 2018:** Andexxa: andexanet alfa; IV factor Xa inhibitor antidote; anticoagulant reversal; Portola.
- **May 13, 2018:** polyethylene glycol (low volume); oral osmotic laxative; colon cleansing; Valeant.
- **May 17, 2018:** erenumab; SC calcitonin gene-related peptide (CGRP) inhibitor; migraine prevention; Amgen.
- **May 21, 2018:** avatrombopag; oral thrombopoietin receptor agonist; thrombocytopenia related to chronic liver disease; Dova.
- **May 24, 2018:** Arnuity® Ellipta®; fluticasone furoate; inhaled corticosteroid; asthma (ages 5 to 11 years); GlaxoSmithKline.
- **May 25, 2018:** Cimzia®; certolizumab pegol; SC tumor necrosis factor inhibitor; plaque psoriasis; UCB.
- **May 25, 2018:** Lenvima®; lenvatinib; oral kinase inhibitor; hepatocellular carcinoma (first-line); Eisai.
- **May 25, 2018:** pegvaliase; SC enzyme replacement; phenylketonuria; Biomarin.
- **May 26, 2018:** lofexidine; oral alpha adrenergic agonist; substance use disorder; US Worldmeds.
- **May 28, 2018:** Prolia®; denosumab; SC RANK ligand inhibitor; glucocorticoid-induced osteoporosis; Amgen.
- **May 28, 2018:** trastuzumab (biosimilar to Genentech's Herceptin®); IV anti-HER2 antibody; HER2+ breast, gastric, and gastroesophageal cancers; Amgen.
- **June 4, 2018:** mogamulizumab; IV anti-CCR4 antibody; cutaneous T cell lymphoma; Kyowa Hakko Kirin.
- **June 4, 2018:** pegfilgrastim (biosimilar to Amgen's Neulasta®); SC colony stimulating factor; neutropenia/leukopenia; Mylan/Biocon.
- **Quarter 2, 2018:** sodium zirconium cyclosilicate; oral potassium binder; hyperkalemia; AstraZeneca.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
efavirenz/ lamivudine/ tenofovir disoproxil fumarate	Symfi™	The FDA approved Symfi, a 3-drug combination product of efavirenz (600 mg), lamivudine (300 mg), and tenofovir disoproxil fumarate (300 mg), as a complete regimen for the treatment of HIV-1 infection in adults and pediatrics who weigh ≥ 40 kg. The medication combines a non-nucleoside reverse transcriptase inhibitor (efavirenz) with 2 nucleo(t)side reverse transcriptase inhibitors (lamivudine, tenofovir disoproxil fumarate). The medication is taken orally as 1 fixed-dose tablet once daily at bedtime. Symfi Lo™ (efavirenz 400 mg/ lamivudine 300 mg/ tenofovir disoproxil fumarate 300 mg) was approved in February 2018 for the treatment of HIV-1 infection in adults and pediatrics who weigh ≥ 35 kg.	Mylan	505(b)(2) NDA Priority approval 03/22/2018
nilotinib	Tasigna®	An expanded indication was granted for the Orphan drug nilotinib (Tasigna), a kinase inhibitor, to include first- and second-line treatment in pediatric patients ≥ 1 year old with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP). Nilotinib is also approved in adults with newly diagnosed Ph+ CML-CP or adults with chronic phase or accelerated phase Ph+ CML that is resistant or intolerant to prior therapy that included imatinib. A new oral 50 mg capsule strength was approved to accommodate dosing in pediatrics; it will be available in addition to the 150 mg and 200 mg capsules. The recommended pediatric dosing is 230 mg/m² orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).	Novartis	sNDA Priority approval 03/22/2018
blinatumomab	Blincyto®	Blinatumomab (Blincyto) received an Accelerated approval for the treatment of adults and pediatrics with B cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease ≥ 0.1%. Previously, blinatumomab, a bispecific CD19-directed CD3 T-cell engager, was approved for the treatment of relapsed or refractory B cell precursor ALL in adults and children. Dosage is dependent on patient weight and schedule. It is administered IV over 24 or 48 hours by a healthcare professional (HCP). Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. Blinatumomab was granted Orphan drug designation.	Amgen	sBLA Priority approval 03/29/2018
sargramostim	Leukine®	The leukocyte growth factor sargramostim (Leukine) gained a new indication to increase survival in adult and pediatric patients from birth to 17 years old acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]). For this indication, sargramostim may be self-administered SC once-daily as 7 mcg/kg (adults and pediatric patients weighing > 40 kg), 10 mcg/kg (pediatric patients 15 kg to 40 kg), or 12 mcg/kg (pediatric patients < 15 kg).	Sanofi-Aventis	sBLA approval 03/29/2018

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application; 505(b)(2) = FDA approval pathway that allows for submission of data from studies not conducted by or for the applicant.

RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
fosaprepitant injection	Emend® injection	The FDA has approved fosaprepitant injection, a substance P/neurokinin-1 (NK1) receptor antagonist, for the prevention of chemotherapy-induced nausea and vomiting in combination with other antiemetics in patients ≥ 6 months of age. Previously, fosaprepitant injection was only approved in adult patients. The approved dosage and infusion time are dependent on age, and length of chemotherapy is dependent on the chemotherapy regimen. It is administered IV by an HCP.	Merck	sNDA approval 04/03/2018
bupivacaine	Exparel®	The Agency expanded the indication of bupivacaine liposome injectable suspension to include administration via interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Exparel is the first long-acting, single-dose nerve block approved for patients having upper extremity surgery. Exparel is also approved for single-dose infiltration into the surgical site to produce postsurgical analgesia. The recommended dose of Exparel for this new indication in adults is 133 mg, and it is administered by an HCP.	Pacira	sNDA approval 04/06/2018
rucaparib	Rubraca®	Rucaparib (Rubraca) tablets gained a new indication for the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults who are in a complete or partial response to platinum-based chemotherapy. Rucaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, also received regular approval for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies; it was previously given Accelerated approval for this indication. Rucaparib is dosed as 600 mg (two 300 mg tablets) taken orally twice daily. Rucaparib is an Orphan drug for treatment of ovarian cancer.	Clovis	sNDA approval 04/06/2018
everolimus	Afinitor® Disperz™	The kinase inhibitor everolimus tablets for oral suspension received approval for adjunctive treatment in patients ≥ 2 years of age with tuberous sclerosis complex (TSC)-associated partial-onset seizures (POS). The recommended starting dose for this indication is 5 mg/m^2 orally once daily with dose adjustments to achieve trough concentrations of 5 to 15 ng/mL. Afinitor Disperz is also indicated for the treatment of adult and pediatric patients ≥ 1 year old with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. The everolimus tablet formulation (Afinitor) is not approved for TSC-associated POS; it is, however, indicated for TSC-SEGA and for breast cancer, neuroendocrine tumors, and renal cell carcinoma (RCC) in select patients. Everolimus is an Orphan drug for the treatment of TSC-associated POS.	Novartis	sNDA approval 04/10/2018

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RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
nivolumab + ipilimumab	Opdivo® + Yervoy®	New indications were approved for the programmed death receptor-1 (PD-1) inhibitor nivolumab (Opdivo) and the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor ipilimumab (Yervoy) for their combined use to treat patients with intermediate or poor risk, previously-untreated, advanced RCC. The recommended dose of nivolumab is 3 mg/kg IV over 30 minutes followed by ipilimumab 1 mg/kg IV over 30 minutes on the same day. Doses are administered by an HCP and repeated every 3 weeks for a maximum of 4 doses. Then, nivolumab is continued as monotherapy as 240 mg every 2 weeks or 480 mg every 4 weeks IV over 30 minutes.	Bristol-Myers Squibb	sBLA Priority approvals 04/16/2018
burosumab-twza	Crysvita®	The FDA approved the fibroblast growth factor 23 (FGF23) blocking antibody burosumab-twza (Crysvita) for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients ≥ 1 year of age. Burosumab-twza is the first therapy approved for this rare condition and the FDA designated it as a Breakthrough therapy and Orphan drug. Administered by an HCP, the initial dose in pediatrics is 0.8 mg/kg SC every 2 weeks, and the initial adult dose is 1 mg/kg SC every 4 weeks. Doses are rounded to the nearest 10 mg to a maximum dose of 90 mg in all patients. Burosumab-twza is approved as 10 mg/mL, 20 mg/mL, and 30 mg/mL single-dose vials. An early May 2018 launch is expected.	Ultragenyx	BLA approval 04/17/2018
fostamatinib disodium hexahydrate	Tavalisse™	The kinase inhibitor fostamatinib disodium hexahydrate (Tavalisse) was approved for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to prior treatment. The initial dose of this Orphan drug is 100 mg orally twice daily, without regard to food. The dose may be increased to 150 mg twice daily after 4 weeks. The lowest dose should be used to maintain a platelet count of ≥ 50 x 10^9/L. Discontinue therapy if response is insufficient within 12 weeks. Availability of the approved 100 mg and 150 mg oral tablets is expected in late May 2018.	Rigel	NDA approval 04/17/2018
osimertinib	Tagrisso®	The kinase inhibitor osimertinib (Tagrisso) garnered a Breakthrough therapy designation and an expanded indication as first-line treatment of metastatic non-small cell lung cancer (NSCLC) in patients whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. Osimertinib is considered an Orphan drug for the treatment of EGFR+ NSCLC. The recommended dose for all indications is 80 mg orally once daily, without regard to food.	AstraZeneca	sNDA approval 04/18/2018

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