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Antiviral Drugs for Influenza for 2022-2023

Influenza is generally a self-limited illness, but complications such as pneumonia, respiratory failure, and death can occur, especially in patients at increased risk for influenza complications (see Table 1). Antiviral drugs recommended for treatment and chemoprophylaxis of influenza this season are listed in Table 2. Updated information on influenza activity and antiviral resistance is available from the CDC at www.cdc.gov/flu. None of the drugs that are FDA-approved for treatment of influenza have clinically relevant antiviral activity against SARS-CoV-2.

TREATMENT RECOMMENDATIONS — Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who is hospitalized, has severe, complicated, or progressive illness, or is at increased risk for complications, even if it is started >48 hours after illness onset.[1-3] False-negative results can occur with some influenza tests; patients in the above groups should receive antiviral treatment even if they test negative, especially when influenza viruses are known to be circulating in the community.[4]

Antiviral treatment can be considered for otherwise healthy symptomatic outpatients with suspected or confirmed influenza who are not at increased risk for influenza complications if it can be started within 48 hours after illness onset.

TREATMENT — A neuraminidase inhibitor (oral oseltamivir, IV peramivir, or inhaled zanamivir) or the oral cap-dependent endonuclease inhibitor baloxavir marboxil is recommended for treatment of suspected or confirmed uncomplicated influenza in nonpregnant outpatients this season. All of these drugs are active against influenza A and B viruses.

Oseltamivir is preferred for use in pregnant women, hospitalized patients, and outpatients with severe, complicated, or progressive illness.[1]

Table 1: Patients at Increased Risk for Influenza Complications

- Children <5 years old (children <2 years old are at highest risk)
- Patients <19 years old receiving long-term treatment with aspirin or salicylate-containing drugs
- Adults ≥65 years old
- Obese patients with a BMI ≥40 kg/m^2
- Women who are pregnant or ≤2 weeks postpartum
- Non-Hispanic Black persons, Hispanic or Latino persons, or persons of American Indian or Alaska Native heritage
- Residents of nursing homes or other chronic care facilities
- Patients who are immunosuppressed
- Patients with a chronic medical condition[1]

1. Including asthma, neurologic and neurodevelopmental conditions, blood disorders, chronic lung disease, endocrine disorders, heart disease, kidney disease, liver disorders, and metabolic disorders.

Effectiveness — Use of a neuraminidase inhibitor or baloxavir for treatment of acute uncomplicated influenza in **adults** shortens the duration of symptoms by about one day.[5-8] In a meta-analysis of 26 randomized, placebo-controlled trials that included 11,897 healthy adults and children with influenza-like illness, zanamivir was associated with the shortest time to alleviation of influenza symptoms and baloxavir was associated with the lowest risk of influenza-related complications.[9] In hospitalized patients, oral oseltamivir and IV peramivir appear to be similarly effective.[10]

A meta-analysis of randomized trials in **children** with influenza found that starting oseltamivir within 48 hours after illness onset reduced illness duration by about 18 hours (by about 30 hours when trials that enrolled children with asthma were excluded) and decreased the risk of otitis media.[11] In children hospitalized with laboratory-confirmed influenza, antiviral treatment started within 48 hours after illness onset was associated with shorter lengths of hospital stay compared to no antiviral treatment.[12]

Although most controlled trials of antiviral drugs have not been powered to assess their efficacy in preventing serious influenza complications, experts have generally interpreted the combined results of

Table 2. Antiviral Drugs for Influenza for 2022-2023

Drug/Formulations	Usual Dosage	Comments	Cost[1]
Neuraminidase Inhibitors			
Oseltamivir – generic *Tamiflu* (Genentech) 30, 45, 75 mg caps; 6 mg/mL oral suspension[2]	**Treatment:** ≥2 wks-<1 yr: 3 mg/kg PO bid[3] x 5 days[4] 1-12 yrs: 30-75 mg[5] PO bid x 5 days[4] ≥13 yrs: 75 mg PO bid x 5 days[4] Renal impairment: See footnote 6 **Chemoprophylaxis:** <1 yr: 3 mg/kg PO once/day[7] x 7 days[8] 1-12 yrs: 30-75 mg[5] PO once/day x 7 days[8] ≥13 yrs: 75 mg PO once/day x 7 days[8] Renal impairment: See footnote 6	▸ FDA-approved for treatment of acute uncomplicated influenza in patients ≥2 weeks old ▸ FDA-approved for chemoprophylaxis of influenza in patients ≥1 year old ▸ Preferred for treatment of influenza in pregnant women, hospitalized patients, and outpatients with severe, complicated, or progressive illness ▸ Taking oseltamivir with food may improve tolerability ▸ Contents of capsules can be mixed in a thick sweetened liquid to mask the bitter taste and consumed immediately thereafter	$32.00 151.90
Peramivir – *Rapivab* (BioCryst) 200 mg/20 mL single-use vials	**Treatment:** 6 months-12 yrs: 12 mg/kg (max 600 mg) IV over 15-30 minutes once[4] ≥13 yrs: 600 mg IV over 15-30 minutes once[4] Renal impairment: See footnote 9	▸ FDA-approved for treatment of acute uncomplicated influenza in otherwise healthy patients ≥6 months old ▸ Not recommended for treatment of severe influenza[10] ▸ Not FDA-approved for chemoprophylaxis	950.00
Zanamivir – *Relenza* (GSK) 5 mg blisters of powder for inhalation	**Treatment:** ≥7 yrs: 2 inh bid x 5 days **Chemoprophylaxis:** ≥5 yrs: 2 inh once/day x 7 days[8]	▸ FDA-approved for treatment of acute uncomplicated influenza in patients ≥7 years old ▸ FDA-approved for chemoprophylaxis of influenza in patients ≥5 years old ▸ Contraindicated in patients with milk protein allergy ▸ Not recommended for patients with underlying airway disease ▸ Not recommended for treatment of severe influenza	59.00
Cap-Dependent Endonuclease Inhibitor			
Baloxavir marboxil – *Xofluza* (Genentech) 40, 80 mg tabs; 40 mg/20 mL oral suspension[11]	**Treatment:** ≥5 yrs and 20-<80 kg: 40 mg PO once ≥5 yrs and ≥80 kg: 80 mg PO once **Chemoprophylaxis:** ≥5 yrs and 20-<80 kg: 40 mg PO once ≥5 yrs and ≥80 kg: 80 mg PO once	▸ FDA-approved for treatment of acute uncomplicated influenza in otherwise healthy patients ≥5 years old or in patients ≥12 years old who are at high risk of influenza-related complications ▸ FDA-approved for post-exposure prophylaxis in patients ≥5 years old ▸ No data in patients with severe influenza ▸ Not recommended for use in severely immuno-compromised patients or pregnant women ▸ Avoid coadministration of dairy products, calcium-fortified beverages, and products containing polyvalent cations	154.50

1. Approximate WAC for 5 days' treatment with oseltamivir capsules or zanamivir, or for a single treatment dose of peramivir or baloxavir marboxil, at the usual adult dosage. WAC = wholesaler acquisition cost, or manufacturer's published price to wholesalers; WAC represents published catalogue or list prices and may not represent an actual transactional price. Source: AnalySource® Monthly. November 5, 2022. Reprinted with permission by First Databank, Inc. All rights reserved. ©2022. www.fdbhealth.com/policies/drug-pricing-policy.
2. Oseltamivir can be administered by oro/nasogastric tube to patients who are unable to swallow.
3. Although not FDA-approved for use in children <2 weeks old, the CDC recommends children <2 weeks old be treated with 3 mg/kg bid. The American Academy of Pediatrics has recommended a dose of 3.5 mg/kg for infants 9-11 months old based on the results of a study showing that a higher dose was needed to achieve the target exposure in this age group (DW Kimberlin et al. J Infect Dis 2013; 207:709). For treatment of premature infants, refer to CDC recommendations (www.cdc.gov/flu).
4. In hospitalized, critically ill, or immunocompromised patients, a longer treatment course of oseltamivir (e.g., 10 days) is often used.
5. FDA-approved doses for children 1-12 years old who weigh ≤15 kg: 30 mg; >15-23 kg: 45 mg; >23-40 kg: 60 mg; >40 kg: 75 mg.
6. Oseltamivir renal dosage adjustment for adults and children who weigh >40 kg (recommended by the CDC): CrCl 31-60 mL/min: 30 mg bid for treatment and 30 mg once/day for prophylaxis; CrCl 11-30 mL/min: 30 mg once/day for treatment and 30 mg every other day for prophylaxis; hemodialysis (HD): 30 mg after every HD for treatment (may be started immediately if influenza symptoms develop between HD sessions) and 30 mg after every other HD for prophylaxis (initial dose can be given before start of HD); continuous ambulatory peritoneal dialysis (CAPD): single 30-mg dose after exchange for treatment and 30 mg once/week after exchange for prophylaxis; end-stage renal disease (ESRD) not on HD: not recommended for treatment or prophylaxis.
7. Although not FDA-approved for chemoprophylaxis in children <1 year old, the American Academy of Pediatrics and the CDC recommend that children 3 months-<1 year old receive 3 mg/kg once/day. Chemoprophylaxis is generally not recommended for premature infants or infants <3 months old (refer to CDC recommendations at: www.cdc.gov/flu).
8. Duration of chemoprophylaxis recommended by the CDC is 7 days after the last known exposure. The recommended duration in the labeling of oseltamivir and zanamivir is 10 days after the last known exposure. For control of outbreaks in institutions, the CDC recommends chemoprophylaxis be given for at least 2 weeks and continued for up to 1 week after the end of the outbreak. Some experts would use twice-daily therapeutic doses for post-exposure prophylaxis in highly immunocompromised patients.
9. Peramivir renal dosage adjustment for patients 2-12 years old: CrCl 30-49 mL/min: 4 mg/kg once; CrCl 10-29 mL/min: 2 mg/kg once. For patients ≥13 years old: CrCl 30-49 mL/min: 200 mg once; CrCl 10-29 mL/min: 100 mg once; hemodialysis (HD): administer dose (based on CrCl) after HD.
10. IV peramivir (for at least 5 days) may be considered for hospitalized, critically ill, or immunocompromised patients who cannot tolerate or absorb oral or enterically administered oseltamivir because of gastric stasis, malabsorption, or GI bleeding.
11. For patients <20 kg, the dose of the oral suspension is 2 mg/kg taken as a single dose. The suspension must be used within 10 hours after reconstitution.

controlled trials, observational studies, and meta-analyses as showing that early antiviral treatment of influenza in high-risk and hospitalized patients can reduce the risk of complications.[6,13-16]

Oseltamivir vs Baloxavir – Oseltamivir is FDA-approved for treatment of acute, uncomplicated influenza in patients ≥2 weeks old. Baloxavir is approved for use in otherwise healthy patients ≥5 years old or in patients ≥12 years old who are at high risk of developing influenza-related complications.

In a randomized, double-blind trial (miniSTONE-2) in 173 **children** 1-11 years old with influenza, the median time to improvement in symptoms was similar with a single dose of baloxavir or 5 days' treatment with oseltamivir (both started within 48 hours after illness onset; 138 vs 150 hours).[17]

In a randomized, double-blind trial (CAPSTONE-2) in 2184 **adolescents and adults** with uncomplicated influenza who were at high risk of developing complications, the median time to improvement of symptoms was similar with a single dose of baloxavir or 5 days' treatment with oseltamivir (both started within 48 hours after illness onset) in the overall population and in those infected with influenza A(H3N2), but was statistically significantly shorter with baloxavir in those infected with influenza B (median difference 27.1 hours). Use of either drug was associated with a lower incidence of influenza-related complications and fewer antibiotic prescriptions compared to placebo.[5]

In a randomized, double-blind trial (FLAGSTONE) in 366 patients ≥12 years old hospitalized with severe influenza, the time to clinical improvement was not statistically significantly different with a combination of a neuraminidase inhibitor (primarily oseltamivir) and baloxavir compared to a neuraminidase inhibitor alone (95.5 vs 100.2 hours).[18]

Timing – Neuraminidase inhibitors are most effective when started within 48 hours after illness onset, but the results of some observational studies in hospitalized and critically ill patients suggest that treatment started as late as 4-5 days after illness onset can shorten the length of hospitalization and reduce the risk of complications such as pneumonia, respiratory failure, and death.[19-22] No data are available on the efficacy of **baloxavir** when it is started >48 hours after illness onset.

Adults with community-acquired pneumonia who test positive for influenza should receive antiviral treatment regardless of the duration of illness.[23]

CHEMOPROPHYLAXIS — Oseltamivir, zanamivir, and baloxavir are FDA-approved for post-exposure prophylaxis of influenza following close contact with an infected individual. Post-exposure prophylaxis should be considered for persons at increased risk of complications who have not received an annual influenza vaccine for the current season, received one within the previous 2 weeks, or might not respond to vaccination, or when the match between the vaccine and circulating strains is poor. It is not recommended for healthy persons exposed to influenza or when >48 hours have elapsed since exposure. Antiviral chemoprophylaxis with oseltamivir or zanamivir is also recommended to help control institutional influenza outbreaks.[1]

Effectiveness – Neuraminidase inhibitors have generally been about 70-90% effective in preventing influenza caused by susceptible strains of influenza A or B viruses.[1] In a randomized, double-blind trial in 752 household contacts of patients with influenza, the efficacy of a single dose of baloxavir in preventing clinical influenza in household contacts was 86%.[24]

Timing – When indicated, chemoprophylaxis should be started no later than 48 hours after exposure and, with oseltamivir or zanamivir, it should be continued for 7 days after the last known exposure.

For institutional outbreaks, the CDC recommends chemoprophylaxis with oral oseltamivir or inhaled zanamivir for at least 2 weeks and continuing for up to 1 week after the end of the outbreak.

PREGNANCY AND LACTATION — Pregnant women are at increased risk for severe complications of influenza. Oseltamivir and zanamivir appear to be safe for use during pregnancy.[25,26] Prompt **treatment** with oseltamivir is recommended for women with suspected or confirmed influenza who are pregnant or ≤2 weeks postpartum.[27-29] Oseltamivir is preferred for treatment of women who are breastfeeding. No data are available on use of baloxavir in pregnant or breastfeeding women.

Antiviral **chemoprophylaxis** can be considered for pregnant women who have had close contact with someone likely to have influenza. Zanamivir may be preferred because of its limited systemic absorption, but oseltamivir is a reasonable alternative, especially in women at increased risk for respiratory problems.

RESISTANCE — Over 99% of the recently circulating influenza virus strains tested by the World Health Organization (WHO) have been susceptible to neuraminidase inhibitors.[30] Reduced susceptibility of some influenza virus strains, particularly influenza A(H1N1), to **oseltamivir** or **peramivir** can emerge during or after treatment, especially in young children and immunocompromised patients with prolonged viral shedding.[31-36] Resistant isolates have usually remained susceptible to **zanamivir**, but reduced susceptibility to zanamivir has been reported.[37] In immunocompromised patients, a double dose of oseltamivir reduced the incidence of oseltamivir resistance compared to standard dosing, but it did not improve efficacy and caused more adverse effects.[38]

Baloxavir is active against neuraminidase inhibitor-resistant strains of influenza A and B viruses, including A(H1N1), A(H5N1), A(H3N2), and A(H7N9). Amino acid substitutions associated with reduced susceptibility to baloxavir have occurred following treatment with a single dose of the drug.[8,39] Reduced susceptibility to baloxavir appears to be more frequent in persons infected with influenza A(H3N2) and A(H1N1)pdm09 viruses, particularly children.[40,41] Baloxavir monotherapy is not recommended for severely immunosuppressed patients because of concerns that prolonged replication of the influenza virus in these patients could lead to emergence of resistance. Oseltamivir and peramivir may be active against influenza virus strains with reduced susceptibility to baloxavir.[42]

The adamantanes **amantadine** and **rimantadine** are active against influenza A viruses, but not influenza B viruses. As in recent past seasons, resistance to these drugs is high (>99%) among circulating influenza A(H3N2) and A(H1N1)pdm09 viruses; neither amantadine nor rimantadine is recommended for treatment or chemoprophylaxis of currently circulating influenza A viruses.

ADVERSE EFFECTS — Nausea, vomiting, and headache are the most common adverse effects of **oseltamivir**; taking the drug with food may minimize GI adverse effects. Oseltamivir has been associated with bradycardia in critically ill patients.[43] Diarrhea, nausea, sinusitis, fever, and arthralgia have been reported with **zanamivir**. Inhalation of zanamivir can cause bronchospasm; the drug should not be used in patients with underlying airway disease. Diarrhea and neutropenia have occurred with **peramivir**.[44]

Baloxavir was well tolerated in clinical trials. It appears to cause less nausea and vomiting than oseltamivir.[45]

Neuropsychiatric events, including self-injury and delirium, have been reported in patients taking neuraminidase inhibitors or baloxavir, but a causal relationship has not been established, and neuropsychiatric dysfunction can be a complication of influenza illness itself.[46] Hypersensitivity reactions, including anaphylaxis, have been reported with all of these drugs.

USE WITH THE LIVE-ATTENUATED VACCINE — Use of oseltamivir or zanamivir within 48 hours before, peramivir within 5 days before, or baloxavir within 17 days before administration of the intranasal live-attenuated influenza vaccine *(FluMist Quadrivalent)* could inhibit replication of the vaccine virus, reducing the vaccine's efficacy, and is not recommended.[47] Persons who receive any of these antiviral drugs during these specified times and through 2 weeks after receiving the live-attenuated vaccine should be revaccinated with an inactivated or recombinant age-appropriate influenza vaccine.[48]

DRUG INTERACTIONS — Coadministration of dairy products, beverages, antacids, laxatives, multivitamins, or other products containing polyvalent cations (e.g., calcium, aluminum, iron, magnesium, selenium, or zinc) can reduce serum concentrations of baloxavir and should be avoided. ■

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