Management of nonalcoholic fatty liver disease in adults

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INTRODUCTION

Nonalcohol-associated fatty liver disease (NAFLD) is a spectrum of disease characterized by hepatic steatosis in the absence of excessive alcohol consumption. NAFLD may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis [1,2].

This topic will review the treatment and prognosis of NAFLD. The pathogenesis, clinical manifestations, and diagnosis of NAFLD are discussed separately. (See "Pathogenesis of nonalcoholic fatty liver disease" and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

Several professional societies have published guidelines on the management of NAFLD, and our approach is generally consistent with these guidelines [3-5].

SPECTRUM OF DISEASE

NAFLD ranges from the more benign condition of nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), which is at the more severe end of the spectrum. In NAFL, hepatic steatosis is present without evidence of inflammation, whereas in NASH, hepatic steatosis is associated with lobular inflammation and apoptosis that can lead to fibrosis and cirrhosis [1,2,6,7]. The histologic findings and scoring systems used to grade disease activity in patients with NAFLD are discussed separately. (See "Histologic scoring systems for chronic liver disease",

section on 'Nonalcoholic fatty liver disease' and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Histologic findings'.)

MANAGEMENT

General measures for all patients — The following measures apply to all patients with NAFLD:

- **Abstain from alcohol** – We suggest that patients refrain from alcohol, and in particular, recommend avoiding heavy alcohol use (ie, >14 drinks per week or >4 drinks on a given day for males and >7 drinks per week or >3 drinks on a given day for females) [8]. Heavy alcohol use is associated with disease progression [9]. Whether light to moderate alcohol consumption is harmful is not as clear, and this is discussed below. In the absence of definitive data, we suggest abstinence from alcohol. (See 'Alcohol use' below.)

- **Immunizations** – Vaccination for hepatitis A virus and hepatitis B virus should be given to patients without serologic evidence of immunity. Additional vaccines for patients with chronic liver disease include pneumococcal vaccination and standard immunizations that are given to the general population (eg, influenza, diphtheria, tetanus boosters) (figure 1 and figure 2). Immunization schedules are described separately. (See "Immunizations for adults with chronic liver disease", section on 'Vaccines in chronic liver disease'.)

- **Modify risk factors for cardiovascular disease** – Patients with NAFLD are at increased risk for cardiovascular disease and often have multiple risk factors for cardiovascular disease (eg, hypertension, hyperlipidemia). (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Association with other disorders'.)

  Management of patients with NAFLD and diabetes includes optimization of blood glucose control. (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus" and 'Patients with NASH and diabetes' below.)

  Most patients with NAFLD who have hyperlipidemia are candidates for lipid-lowering therapy, which is discussed separately. (See "Statins: Actions, side effects, and administration", section on 'Chronic liver disease' and "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease".)

Weight loss — Weight loss is the primary therapy for most patients with NAFLD. We recommend weight loss for all patients with NAFLD who are overweight (body mass index [BMI]

≥25 kg/m^2) or have obesity (BMI ≥30 kg/m^2) because weight loss can lead to improvement in liver biochemical tests, liver histology, serum insulin levels, and quality of life in patients with NAFLD [10-13]. We begin with lifestyle interventions including diet modification and exercise. For patients who do not meet weight loss goals after six months, we discuss bariatric surgery. Drug therapy is also an option in certain patients.

Initial lifestyle interventions — We advise patients who are overweight or have obesity to lose five to seven percent of body weight at a rate of 0.5 to 1.0 kg per week (1 to 2 lb per week) through lifestyle modifications including dietary therapy and exercise. For patients with suspected or biopsy-proven NASH, the weight loss goal is higher (7 to 10 percent of body weight). We provide dietary counseling for patients and also refer them to a nutritionist. Lifestyle interventions to promote weight loss are discussed separately. (See "Obesity in adults: Overview of management" and "Strength training for health in adults: Terminology, principles, benefits, and risks", section on 'Nonalcoholic fatty liver disease'.)

For some patients, weight loss beyond these initial targets may be required. If the serum alanine aminotransferase (ALT) level does not normalize (ALT <20 for females and <30 for males) after achieving the weight loss goal, we advise patients to lose additional weight. (See 'Laboratory monitoring' below.)

For patients with nonalcoholic steatohepatitis (NASH) or advanced fibrosis who do not meet their weight loss goals after six months of lifestyle interventions, we discuss additional options, including bariatric surgery, which is presented below (see 'Bariatric surgery' below).

Several studies suggest that weight loss of at least 5 percent of body weight is necessary to improve hepatic steatosis, although the long-term benefits of such weight loss are unknown. In a meta-analysis of eight trials including 373 patients, losing ≥5 percent of body weight resulted in improvement in hepatic steatosis, while losing of ≥7 percent of body weight was associated with improvement in NALFD activity score (NAS), which is used to grade disease activity [14]. The NAS is discussed separately. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'NAFLD activity score'.)

In another trial including 31 patients with BMI ranging from 25 to 40 kg/m^2 who had biopsy-proven NASH, enrollment in a weight loss and exercise program resulted in greater weight loss after one year compared with a structured education program (9 versus 0.2 percent of body weight) [11]. Patients in the weight loss and exercise group had higher rates of histologic improvement compared with the education group (72 versus 30 percent).

Increasing physical activity has been linked to a survival benefit for patients with NAFLD [15,16]. In a longitudinal study of the National Health and Nutrition Examination Survey including 2793

individuals with NAFLD, longer duration of physical activity (measured by accelerometers) was associated with lower risk of all-cause mortality during an average follow-up of nearly 11 years (highest quartile of activity compared with lowest quartile: adjusted hazard ratio [aHR] 0.46, 95% CI 0.28-0.75) [16]. In addition, duration of physical activity was associated with lower risk of cardiovascular disease-related mortality (highest quartile of activity compared with lowest quartile: aHR 0.28, 95% CI 0.08-0.98).

Additional treatments

Bariatric surgery — We refer patients with NASH or advanced fibrosis (but without decompensated cirrhosis) for bariatric surgery if they do not meet their weight loss goals after six months of lifestyle interventions, including two visits for nutritional counseling. Bariatric surgery is a promising approach for patients with NAFLD, and histologic improvement has been observed postoperatively [17-28]. However, worsening fibrosis occurs in some patients following bariatric surgery, and all patients should have their liver biochemical tests monitored postoperatively (eg, at six weeks, three months, and six months after surgery). We also monitor patients with cirrhosis at one month and three months postoperatively for signs of decompensated cirrhosis (eg, ascites, hepatic encephalopathy), which can occur as a result of surgery. (See "Outcomes of bariatric surgery", section on 'Nonalcoholic fatty liver disease'.)

Drug therapy — Pharmacologic therapy can be used to promote weight loss in patients who fail to achieve their goals through diet and exercise alone. Recommendations for the use of drug therapy to promote weight loss vary greatly among clinicians. Some UpToDate contributors do not use drug therapy often, whereas others prescribe medications in selected patients after providing extensive counseling about lifestyle measures.

We may use a GLP-1 receptor agonist (off-label) for patients with biopsy-proven NASH with fibrosis stage ≥F2 who do not achieve weight loss with lifestyle interventions. We typically begin a GLP-1 receptor agonist (eg, semaglutide, liraglutide) with the same dosing that is used for the labeled indication (obesity) (table 1). We titrate the dose to achieve a weight loss goal of 7 to 10 percent of body weight. For such patients, we also continue to promote lifestyle interventions as long-term therapy. (See 'Initial lifestyle interventions' above.)

Drug therapies for weight loss including administration, dosing, and adverse effects are discussed in more detail separately. (See "Obesity in adults: Drug therapy".)

Potential pharmacologic therapies — Options for pharmacologic, liver-targeted therapy for NAFLD are limited (eg, vitamin E, some insulin sensitizers), and we do not use them in all patients. We reserve pharmacologic therapy for patients who do not achieve their weight loss

goals and who have biopsy-proven NASH with fibrosis stage ≥2. The approach also depends on whether the patient has diabetes mellitus.

Pharmacologic therapies have been studied for the treatment of patients with NASH. However, most trials have been too short to determine an impact on important patient-centered clinical outcomes (eg, decompensated cirrhosis), and instead report on surrogate outcomes, such as serum aminotransferases levels or histologic findings, often with conflicting results [29].

Patients with NASH but without diabetes — For patients with biopsy-proven NASH and fibrosis stage ≥2 who do not have diabetes mellitus, we generally suggest vitamin E, at a dose of 800 international units daily. Some studies suggest that vitamin E improves steatosis and inflammation in such patients. However, because data are mixed and there are potential safety concerns with high-dose vitamin E, we discuss the potential risks and benefits of vitamin E therapy and individualize the decision based on patient preference.

Since the studies showing a benefit of vitamin E did not include patients with diabetes mellitus or decompensated cirrhosis, we do not use vitamin E in such patients. This is consistent with recommendations from the American Association for the Study of Liver Diseases (AASLD) [3].

We do not use pioglitazone for patients with NASH but without diabetes mellitus because of its potential adverse effects as discussed below. (See 'Patients with NASH and diabetes' below.)

Some, but not all, randomized trials support the use of vitamin E for NASH, but the conflicting findings may be related to differences in trial design [30-37]. A meta-analysis that included five trials found no histologic benefits with vitamin E, though there was significant heterogeneity among the studies with respect to the formulation of vitamin E used, the patient population, the duration of treatment, and the addition of lifestyle modifications [29].

However, the largest randomized trial included in the meta-analysis (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH) did suggest a benefit with vitamin E. The trial included 247 adults with NASH without diabetes who were randomly assigned to pioglitazone (30 mg daily), vitamin E (800 international units daily), or placebo for 96 weeks [32]. Patients treated with vitamin E were more likely to have improvement in their global histology score compared with patients who received placebo (43 versus 19 percent). A subsequent report from the trial found that improvement in ALT was more common in patients receiving vitamin E compared with placebo (48 versus 16 percent) [38]. This is consistent with observational studies that suggested improvement in aminotransferase levels in patients with NASH who received vitamin E [39]. The potential benefit is thought to be related to its antioxidant properties. (See "Overview of vitamin E".)

High-dose vitamin E supplementation (≥400 international units per day) has been inconsistently associated with an increase in all-cause mortality. Underlying comorbidities or use of other supplements in patients using higher doses may have confounded the results, making their interpretation uncertain. Therefore, we feel that vitamin E is a reasonable intervention for patients with NASH and fibrosis stage ≥2 who do not have diabetes mellitus. (See "Vitamin intake and disease prevention", section on 'All-cause mortality'.)

We avoid vitamin E in male patients with either a personal history or strong family history of prostate cancer. The association of vitamin E supplementation with the risk of prostate cancer is discussed separately. (See "Chemoprevention strategies in prostate cancer", section on 'Vitamin E'.)

Patients with NASH and diabetes — For patients with diabetes mellitus, the presence of NASH can inform the choice of glucose lowering therapy in some cases. Although initial therapy for type 2 diabetes mellitus is typically with metformin, which does not improve liver histology [40,41], the beneficial impact on liver histology with certain other insulin-sensitizing agents could be a consideration when choosing a second-line agent for patients with NASH who cannot take metformin or need additional glucose-lowering therapy. In this setting, pioglitazone and glucagon-like peptide-1 (GLP-1) receptor agonists are reasonable options.

In patients with diabetes mellitus and biopsy-proven NASH, pioglitazone improves fibrosis as well as inflammation and steatosis. GLP-1 receptor agonists also appear to provide some benefits for patients with NASH. The potential benefits of these drugs must be balanced with their associated adverse effects. For example, use of pioglitazone is limited because it is associated with increased risk of weight gain, heart failure, and fractures. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Monotherapy failure' and "Thiazolidinediones in the treatment of type 2 diabetes mellitus" and "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Adverse effects'.)

The overall approach to management of blood glucose in type 2 diabetes is discussed elsewhere. (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus".)

Several trials have demonstrated the impact of these agents in patients with NASH:

- Pioglitazone – Thiazolidinediones, and specifically pioglitazone, improve liver biochemical and histologic parameters in patients with NASH [30,32,42-48]. The effect of thiazolidinediones on histologic parameters in NASH was examined in a meta-analysis of four trials that compared thiazolidinediones with placebo in 334 patients with NASH [49]. The analysis found that compared with placebo, thiazolidinediones were more likely to

improve hepatic histologic parameters such as ballooning degeneration (OR 2.1, 95% CI 1.3-3.4), lobular inflammation (OR 2.6, 95% CI 1.7-4.0), and steatosis (OR 3.4, 95% CI 2.2-5.3). Improvement in fibrosis was not seen when all thiazolidinediones were examined, but when the analysis was limited to three studies that used pioglitazone, there was a significant improvement in fibrosis among patients treated with pioglitazone compared with placebo (OR 1.7, 95% CI 1.0-2.8).

It is likely that long-term treatment is required to achieve a clinically important benefit because the improvements seen with pioglitazone may reverse if the drug is stopped [42].

- GLP-1 receptor agonists [50-52]:

  - Liraglutide – In a trial including 52 patients with NASH who were assigned to receive liraglutide or placebo for 48 weeks, an end-of-treatment biopsy was performed in 23 patients in the liraglutide arm and in 22 patients in the placebo arm [50]. NASH resolved in nine patients (39 percent) who received liraglutide, and in two patients (9 percent) who received placebo (RR 4.3; 95% CI 1.0-17). With regard to fibrosis progression, patients who received liraglutide were less likely to have progression of fibrosis (9 versus 36 percent; RR 0.2; 95% CI 0.1-1.0).

  - Semaglutide – In a phase 2 trial including 320 patients with biopsy-proven NASH and liver fibrosis of stage F1, F2 or F3, semaglutide (0.4 mg once daily) resulted in higher rates of histologic resolution of NASH compared with placebo after 72 weeks (59 versus 17 percent; OR 6.87, 95% CI 2.60-17.63) [52]. Lower doses of semaglutide (0.1 mg or 0.2 mg once daily) were less effective but were also more likely to result in histologic resolution compared with placebo (40 percent; OR 3.36, 95% CI 1.29-8.86, and 36 percent; OR 2.71, 95% CI 1.06-7.56, respectively). However, rates of improvement in liver fibrosis stage were not significantly different between the treatment groups and placebo. Gastrointestinal side effects (eg, nausea, vomiting) were more frequently reported with semaglutide compared with placebo, although statistical analysis was not provided. Additional data on histologic outcomes and side effects are needed before semaglutide is used routinely for patients with NASH in the absence of other indications (eg, type 2 diabetes mellitus). (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Adverse effects'.)

The apparent benefit of certain insulin-sensitizing agents for NAFLD is likely related to the role insulin resistance plays in the development of NAFLD. (See "Pathogenesis of nonalcoholic fatty liver disease", section on 'Insulin resistance'.)

We do not use vitamin E in patients with diabetes because studies showing a benefit from vitamin E did not include these patients [32,38].

Therapies with uncertain benefit — Other medical therapies have been examined for the treatment of NAFLD, but none has been studied sufficiently to recommend its use as treatment for fatty liver or NASH:

- Atorvastatin – Pilot studies found a benefit from atorvastatin on aminotransferase levels in patients with NAFLD [53,54]. The use of atorvastatin was then examined in a secondary analysis of a trial looking at the effect of atorvastatin, vitamin C, and vitamin E on the development of cardiovascular events in healthy adults [55]. Two of the exclusion criteria for the study were diabetes and serum aminotransferases >1.5 times the upper limit of normal. At baseline, 80 patients had NAFLD based upon imaging criteria. After a mean of 3.6 years of follow-up, fewer patients in the treatment arm still had NAFLD compared with the placebo arm (34 versus 70 percent; adjusted OR 0.36, 95% CI 0.16-0.83).

  However, the conclusions that can be drawn from the trial are limited because patients did not receive atorvastatin alone, only in combination with vitamin E and C, because the diagnosis of NAFLD was based upon imaging criteria and not histology, and because the exclusion criteria (diabetes or elevated aminotransferases) limit its generalizability.

- **Omega-3 fatty acids** – Studies have suggested a benefit of omega-3 fatty acids in patients with NAFLD [56,57]. In a meta-analysis of nine studies with 355 patients, treatment with omega-3 fatty acids was associated with improvement in hepatic steatosis as well as aspartate aminotransferase levels [57]. There was also a trend toward improvement in alanine aminotransferase levels. When the analysis was restricted to data from randomized trials, only hepatic steatosis continued to show improvement with omega-3 fatty acid treatment [57-60].

- Aspirin – Limited data suggest that daily aspirin use is beneficial for patients with NAFLD [61-63]. In the enrollment phase of a prospective cohort study including 361 patients with biopsy-proven NAFLD, daily aspirin users were less likely to have NASH (adjusted odds ratio [aOR] 0.68, 95% CI 0.37-0.89) and fibrosis (aOR 0.54, 95% CI 0.31-0.82) compared with daily aspirin nonusers [61]. In addition, among 317 patients without advanced fibrosis at baseline, daily aspirin users were less likely to progress to advanced fibrosis compared with nonusers (adjusted hazard ratio 0.63, 95% CI 0.43-0.85) during 3692 person-years of follow-up. These results are promising, and future trials may add to data supporting the hepatoprotective effects of aspirin.

Laboratory monitoring — We obtain serum aminotransferases (ALT and aspartate aminotransferase) every three to six months after patients implement lifestyle interventions to achieve and maintain their weight loss goals. If the aminotransferases do not return to normal levels with weight loss or if they increase, we evaluate the patient for an alternative cause of liver disease. The evaluation of patients with abnormal liver biochemical tests is discussed separately. (See "Approach to the patient with abnormal liver biochemical and function tests".)

Monitoring for fibrosis — Our approach to monitoring patients for advanced fibrosis depends on whether they have biopsy-proven NASH and if they achieved weight loss goals and normalization of serum aminotransferases:

- **Patients with biopsy-proven NASH** – For patients with biopsy-proven NASH, we obtain a noninvasive assessment for advanced fibrosis at a time interval determined by their clinical course:

  - For patients who have not been able to lose at least five to seven percent of their body weight and/or have elevated serum aminotransferases, we obtain noninvasive assessment every three years.

  - For patients who achieve their weight loss goals and have normal serum aminotransferases, we obtain noninvasive assessment every four years.

  If the noninvasive assessment shows a low risk fibrosis score (≤F1), we continue monitoring patients every four years (if weight loss was achieved and maintained) or every three years (if weight loss was not achieved or maintained). Patients with NASH and no fibrosis or minimal fibrosis have an excellent prognosis and thus, close follow-up is not needed [64].

  If the noninvasive assessment shows an increased, high risk fibrosis score (≥F2) we discuss obtaining a follow-up liver biopsy with the patient to evaluate for advanced fibrosis. If the biopsy does not show cirrhosis, we continue to monitor the patient with noninvasive imaging at intervals as described above. If the liver biopsy shows cirrhosis, further management includes preventing and identifying complications of cirrhosis (eg, variceal hemorrhage, hepatocellular carcinoma), and this is discussed separately. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

- **Patients without biopsy proven NASH** – We do not routinely obtain a noninvasive assessment for fibrosis in patients with nonalcoholic fatty liver but without biopsy-proven NASH. If the patient's clinical status subsequently changes (eg, additional weight gain, development of other features of metabolic syndrome), we obtain a noninvasive

assessment of fibrosis every three to four years. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)", section on 'Definition'.)

The method of noninvasive evaluation depends on the availability, and options include elastography (vibration-controlled transient elastography, ultrasound shear wave or magnetic resonance elastography) and serum fibrosis markers. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography" and "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations", section on 'Imaging examinations'.)

We monitor patients with vibration-controlled transient elastography (VCTE), a noninvasive, point-of-care tool that can exclude advanced fibrosis based on liver stiffness measurements [65]. In a prospective study of 120 patients with biopsy-proven NAFLD, VCTE correctly identified 74 patients (45 percent) as having low risk for advanced fibrosis. This approach would avoid the need for liver biopsy in these low-risk patients while those at high risk for fibrosis generally require confirmatory biopsy or further imaging. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Vibration controlled transient elastography'.)

SPECIAL POPULATIONS

Patients with cirrhosis — The management of cirrhosis due to NAFLD is similar to that for cirrhosis due to other causes and includes management of portal hypertension, screening for hepatocellular carcinoma, and evaluation for liver transplantation for patients with decompensated cirrhosis. The approach to managing patients with cirrhosis is presented elsewhere. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis" and "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

DISEASE COURSE

Advanced fibrosis — Patients with NAFLD are at risk for advanced fibrosis, defined histologically as stage F2 or higher (table 2). Cirrhosis develops when simple steatosis progresses to steatohepatitis and then to fibrosis. The fibrosis stage is the only measure that correlates with outcomes such as liver-related illness, liver transplantation and liver-related mortality in patients with NAFLD [64,66,67]. (See 'Monitoring for fibrosis' above.)

While the risk of disease progression among patients with NAFLD has been evaluated in multiple studies, the results have been variable, and the risk of developing advanced fibrosis

among patients with NAFLD is unclear [1,2,6,7,68-76]. A meta-analysis that included 11 studies looked at progression to fibrosis in 366 patients with NAFLD [77]. Overall, the fibrosis stage progressed in 132 patients (36 percent), remained stable in 158 patients (46 percent), and improved in 76 patients (21 percent). It appears that patients with simple steatosis on biopsy are at lower risk for developing advanced fibrosis, whereas those with nonalcoholic steatohepatitis are at higher risk [78]. In addition, some patients with fibrosis show regression of their disease [68-70].

In a cohort study of 129 patients with NAFLD who had two follow-up biopsies in addition to clinical and biochemical evaluations, 12 patients (9 percent) developed symptoms of end-stage liver disease in mean follow-up time of 19.8 years [6]. In 113 patients with baseline low fibrosis (defined as stage <F3), 18 patients (16 percent) developed advanced fibrosis (F3 or F4) by the end of the study period. (See "Histologic scoring systems for chronic liver disease", section on 'Nonalcoholic fatty liver disease'.)

Risk factors — Factors that have been associated with advanced fibrosis can be classified as patient- or disease-related:

- Patient-related risk factors:
  - Alcohol use (see 'Alcohol use' below).
  - Body mass index ≥28 kg/m^2 [79,80].
  - Diabetes mellitus [66,81].
  - Older age (eg, ≥50 years) [70,82].
- Disease-related risk factors
  - Histologic evidence of inflammation on liver biopsy (see 'Hepatic inflammation' below).
  - Ballooning degeneration plus Mallory hyaline or fibrosis on biopsy [66].
  - Elevated serum aminotransferases (eg, ≥2 times the upper limit of normal) [79,81-83].

Coffee consumption has been associated with a lower risk of progressing to fibrosis [84].

Several statistical models have been described to predict fibrosis, but none have been extensively validated [79,83,85-87].

Alcohol use — We suggest that patients refrain from alcohol, and in particular, we recommend avoiding heavy alcohol use (ie, >14 drinks per week or >4 drinks on a given day for

males and >7 drinks per week or >3 drinks on a given day for females) [8]. (See 'General measures for all patients' above and "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment", section on 'Terminology'.)

Heavy alcohol use among patients with NAFLD has been associated with hepatic steatosis, hepatic injury, and fibrosis progression [9]. In a study of 71 patients with NAFLD followed for a mean of 14 years, 17 patients (24 percent) had fibrosis progression [9]. Heavy episodic drinking (defined in this study as more than 60 grams of alcohol on one occasion for males or 48 grams for females) was more common in those with fibrosis progression than in those without progression (47 versus 11 percent).

We also suggest that patients with NAFLD abstain from consuming any alcohol. The effect of light or moderate alcohol consumption on disease progression is less clear because data provide mixed results and prospective studies are limited. Some studies suggest that the consumption of as little as two drinks per day in those who are overweight (and one drink per day in those with obesity) is associated in hepatic injury [88-90]. In a cohort study of 285 patients with NAFLD, modest alcohol use, compared to no alcohol use, was also associated with less improvement in steatosis and level of aspartate transaminase as well as decreased chance of NASH resolution. In addition, moderate alcohol consumption does not appear to lower the risk of cardiovascular disease for patients with NAFLD, in contrast to the general population [91]. (See "Cardiovascular benefits and risks of moderate alcohol consumption".)

However, other data suggest that light or moderate alcohol consumption may have beneficial effects on the liver [92,93]. This was seen in a cross-sectional study that compared 251 lifetime nondrinkers with NAFLD with 331 modest drinkers with NAFLD [92]. Modest drinkers had lower odds for fibrosis (OR 0.56; 95% CI 0.41-0.77) and ballooning hepatocellular injury (OR 0.66; 95% CI 0.48-0.92) compared with nondrinkers.

Hepatic inflammation — Histologic evidence of hepatic inflammation is an important risk factor for developing advanced fibrosis. In a systematic review that included 187 patients with paired biopsies, the median time to develop advanced fibrosis among those with inflammation on the initial biopsy was 4.2 years, compared with 13.4 years for those without inflammation [70]. After adjusting for potential confounders, the presence of any inflammation on the initial biopsy increased the chance of progressing to advanced fibrosis 2.5-fold compared with patients who did not have inflammation.

Hepatocellular carcinoma — Surveillance for hepatocellular carcinoma (HCC) is recommended for patients with NASH-related cirrhosis. Routine surveillance intervals, imaging tests, and

management of imaging results are discussed separately. (See "Surveillance for hepatocellular carcinoma in adults".)

We do not obtain surveillance imaging for patients without cirrhosis, because the risk of HCC-related mortality is low in the absence of cirrhosis.

Patients with cirrhosis due to NAFLD are at higher risk for HCC compared with patients without cirrhosis [94,95]. In a systematic review of 61 studies and case series of patients with NAFL or NASH, the risk of HCC among those with cirrhosis ranged from 2.4 percent over seven years to 12.8 percent over three years [94]. Among those without cirrhosis, the risk of mortality from HCC was 0 to 3 percent after follow-up periods of up to 20 years.

It has been shown across different care settings that patients with NASH-related cirrhosis have lower rates of HCC surveillance compared with patients with cirrhosis from other etiologies such as hepatitis C virus infection [96-98].

Mortality — Whether patients with NAFLD have increased overall mortality rates compared with the general population is not clear. While small population-based studies have suggested a mortality risk [67,99,100], the largest study from the United States suggests that the overall mortality rate is not increased in the absence of fibrosis. The National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2012 included 6000 adults in whom rates of NAFLD and advanced fibrosis, as determined by the NAFLD activity score, were 30 and 10.3 percent, respectively [101]. Compared with individuals without NAFLD, overall mortality was lower in NAFLD participants without fibrosis (HR 0.41, 95% CI 0.22-0.76), while mortality was higher in NAFLD participants with advanced fibrosis (HR 3.13, 95% CI 1.93-5.08).

Fibrosis stage has been associated with risk of mortality. In a study including 1773 adults with NAFLD who were followed for a median of four years, the risk of all-cause mortality was higher for patients with stage F4 fibrosis (cirrhosis, HR 3.9) and stage F3 fibrosis (bridging fibrosis, HR 1.9) compared with F0 to F2 fibrosis (1.76 and 0.89 deaths per 100 person-years, respectively, versus 0.32 deaths per 100 person-years) [102]. The risk of liver-related mortality was higher for patients with stage F4 fibrosis (HR 12.7) and stage F3 fibrosis (HR 5.8) compared with F0 to F2 fibrosis (0.68 and 0.28 deaths per 100 person-years, respectively, versus 0.04 deaths per 100 person-years). These data underscore the importance of preventing disease progression in patients without advanced fibrosis or cirrhosis and the impact of achieving regression in patients with advanced disease.

Cardiovascular disease is the most common cause of death among patients with NAFLD. A previous study (NHANES III), which showed similar trends in mortality, found that the increase in mortality in NAFLD patients with fibrosis (as measured by the NAFLD fibrosis score) was due

almost exclusively to cardiovascular causes (HR 3.46, 95% CI 1.91-6.25) [103]. Risk factors for cardiovascular disease (eg, diabetes, hyperlipidemia) can be identified and managed in patients with NAFLD. (See 'General measures for all patients' above.)

Patients with NASH are at increased risk for liver-related death compared with patients with fatty liver but without NASH [67,99,104,105].

Liver decompensation — Fibrosis stage has been associated with risk of liver decompensation. In a study including 1773 adults with NAFLD who were followed for a median of four years, the risk of new onset hepatic decompensation was higher for patients with stage F4 fibrosis (cirrhosis) and stage F3 fibrosis (bridging fibrosis) compared with F0 to F2 fibrosis (2.69 and 0.99 events per 100 person-years, respectively, versus 0.05 events per 100 person-years) [102].

WHEN TO REFER

Referral to a hepatologist is indicated for patients with NAFLD and any of the following features (see 'Monitoring for fibrosis' above and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'):

- Aminotransferases (alanine aminotransferase and aspartate aminotransferase) that remain elevated despite loss of ≥5 percent of body weight (to evaluate for other etiologies of liver disease)
- Clinical features of advanced liver disease (eg, ascites, splenomegaly, jaundice)
- Steatohepatitis on liver biopsy
- Advanced fibrosis (fibrosis stage ≥F3) on a noninvasive liver assessment

Patients who develop cirrhosis and have complications (eg, ascites, variceal bleeding) or a model for end-stage liver disease (MELD) score ≥10 (MELDNa score) should be referred for a liver transplantation evaluation. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Nonalcoholic fatty liver disease".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Nonalcoholic fatty liver disease (The Basics)").
- Beyond the Basics topics (see "Patient education: Nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH) (Beyond the Basics)").

SUMMARY AND RECOMMENDATIONS

- **General measures** – The following general measures apply to patients with nonalcoholic fatty liver disease (NAFLD) (see 'General measures for all patients' above):
  - For patients without serologic evidence of immunity, vaccination for hepatitis A virus and hepatitis B virus.
  - Standard, age-appropriate immunizations (figure 1 and figure 2).
  - For patients with hyperlipidemia, lipid-lowering therapy. (See "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease".)
  - For patients with diabetes, optimizing blood glucose control. (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)
- **Weight management** – We recommend weight loss for patients with obesity (**Grade 1B**). Weight loss has been associated with histologic improvement in patients with NAFLD. We advise patients to lose a minimum of five to seven percent of body weight at a rate of 0.5

to 1.0 kg per week (1 to 2 lb per week) through lifestyle modifications, including dietary therapy and exercise. (See 'Weight loss' above and "Obesity in adults: Overview of management".)

- **Avoiding alcohol** – For patients with NAFLD, we recommend refraining from heavy alcohol consumption (**Grade 1A**) and suggest abstinence from alcohol (**Grade 2C**). Heavy alcohol use is associated with alcohol-related liver disease and other adverse consequences, including cancers of the mouth and esophagus. In patients with or at risk for NAFLD, heavy alcohol use is associated with hepatic steatosis, hepatic injury, and fibrosis progression. Whether light to moderate alcohol consumption is harmful remains somewhat uncertain as data are mixed. In the absence of definitive data, we suggest abstinence from alcohol for patients with NAFLD. (See 'General measures for all patients' above and 'Alcohol use' above and "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)

- **Medical therapy**

  - Patients with NASH but without diabetes mellitus – For patients with biopsy-proven nonalcoholic steatohepatitis (NASH) and fibrosis stage ≥2 but without diabetes, we suggest using vitamin E (800 international units per day) (**Grade 2C**). Limited evidence supports a benefit of vitamin E in patients without diabetes, but some observational studies suggest a possible increase in all-cause mortality with higher dose vitamin E. As a result, we discuss the risks and benefits with the patient before starting treatment. (See 'Patients with NASH but without diabetes' above.)

  - Patients with NASH and diabetes mellitus – For patients with NASH and diabetes mellitus, the presence of NASH can inform the choice of glucose-lowering therapy. Although initial therapy for type 2 diabetes mellitus is typically with metformin, the beneficial impact on liver histology with certain other insulin-sensitizing agents could be a consideration when choosing a second-line agent for patients with NASH who cannot take metformin or need additional glucose-lowering therapy. In this setting, pioglitazone and GLP-1 receptor agonists (eg, liraglutide, semaglutide) are reasonable options. (See 'Patients with NASH and diabetes' above and "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Monotherapy failure'.)

- **Laboratory monitoring** – We obtain serum aminotransferases (alanine aminotransferase and aspartate aminotransferase) three and six months after patients with NAFLD implement lifestyle interventions for weight loss. If the aminotransferases do not return to normal levels with weight loss or if they increase, we evaluate for an alternative cause of

liver disease. (See 'Laboratory monitoring' above and "Approach to the patient with abnormal liver biochemical and function tests".)

- **Monitoring for fibrosis** – For patients with biopsy-proven NASH, we obtain a noninvasive assessment for advanced fibrosis at a time interval determined by their clinical course (see 'Monitoring for fibrosis' above):
  - For patients who have not been able to lose at least five to seven percent of their body weight and/or have elevated serum aminotransferases, we obtain a noninvasive assessment every three years.
  - For patients who achieve their weight loss goals and have normal serum aminotransferases, we obtain a noninvasive assessment every four years.

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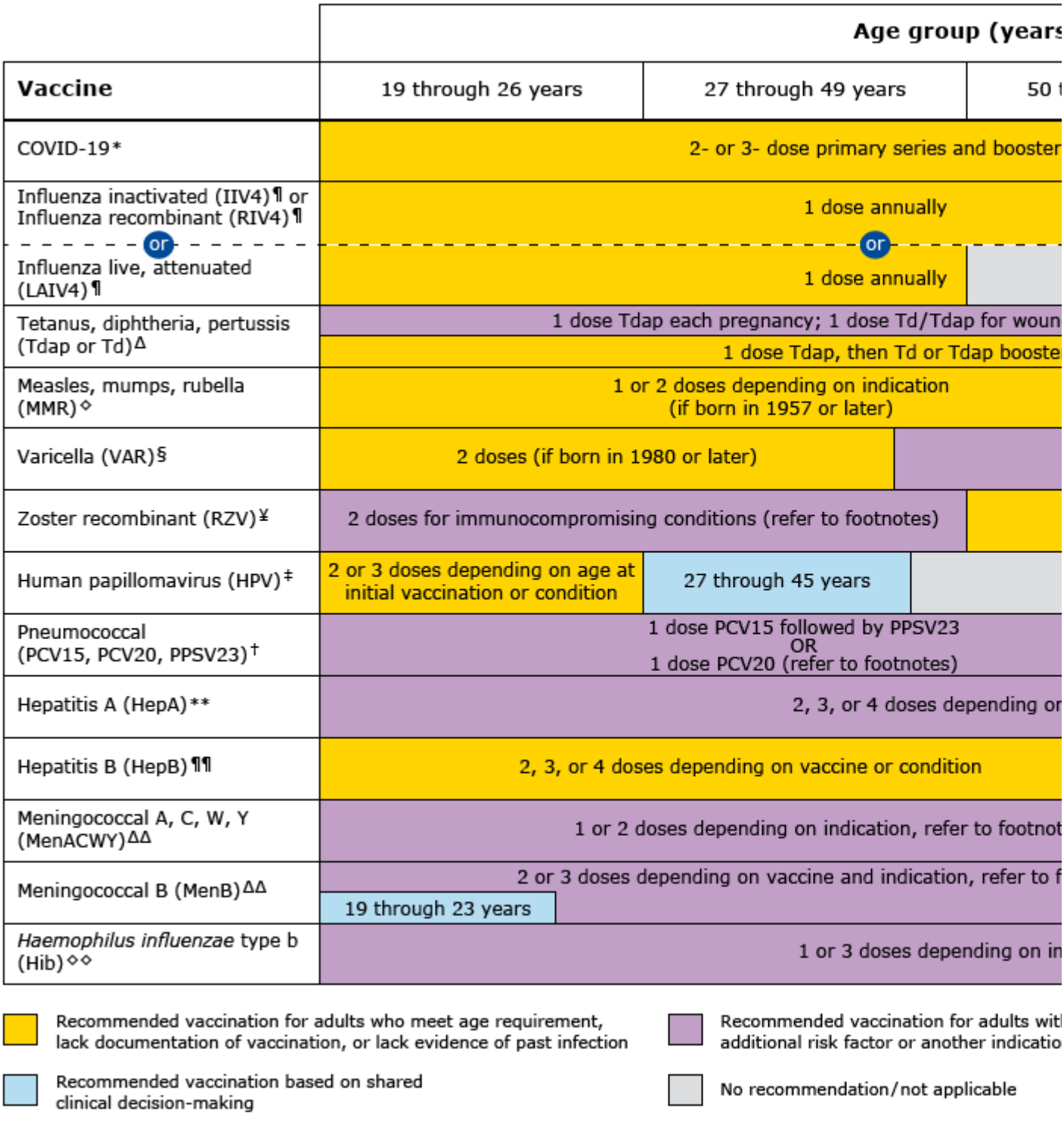
Topic 3600 Version 65.0

GRAPHICS

Recommended adult immunization schedule by age group - United States, 2023



Administer recommended vaccines if vaccination history is incomplete or unknown. Do not restart or add do between doses. The use of trade names is for identification purposes only and does not imply endorsement

Polio vaccination

- **Routine vaccination:**
  - Routine poliovirus vaccination of adults residing in the United States is not necessary.
- **Special situations:**
  - **Adults at increased risk of exposure to poliovirus with:**
    - **No evidence of a complete polio vaccination series (ie, at least 3 doses):** Administer remain series.
    - **Evidence of completed polio vaccination series (ie, at least 3 doses):** May administer one life
  - For detailed information, refer to www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html.

*** COVID-19 vaccination**

- **Routine vaccination:**
  - **Primary series:** 2-dose series at 0, 4 to 8 weeks (Moderna) or 2-dose series at 0, 3 to 8 weeks (Nov
  - **Booster dose:** Refer to www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerati
- **Special situations:**
  - **Persons who are moderately or severely immunocompromised**.
    - **Primary series:**
      - 3-dose series at 0, 4, 8 weeks (Moderna) or 3-dose series at 0, 3, 7 weeks (Pfizer-BioNTech).
      - 2-dose series at 0, 3 weeks (Novavax).
    - **Booster dose:** Refer to www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-conside
    - **Pre-exposure prophylaxis (eg, monoclonal antibodies)** may be considered to complement C www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immur
  - **For Janssen COVID-19 Vaccine recipients** refer to COVID-19 schedule at www.cdc.gov/vaccines/c considerations-us.html.
  - **NOTE:** Current COVID-19 schedule available at www.cdc.gov/vaccines/covid-19/downloads/COVID- For more information on Emergency Use Authorization (EUA) indications for COVID-19 vaccines, p and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines.
- **Contraindications and precautions:**
  - Refer to contraindications and precautions to COVID-19 vaccination.

¶ Influenza vaccination

- **Routine vaccination:**
  - **Age 19 years or older:** 1 dose any influenza vaccine appropriate for age and health status annual
  - **Age 65 years or older:** Any one of quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4) is preferred. If none of these thre appropriate influenza vaccine should be used.
  - For the 2022–2023 season, refer to www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm.
  - For the 2023–2024 season, refer to the 2023–2024 ACIP influenza vaccine recommendations.
- **Special situations:**
  - **Egg allergy, hives only:** Any influenza vaccine appropriate for age and health status annually.
  - **Egg allergy–any symptom other than hives** (eg, angioedema, respiratory distress, or required e intervention): Any influenza vaccine appropriate for age and health status may be administered. If medical setting under supervision of health care provider who can recognize and manage severe
  - **Close contacts (eg, caregivers, health care workers) of severely immunosuppressed persons** persons should not receive LAIV4. If LAIV4 is given, they should avoid contact with/caring for such vaccination.

- **Severe allergic reaction (eg, anaphylaxis) to a vaccine component or a previous dose of any i** contraindications and precautions.
- **History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine:** vaccination benefits outweigh risks for those at higher risk for severe complications from influenz

▪ **Contraindications and precautions:**

- For contraindications and precautions to influenza vaccination, refer to IIV4 Appendix, LAIV4 Appe

Δ **Tetanus, diphtheria, and pertussis (Tdap) vaccination**

▪ **Routine vaccination:**

- **Previously did not receive Tdap at or after age 11 years:** 1 dose Tdap, then Td or Tdap every 10

▪ **Special situations:**

- **Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis:** 1 weeks later and a third dose of Td or Tdap 6 to 12 months later (Tdap can be substituted for any T 10 years thereafter.
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27 t
- **Wound management:** Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For cle more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, adr dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons who have not previously tetanus-toxoid-containing vaccine is indicated for a pregnant woman, use Tdap. For detailed infor www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.

▪ **Contraindications and precautions:**

- For contraindications and precautions to tetanus, diphtheria, and acellular pertussis (Tdap), refer t

◇ **Measles, mumps, and rubella vaccination**

▪ **Routine vaccination:**

- **No evidence of immunity to measles, mumps, or rubella:** 1 dose.
  - **Evidence of immunity:** Born before 1957 (health care personnel, refer below), documentatior immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of i

▪ **Special situations:**

- **Pregnancy with no evidence of immunity to rubella:** MMR contraindicated during pregnancy; a facility), 1 dose.
- **Nonpregnant persons of childbearing age with no evidence of immunity to rubella:** 1 dose.
- **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 for at least 6 mon mumps, or rubella:** 2-dose series at least 4 weeks apart; MMR contraindicated for HIV infection w cells/mm^3.
- **Severe immunocompromising conditions:** MMR contraindicated.
- **Students in postsecondary educational institutions, international travelers, and household immunocompromised persons with no evidence of immunity to measles, mumps, or rubella** did not receive any doses of MMR or 1 dose if previously received 1 dose MMR.
- **In mumps outbreak settings**, for information about additional doses of MMR (including 3rd dos https://www.cdc.gov/mmwr/volumes/67/wr/mm6701a7.htm.
- **Health care personnel:**
  - **Born before 1957 with no evidence of immunity to measles, mumps, or rubella:** Consider against measles or mumps or 1 dose for protection against rubella.
  - **Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella:** 2-dos measles or mumps or at least 1 dose for protection against rubella.

▪ **Contraindications and precautions:**

- For contraindications and precautions to measles, mumps, rubella (MMR), refer to MMR Appendix

§ **Varicella vaccination**

- **Routine vaccination:**
  - **No evidence of immunity to varicella:** 2-dose series 4 to 8 weeks apart if previously did not rece [measles-mumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-con dose.
    - **Evidence of immunity:** US-born before 1980 (except for pregnant women and health care per varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varice laboratory evidence of immunity or disease.
- **Special situations:**
  - **Pregnancy with no evidence of immunity to varicella:** VAR contraindicated during pregnancy; a facility), 1 dose if previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series receive any varicella-containing vaccine, regardless of whether US-born before 1980.
  - **Health care personnel with no evidence of immunity to varicella:** 1 dose if previously received to 8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of wheth
  - **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 with no evidence** doses 3 months apart); VAR contraindicated for HIV infection with CD4 percentage <15% or CD4 c
  - **Severe immunocompromising conditions:** VAR contraindicated.
- **Contraindications and precautions:**
  - For contraindications and precautions to varicella (VAR), refer to VAR Appendix.

¥ **Zoster vaccination**

- **Routine vaccination:**
  - **Age 50 years or older** (NOTE: Serologic evidence of prior varicella is not necessary for zoster vacc susceptibility becomes available, providers should follow ACIP guidelines for varicella vaccination varicella, and there are limited data on the use of RZV in persons without a history of varicella or v zoster vaccine (RZV, Shingrix) 2 to 6 months apart (minimum interval: 4 weeks; repeat dose if adm zoster or history of zoster vaccine live (ZVL, Zostavax) vaccination.
- **Special situations:**
  - **Pregnancy:** There is currently no ACIP recommendation for RZV use in pregnancy. Consider delay
  - **Immunocompromising conditions** (including persons with HIV regardless of CD4 count; NOTE: I varicella vaccination, or herpes zoster, providers should refer to the clinical considerations for use years and the ACIP varicella vaccine recommendations for further guidance: www.cdc.gov/mmwr/ recombinant zoster vaccine (RZV, Shingrix) 2 to 6 months apart (minimum interval: 4 weeks; repea information, refer to www.cdc.gov/shingles/vaccination/immunocompromised-adults.html.
- **Contraindications and precautions:**
  - For contraindications and precautions to zoster recombinant vaccine (RZV), refer to RZV Appendix

‡ **Human papillomavirus vaccination**

- **Routine vaccination:**
  - **HPV vaccination recommended for all persons through age 26 years:** 2- or 3-dose series depe
    - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1 to 2 months, 6 months (min to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon).
    - **Age 9 to 14 years at initial vaccination and received 1 dose or 2 doses less than 5 months**
    - **Age 9 to 14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV needed.
  - **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be rest

- **No additional dose recommended when any HPV vaccine series has been completed using t**
- **Shared clinical decision-making:**
  - **Some adults age 27 to 45 years:** Based on shared clinical decision-making, 2- or 3-dose series as
- **Special situations:**
  - **Age ranges recommended above for routine and catch-up vaccination or shared clinical dec**
    - **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those w
    - **Pregnancy:** Pregnancy testing is not needed before vaccination; HPV vaccination is not recom needed if inadvertently vaccinated while pregnant.
- **Contraindications and precautions:**
  - For contraindications and precautions to human papillomavirus (HPV) vaccination, refer to HPV Ap

† **Pneumococcal vaccination**

- **Routine vaccination:**
  - **Age 65 years or older who have:**
    - **Not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccination** PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after between PCV15 and PPSV23 can be considered for adults with an immunocompromising cond include chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosupp immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid orga cell disease, or other hemoglobinopathies), cochlear implant, or cerebrospinal fluid leak to mi caused by serotypes unique to PPSV23 in these vulnerable groups.
    - **Previously received only PCV7:** Follow the recommendation above.
    - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR compl here: https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
    - **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PPS by another dose of PPSV23.
    - **Previously received both PCV13 and PPSV23 but NO PPSV23 was received at age 65 years** last pneumococcal vaccine dose OR complete the recommended PPSV23 series as described h www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
    - **Previously received both PCV13 and PPSV23, AND PPSV23 was received at age 65 years or** dose of PCV20 at least 5 years after the last pneumococcal vaccine dose.
    - For guidance on determining which pneumococcal vaccines a patient needs and when, please here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html.
- **Special situations:**
  - **Age 19 to 64 years with certain underlying medical conditions or other risk factors who hav** factors include alcoholism, chronic heart/liver/lung disease, chronic renal failure, cigarette smokir CSF leak, diabetes mellitus, generalized malignancy, HIV, Hodgkin disease, immunodeficiency, iatr multiple myeloma, nephrotic syndrome, solid organ transplants, or sickle cell disease, or other he
    - **Not previously received a PCV13, PCV15, or PCV20 or whose previous vaccination history** PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after the PCV1 PCV15 and PPSV23 can be considered for adults with an immunocompromising condition (NO chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, conc other hemoglobinopathies), cochlear implant, or cerebrospinal fluid leak.
    - **Previously received only PCV7:** Follow the recommendation above.
    - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR compl here: www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.

- **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PPS by another dose of PPSV23.
- **Previously received both PCV13 and PPSV23 but have not completed the recommended s** pneumococcal vaccine dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.

- For guidance on determining which pneumococcal vaccines a patient needs and when, please refe www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html.

- **Contraindications and precautions:**
  - For contraindications and precautions to Pneumococcal conjugate (PCV15 and PCV20), refer to PC (PPSV23), refer to PPSV23 Appendix.

** **Hepatitis A vaccination**

- **Routine vaccination:**
  - **Not at risk but want protection from hepatitis A (identification of risk factor not required):** Vaqta 6 to 18 months apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix a 2: 4 weeks / dose 2 to dose 3: 5 months]).
- **Special situations:**
  - **At risk for hepatitis A virus infection:** 2-dose series HepA or 3-dose series HepA-HepB as above
    - **Chronic liver disease** (eg, persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, a aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upp
    - **HIV infection**.
    - **Men who have sex with men**.
    - **Injection or noninjection drug use**.
    - **Persons experiencing homelessness**.
    - **Work with hepatitis A virus** in research laboratory or with nonhuman primates with hepatit
    - **Travel in countries with high or intermediate endemic hepatitis A** (HepA-HepB [Twinrix] r doses at 0, 7, and 21 to 30 days, followed by a booster dose at 12 months).
    - **Close, personal contact with international adoptee** (eg, household or regular babysitting) or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at lea
    - **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy.
    - **Settings for exposure**, including health care settings targeting services to injection or noninj nonresidential day care facilities for developmentally disabled persons (individual risk factor s
- **Contraindications and precautions:**
  - For contraindications and precautions to hepatitis A (HepA) vaccination, refer to HepA Appendix.

¶¶ **Hepatitis B vaccination**

- **Routine vaccination:**
  - **Age 19 through 59 years:** Complete a 2- or 3-, or 4-dose series.
    - 2-dose series only applies when 2 doses of Heplisav-B (NOTE: Heplisav-B and PreHevbrio are data in pregnant persons) are used at least 4 weeks apart.
    - 3-dose series Engerix-B, PreHevbrio (NOTE: Heplisav-B and PreHevbrio are not recommended persons), or Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks weeks]).
    - 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 w
    - 4-dose series HepA-HepB (Twinrix) accelerated schedule of 3 doses at 0, 7, and 21 to 30 days,
  - **Age 60 years or older with** known risk factors for hepatitis B virus infection **should** complete a H
  - **Age 60 years or older without** known risk factors for hepatitis B virus infection **may** complete a

- **Risk factors for hepatitis B infection include:**
  - **Chronic liver disease** (eg, persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice uppe
  - **HIV infection**.
  - **Sexual exposure risk** (eg, sex partners of hepatitis B surface antigen [HBsAg]-positive pe monogamous relationships; persons seeking evaluation or treatment for a sexually transı
  - **Current or recent injection drug use**.
  - **Percutaneous or mucosal risk for exposure to blood** (eg, household contacts of HBsAg developmentally disabled persons; health care and public safety personnel with reasonab contaminated body fluids; persons on maintenance dialysis, including in-center or home who are predialysis; patients with diabetes).
  - **Incarceration**.
  - **Travel in countries with high or intermediate endemic hepatitis B**.
- **Special situations**
  - **Patients on dialysis:** Complete a 3- or 4-dose series.
    - 3-dose series Recombivax HB at 0, 1, 6 months (NOTE: use Dialysis Formulation 1 mL = 40 mc
    - 4-dose series Engerix-B at 0, 1, 2, and 6 months (NOTE: use 2 mL dose instead of the normal a
- **Contraindications and precautions:**
  - For contraindications and precautions to hepatitis B (HepB) vaccination, refer to HepB Appendix.

ΔΔ **Meningococcal vaccination**

- **Special situations for MenACWY:**
  - **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent c inhibitor (eg, eculizumab, ravulizumab) use:** 2-dose series MenACWY-D (Menactra, Menveo, or every 5 years if risk remains.
  - **Travel in countries with hyperendemic or epidemic meningococcal disease or microbiologis** dose MenACWY (Menactra, Menveo, or MenQuadfi) and revaccinate every 5 years if risk remains.
  - **First-year college students who live in residential housing (if not previously vaccinated at a** MenACWY (Menactra, Menveo, or MenQuadfi).
  - For MenACWY **booster dose recommendations** for groups listed under "Special situations" and organizational settings and among men who have sex with men) and additional meningococcal v www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.
- **Shared clinical decision-making for MenB:**
  - **Adolescents and young adults age 16 to 23 years (age 16 to 18 years preferred) not at increa** shared clinical decision-making, 2-dose series MenB-4C (Bexsero) at least 1 month apart or 2-dos dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months af interchangeable (use same product for all doses in series).
- **Special situations for MenB:**
  - **Anatomical or functional asplenia (including sickle cell disease), persistent complement co eculizumab, ravulizumab) use, or microbiologists routinely exposed to *Neisseria meningitidi*** simultaneously with MenACWY vaccines if indicated but at a different anatomic site, if feasible)**:** 2 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1 to 2, 6 months (if dose 2 wa 3 not needed; if dose 3 is administered earlier than 4 months after dose 2, a fourth dose should b MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 d revaccinate every 2 to 3 years if risk remains.
  - **Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefits o

- For MenB **booster dose recommendations** for groups listed under "Special situations" and in ar organizational settings and among men who have sex with men) and additional meningococcal v www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

- **Contraindications and precautions:**
  - For contraindications and precautions to meningococcal ACWY (MenACWY) [MenACWY-CRM (Mer (MenQuadfi)], refer to MenACWY Appendix.
  - For contraindications and precautions to meningococcal B (MenB) [MenB-4C (Bexsero); MenB-FH

◇◇ ***Haemophilus influenzae*** **type b vaccination**

- **Special situations:**
  - **Anatomical or functional asplenia (including sickle cell disease):** 1 dose if previously did not r preferably at least 14 days before splenectomy.
  - **Hematopoietic stem cell transplant (HSCT):** 3-dose series 4 weeks apart starting 6 to 12 month vaccination history.
- **Contraindications and precautions:**
  - For contraindications and precautions to *Haemophilus influenzae* type b (Hib) vaccination, refer to

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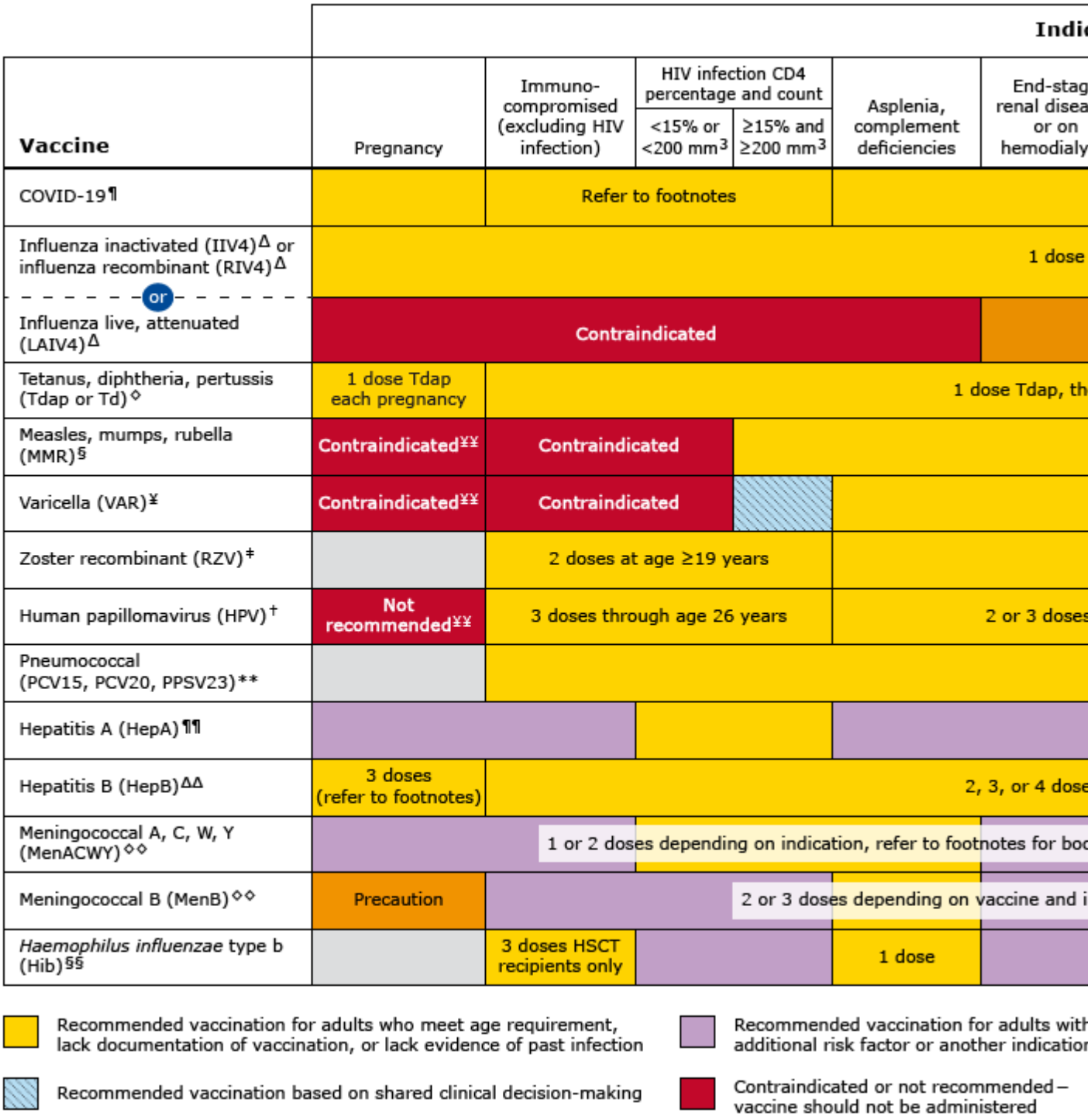
Reproduced from: Advisory Committee on Immunization Practices. Recommended Adult Immunization Schedule for ages 19 years or Prevention. Available at: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html (Accessed on February 15, 2023).

Graphic 82634 Version 35.0

Recommended adult immunization schedule by medical condition and other in



Administer recommended vaccines if vaccination history is incomplete or unknown. Do not restart or add d use of trade names is for identification purposes only and does not imply endorsement by the ACIP or CDC.

Polio vaccination

- **Routine vaccination:**
  - Routine poliovirus vaccination of adults residing in the United States is not necessary.
- **Special situations:**

- **Adults at increased risk of exposure to poliovirus with:**
  - **No evidence of a complete polio vaccination series (ie, at least 3 doses):** Administer remain
  - **Evidence of completed polio vaccination series (ie, at least 3 doses):** May administer one life
- For detailed information, refer to www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html.

HSCT: hematopoietic stem cell transplant.

* Precaution for LAIV4 does not apply to alcoholism.

¶ COVID-19 vaccination

- **Routine vaccination:**
  - **Primary series:** 2-dose series at 0, 4 to 8 weeks (Moderna) or 2-dose series at 0, 3 to 8 weeks (Nov
  - **Booster dose:** Refer to www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerati
- **Special situations:**
  - **Persons who are moderately or severely immunocompromised**.
    - **Primary series:**
      - 3-dose series at 0, 4, 8 weeks (Moderna) or 3-dose series at 0, 3, 7 weeks (Pfizer-BioNTech).
      - 2-dose series at 0, 3 weeks (Novavax).
    - **Booster dose:** Refer to www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-conside
    - **Pre-exposure prophylaxis (eg, monoclonal antibodies)** may be considered to complement C considerations/interim-considerations-us.html#immunocompromised.
  - **For Janssen COVID-19 Vaccine recipients** refer to COVID-19 schedule at www.cdc.gov/vaccines/c
  - **NOTE:** Current COVID-19 schedule available at www.cdc.gov/vaccines/covid-19/downloads/COVID- information on Emergency Use Authorization (EUA) indications for COVID-19 vaccines, please visit disease-2019-covid-19/covid-19-vaccines.
- **Contraindications and precautions:**
  - Refer to contraindications and precautions to COVID-19 vaccination.

Δ Influenza vaccination

- **Routine vaccination:**
  - **Age 19 years or older:** 1 dose any influenza vaccine appropriate for age and health status annual
  - **Age 65 years or older:** Any one of quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), adjuvanted inactivated influenza vaccine (aIIV4) is preferred. If none of these three vaccines is ava
  - For the 2022–2023 season, refer to www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm.
  - For the 2023–2024 season, refer to the 2023–2024 ACIP influenza vaccine recommendations.
- **Special situations:**
  - **Egg allergy, hives only:** Any influenza vaccine appropriate for age and health status annually.
  - **Egg allergy–any symptom other than hives** (eg, angioedema, respiratory distress, or required e vaccine appropriate for age and health status may be administered. If using egg-based IIV4 or LA provider who can recognize and manage severe allergic reactions.
  - **Close contacts (eg, caregivers, health care workers) of severely immunosuppressed persons** receive LAIV4. If LAIV4 is given, they should avoid contact with/caring for such immunosuppresse
  - **Severe allergic reaction (eg, anaphylaxis) to a vaccine component or a previous dose of any i** precautions.
  - **History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine:** risks for those at higher risk for severe complications from influenza.
- **Contraindications and precautions:**
  - For contraindications and precautions to influenza vaccination, refer to IIV4 Appendix, LAIV4 Appe

◇ **Tetanus, diphtheria, and pertussis (Tdap) vaccination**

- **Routine vaccination:**
  - **Previously did not receive Tdap at or after age 11 years:** 1 dose Tdap, then Td or Tdap every 10
- **Special situations:**
  - **Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis:** 1 dose of Td or Tdap 6 to 12 months later (Tdap can be substituted for any Td dose, but preferred as
  - **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27 t
  - **Wound management:** Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For cle last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more preferred for persons who have not previously received Tdap or whose Tdap history is unknown. I use Tdap. For detailed information, refer to www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.
- **Contraindications and precautions:**
  - For contraindications and precautions to tetanus, diphtheria, and acellular pertussis (Tdap), refer t

§ **Measles, mumps, and rubella vaccination**

- **Routine vaccination:**
  - **No evidence of immunity to measles, mumps, or rubella:** 1 dose.
    - **Evidence of immunity:** Born before 1957 (health care personnel, refer below), documentatior (diagnosis of disease without laboratory confirmation is not evidence of immunity).
- **Special situations:**
  - **Pregnancy with no evidence of immunity to rubella:** MMR contraindicated during pregnancy; a
  - **Nonpregnant women of childbearing age with no evidence of immunity to rubella:** 1 dose.
  - **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 for at least 6 mon** dose series at least 4 weeks apart; MMR contraindicated for HIV infection with CD4 percentage <1
  - **Severe immunocompromising conditions:** MMR contraindicated.
  - **Students in postsecondary educational institutions, international travelers, and household evidence of immunity to measles, mumps, or rubella:** 2-dose series at least 4 weeks apart if pr 1 dose MMR.
  - **In mumps outbreak settings**, for information about additional doses of MMR (including 3rd dos
  - **Health care personnel:**
    - **Born before 1957 with no evidence of immunity to measles, mumps, or rubella:** Consider rubella.
    - **Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella:** 2-dos rubella.
- **Contraindications and precautions:**
  - For contraindications and precautions to measles, mumps, rubella (MMR), refer to MMR Appendix

¥ **Varicella vaccination**

- **Routine vaccination:**
  - **No evidence of immunity to varicella:** 2-dose series 4 to 8 weeks apart if previously did not rece varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine, 1 dose at
    - **Evidence of immunity:** US-born before 1980 (except for pregnant women and health care per vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster
- **Special situations:**
  - **Pregnancy with no evidence of immunity to varicella:** VAR contraindicated during pregnancy; a previously received 1 dose varicella-containing vaccine or dose 1 of 2-dose series (dose 2: 4 to 8 w regardless of whether US-born before 1980.

- **Health care personnel with no evidence of immunity to varicella:** 1 dose if previously received previously did not receive any varicella-containing vaccine, regardless of whether US-born before
- **HIV infection with CD4 percentages ≥15% and CD4 count ≥200 cells/mm^3 with no evidence** VAR contraindicated for HIV infection with CD4 percentage <15% or CD4 count <200 cells/mm^3.
- **Severe immunocompromising conditions:** VAR contraindicated.

▪ **Contraindications and precautions:**

- For contraindications and precautions to varicella (VAR), refer to VAR Appendix.

‡ **Zoster vaccination**

▪ **Routine vaccination:**

- **Age 50 years or older** (NOTE: Serologic evidence of prior varicella is not necessary for zoster vacc available, providers should follow ACIP guidelines for varicella vaccination first. RZV is not indicate RZV in persons without a history of varicella or varicella vaccination)**:** 2-dose series recombinant zo weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of zo

▪ **Special situations:**

- **Pregnancy:** There is currently no ACIP recommendation for RZV use in pregnancy. Consider delay
- **Immunocompromising conditions** (including persons with HIV regardless of CD4 count; NOTE: I herpes zoster, providers should refer to the clinical considerations for use of RZV in immunocomp recommendations for further guidance: www.cdc.gov/mmwr/volumes/71/wr/mm7103a2.htm)**:** 2-((minimum interval: 4 weeks; repeat dose if administered too soon). For detailed information, refer

▪ **Contraindications and precautions:**

- For contraindications and precautions to zoster recombinant vaccine (RZV), refer to RZV Appendix

† **Human papillomavirus vaccination**

▪ **Routine vaccination:**

- **HPV vaccination recommended for all persons through age 26 years:** 2- or 3-dose series depe
  - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1 to 2 months, 6 months (min dose 1 to dose 3: 5 months; repeat dose if administered too soon).
  - **Age 9 to 14 years at initial vaccination and received 1 dose or 2 doses less than 5 months**
  - **Age 9 to 14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be rest
- **No additional dose recommended when any HPV vaccine series has been completed using th**

▪ **Shared clinical decision-making:**

- **Some adults age 27 to 45 years:** Based on shared clinical decision-making, 2- or 3-dose series as

▪ **Special situations:**

- **Age ranges recommended above for routine and catch-up vaccination or shared clinical deci**
  - **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those w
  - **Pregnancy:** Pregnancy testing is not needed before vaccination; HPV vaccination is not recom vaccinated while pregnant.

▪ **Contraindications and precautions:**

- For contraindications and precautions to human papillomavirus (HPV) vaccination, refer to HPV Ap

** **Pneumococcal vaccination**

▪ **Routine vaccination:**

- **Age 65 years or older who have:**
  - **Not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccinatior** this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A min for adults with an immunocompromising condition (NOTE: Immunocompromising conditions

iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Ho transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable gr

- **Previously received only PCV7:** Follow the recommendation above.
- **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR comp www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
- **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PP PPSV23.
- **Previously received both PCV13 and PPSV23 but NO PPSV23 was received at age 65 years** vaccine dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/
- **Previously received both PCV13 and PPSV23, AND PPSV23 was received at age 65 years o** least 5 years after the last pneumococcal vaccine dose.
- For guidance on determining which pneumococcal vaccines a patient needs and when, pleas www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html.

- **Special situations:**
  - **Age 19 to 64 years with certain underlying medical conditions or other risk factors who hav** alcoholism, chronic heart/liver/lung disease, chronic renal failure, cigarette smoking, cochlear im generalized malignancy, HIV, Hodgkin disease, immunodeficiency, iatrogenic immunosuppressio organ transplants, or sickle cell disease, or other hemoglobinopathies**):**
    - **Not previously received a PCV13, PCV15, or PCV20 or whose previous vaccination history** should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose. A minimu adults with an immunocompromising condition(NOTE: Immunocompromising conditions inc iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Ho transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies
    - **Previously received only PCV7:** Follow the recommendation above.
    - **Previously received only PCV13:** 1 dose PCV20 at least 1 year after the PCV13 dose OR comp www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.
    - **Previously received only PPSV23:** 1 dose PCV15 OR 1 dose PCV20 at least 1 year after the PP PPSV23.
    - **Previously received both PCV13 and PPSV23 but have not completed the recommended** dose OR complete the recommended PPSV23 series as described here: www.cdc.gov/vaccines
  - For guidance on determining which pneumococcal vaccines a patient needs and when, please re www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html.
- **Contraindications and precautions:**
  - For contraindications and precautions to Pneumococcal conjugate (PCV15 and PCV20), refer to P PPSV23 Appendix.

¶¶ Hepatitis A vaccination

- **Routine vaccination:**
  - **Not at risk but want protection from hepatitis A (identification of risk factor not required):** apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [mini
- **Special situations:**
  - **At risk for hepatitis A virus infection:** 2-dose series HepA or 3-dose series HepA-HepB as above
    - **Chronic liver disease** (eg, persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, a [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal).
    - **HIV infection**.
    - **Men who have sex with men**.

- **Injection or noninjection drug use**.
- **Persons experiencing homelessness**.
- **Work with hepatitis A virus** in research laboratory or with nonhuman primates with hepatit
- **Travel in countries with high or intermediate endemic hepatitis A** (HepA-HepB [Twinrix] r to 30 days, followed by a booster dose at 12 months).
- **Close, personal contact with international adoptee** (eg, household or regular babysitting) endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks befo
- **Pregnancy** if at risk for infection or severe outcome from infection during pregnancy.
- **Settings for exposure**, including health care settings targeting services to injection or noninj for developmentally disabled persons (individual risk factor screening not required).

- **Contraindications and precautions:**
  - For contraindications and precautions to hepatitis A (HepA) vaccination, refer to HepA Appendix.

ΔΔ **Hepatitis B vaccination**

- **Routine vaccination:**
  - **Age 19 through 59 years:** Complete a 2- or 3-, or 4-dose series.
    - 2-dose series only applies when 2 doses of Heplisav-B (NOTE: Heplisav-B and PreHevbrio are persons) are used at least 4 weeks apart.
    - 3-dose series Engerix-B, PreHevbrio (NOTE: Heplisav-B and PreHevbrio are not recommended Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to d
    - 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 w
    - 4-dose series HepA-HepB (Twinrix) accelerated schedule of 3 doses at 0, 7, and 21 to 30 days,
  - **Age 60 years or older with** known risk factors for hepatitis B virus infection **should** complete a H
  - **Age 60 years or older without** known risk factors for hepatitis B virus infection **may** complete a
    - **Risk factors for hepatitis B virus infection include:**
      - **Chronic liver disease** (eg, persons with hepatitis C, cirrhosis, fatty liver disease, alcoholic aspartate aminotransferase [AST] level greater than twice upper limit of normal).
      - **HIV infection**.
      - **Sexual exposure risk** (eg, sex partners of hepatitis B surface antigen [HBsAg]-positive pe persons seeking evaluation or treatment for a sexually transmitted infection; men who ha
      - **Current or recent injection drug use**.
      - **Percutaneous or mucosal risk for exposure to blood** (eg, household contacts of HBsAg disabled persons; health care and public safety personnel with reasonably anticipated risl maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, a
      - **Incarceration**.
      - **Travel in countries with high or intermediate endemic hepatitis B**.
- **Special situations:**
  - **Patients on dialysis:** complete a 3- or 4-dose series.
    - 3-dose series Recombivax HB at 0, 1, 6 months (NOTE: use Dialysis Formulation 1 mL = 40 mc
    - 4-dose series Engerix-B at 0, 1, 2, and 6 months (NOTE: use 2 mL dose instead of the normal a
- **Contraindications and precautions:**
  - For contraindications and precautions to hepatitis B (HepB) vaccination, refer to HepB Appendix.

◇◇ **Meningococcal vaccination**

- **Special situations for MenACWY:**
  - **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent c eculizumab, ravulizumab) use:** 2-dose series MenACWY-D (Menactra, Menveo, or MenQuadfi) a

- **Travel in countries with hyperendemic or epidemic meningococcal disease, or microbiologi** (Menactra, Menveo, or MenQuadfi) and revaccinate every 5 years if risk remains.
- **First-year college students who live in residential housing (if not previously vaccinated at a** Menveo, or MenQuadfi).
- For MenACWY **booster dose recommendations** for groups listed under "Special situations" and among men who have sex with men) and additional meningococcal vaccination information, refe

▪ **Shared clinical decision-making for MenB:**
- **Adolescents and young adults age 16 to 23 years (age 16 to 18 years preferred) not at increa** making, 2-dose series MenB-4C (Bexsero) at least 1 month apart or 2-dose series MenB-FHbp (Tru after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not

▪ **Special situations for MenB:**
- **Anatomical or functional asplenia (including sickle cell disease), persistent complement co ravulizumab) use, or microbiologists routinely exposed to *Neisseria meningitidis*** (NOTE: Men if indicated, but at a different anatomic site, if feasible)**:** 2-dose primary series MenB-4C (Bexsero) at 0, 1 to 2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not need dose should be administered at least 4 months after dose 3); MenB-4C and MenB-FHbp are not in booster 1 year after primary series and revaccinate every 2 to 3 years if risk remains.
- **Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefits o
- For MenB **booster dose recommendations** for groups listed under "Special situations" and in an among men who have sex with men) and additional meningococcal vaccination information, refe

▪ **Contraindications and precautions:**
- For contraindications and precautions to meningococcal ACWY (MenACWY) [MenACWY-CRM (Men MenACWY Appendix.
- For contraindications and precautions to meningococcal B (MenB) [MenB-4C (Bexsero); MenB-FH

§§ ***Haemophilus influenzae*** **type b vaccination**

▪ **Special situations:**
- **Anatomical or functional asplenia (including sickle cell disease):** 1 dose if previously did not r before splenectomy.
- **Hematopoietic stem cell transplant (HSCT):** 3-dose series 4 weeks apart starting 6 to 12 month

▪ **Contraindications and precautions:**
- For contraindications and precautions to *Haemophilus influenzae* type b (Hib) vaccination, refer to

¥¥ Vaccinate after pregnancy.

Reproduced from: Advisory Committee on Immunization Practices. Recommended Adult Immunization Schedule for ages 19 years or https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html (Accessed on February 15, 2023).

Graphic 62130 Version 23.0

Drugs available as adjuncts to diet and exercise for treatment of obesity

Generic name	Usual dosing (adults)	US DEA schedule	Adverse effects and precautions*
Pancreatic lipase inhibitor approved for long-term use			
Orlistat	120 mg 3 times daily with fat-containing meals. A reduced dose of 60 mg¶ is an option for patients who do not tolerate 120 mg.	Not a controlled substance	Cramps, flatulence, fecal incontinence, oily spotting, absorption of fat-soluble vitamins may be reduced. Rarely reported: severe liver injury, oxalate-kidney injury. Contraindicated during pregnancy.
Combination of phentermine-topiramate approved for long-term use			
Phentermine-topiramate	Initial: 3.75 mg phentermine/23 mg topiramate once daily in the morning for 14 days, followed by 7.5 mg phentermine/46 mg topiramate daily for 12 weeks. Then titrate based upon response: 11.25 mg phentermine/69 mg topiramate daily for 14 days, and then to a maximum dose of 15 mg phentermine/92 mg topiramate once daily.	C-IV (due to phentermine component)	Dry mouth, taste disturbance, constipation, paraesthesias, depression, anxiety, elevated heart rate, cognitive disturbances, insomnia (higher dose). Abuse potential due to phentermine component. Topiramate is teratogenic (increased risk of oral cleft defects, T1); negative pregnancy test prior to and during treatment and 2 forms of contraception necessary for women of child-bearing potential. Actions of topiramate component include inhibition of carbonic anhydrase; rarely metabolic acidosis and kidney stones may result from renal bicarbonate loss. Maximum dose with moderate hepatic or renal impairment (CrCl <50 mL/min) 7.5 mg phentermine/46 mg topiramate once daily.

			Upon discontinuation, tapering of dose over at least 1 week using every-other-day dosing is recommended. Contraindicated during pregnancy, hyperthyroidism, glaucoma, patients taking MAO inhibitors.
Combination of bupropion-naltrexone approved for long-term use			
Bupropion-naltrexone	Week 1: 1 tablet (8 mg naltrexone/90 mg bupropion) once daily. Week 2: 1 tablet twice daily. Week 3: 2 tablets in morning and one tablet in evening. Week 4: 2 tablets twice daily. Maximum daily dose: 4 tablets (32 mg naltrexone/360 mg bupropion).	Not a controlled substance	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth. Transient increase in blood pressure (1 to 2 mmHg on average) during initial 12 weeks of treatment; heart rate may also be increased. Contraindicated in patients with uncontrolled hypertension, seizure disorder, eating disorder, use of other bupropion-containing products, chronic opioid use, use within 14 days of MAO inhibitors, pregnancy, or breastfeeding.[Δ]
GLP-1 agonists approved for long-term use			
Liraglutide	Initial: 0.6 mg subcutaneously daily. Increase at weekly intervals (1.2, 1.8, 2.4, 3 mg) until recommended dose of 3 mg daily. If increased dose is not tolerated, consider delaying dose escalation by an additional week.[◇]	Not controlled substances	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM (more common if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions, increased lipase, increased heart rate. Rarely reported: pancreatitis, gallbladder disease, renal impairment, suicidal thoughts. Causes a modest delay of gastric emptying.

			Advise patients to avoid dehydration in relation to GI side effects. Monitor blood glucose in diabetic patients and adjust co-administered sulfonylureas (eg, reduce dose by 50%) and other anti-diabetic medications as needed to prevent potentially severe hypoglycemia. Possible increase in thyroid cancer risk based on murine model data. Contraindicated in pregnancy and in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B. For semaglutide, monitor patients with diabetic retinopathy for eye complications.
Semaglutide	Initial: 0.25 mg subcutaneously once weekly. Increase dose at 4-week intervals (0.5, 1, 1.7, 2.4 mg) until recommended dose of 2.4 mg weekly. If increased dose is not tolerated, consider delaying dose escalation by 4 weeks.[§]		
Noradrenergic sympathomimetic drugs approved for short-term use			
Benzphetamine	Initial: 25 mg once daily; may titrate up to 25 to 50 mg one to 3 times daily. Maximum dose: 50 mg 3 times daily.	C-III	Applies to all sympathomimetic agents: ▪ Due to their side effects and potential for abuse, we suggest **not** prescribing sympathomimetics for weight loss. ▪ If prescribed, limit to short-term (≤12 weeks) use. ▪ Adverse effects include increase in heart rate, blood pressure, insomnia, dry mouth, constipation, nervousness. ▪ Abuse potential due to amphetamine-like effects. ▪ May counteract effect of blood pressure medications.
Diethylpropion	Immediate release: 25 mg 3 times daily, 1 hour before meals. Controlled release: 75 mg every morning.	C-IV	
Phentermine	Immediate release: 15 to 37.5 mg daily or divided twice daily. Orally disintegrating tablet (ODT): 15 to 37.5 mg once daily in the morning. Immediate release (Lomaira): 8 mg 3 times daily before	C-IV	

	meals.		▪ Avoid in patients with heart disease, poorly controlled hypertension, pulmonary hypertension, or history of addiction or drug abuse. ▪ Contraindicated in patients with a history of CVD, hyperthyroidism, glaucoma, MAO inhibitor-therapy, agitated states, pregnancy, or breast feeding.
Phendimetrazine	Immediate release: 17.5 to 35 mg 2 or 3 times daily, 1 hour before meals. Maximum dose: 70 mg 3 times daily. Sustained release: 105 mg daily in the morning.	C-III	

Dosing in this table is for adults with normal kidney and liver function. Patients are reevaluated after 12 weeks on the maximum tolerated dose of a weight loss drug to determine efficacy.

CrCl: creatinine clearance; CVD: cardiovascular disease (arrhythmias, congestive heart failure, coronary artery disease, stroke, uncontrolled hypertension); GI: gastrointestinal; GLP-1: glucagon-like peptide 1; MAO inhibitors: monamine oxidase inhibitors; T1: first trimester pregnancy; T2DM: type 2 diabetes mellitus; US DEA: United States Drug Enforcement Agency; FDA: US Food and Drug Administration.

* Applies to all drugs except orlistat: May increase risk of hypoglycemia in type 2 diabetics. For additional information on potential interactions of anti-obesity drugs with other medications, use Lexi-Interact program included with UpToDate.

¶ Orlistat 60 mg is available without a prescription in the United States and some other countries.

Δ FDA recommends warning young adults (age 18 to 24 years) of the risk of becoming suicidal during initial treatment of psychiatric disorders with any antidepressant.

◇ According to United States labeling, if weight loss is not ≥4% after 16 weeks or 3 mg/day is not tolerated, discontinue use. Labeling in the European Union recommends discontinuation of use if weight loss is not ≥5% after 12 weeks of 3 mg/day.

§ According to United States labeling, if 2.4 mg/week is not tolerated, discontinue use.

Courtesy of authors.

With additional data from:

1. *The US National Library of Medicine DailyMed website. Availablet at: https://dailymed.nlm.nih.gov/dailymed/ (Accessed October 8, 2014).*
2. *Kim GW, Lin JE, Blomain ES, Waldman SA. Antiobesity pharmacotherapy: new drugs and emerging targets. Clin Pharmacol Ther 2014; 95:1.*
3. *US Food and Drug Administration. FDA approves new drug treatment for chronic weight management, first since 2014. 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014 (Accessed on June 8, 2021).*

Graphic 86204 Version 21.0

Nonalcoholic steatohepatitis grading and staging system

Grade	Description
Mild (grade 1)	Steatosis (predominantly macrovesicular) involving up to 66% of biopsy; may see occasional ballooned zone 3 hepatocytes; scattered intra-acinar polymorphonuclear cells, intra-acinar lymphocytes; no or mild portal chronic inflammation
Moderate (grade 2)	Steatosis of any degree; ballooning of hepatocytes (predominantly zone 3) obvious; intra-acinar polymorphonuclear cells noted, may be associated with zone 3 pericellular fibrosis; portal and intra-acinar chronic inflammation noted, mild to moderate
Severe (grade 3)	Panacinar steatosis; ballooning and disarray obvious, predominantly in zone 3; intra-acinar inflammation noted as scattered polymorphonuclear cells, ballooned hepatocytes, mild chronic inflammation; portal chronic inflammation mild or moderate
Stage*	**Description**
Fibrosis stage 1 (F1)	Zone 3 perisinusoidal fibrosis; focally or extensively present
Fibrosis stage 2 (F2)	Zone 3 perisinusoidal fibrosis with portal fibrosis
Fibrosis stage 3 (F3)	Zone 3 perisinusoidal fibrosis and portal fibrosis with bridging fibrosis
Fibrosis stage 4 (F4)	Cirrhosis

* Fibrosis stage 0 (F0) is the absence of fibrosis.

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