



CLINICAL REPORT

Antiviral Therapy and Prophylaxis for Influenza in Children

Committee on Infectious Diseases

Guidance for the Clinician in Rendering
Pediatric Care**ABSTRACT**

Antiviral agents are available that are safe and effective for the treatment and prophylaxis of influenza virus infections in children. The neuraminidase inhibitors (oseltamivir [Tamiflu] and zanamivir [Relenza]) are preferred agents because of current widespread resistance to the adamantanes (amantadine [Symmetrel] and rimantadine [Flumadine]). Therapy should be provided to children with influenza infection who are at high risk of severe infection and to children with moderate-to-severe influenza infection who may benefit from a decrease in the duration of symptoms. Prophylaxis should be provided (1) to high-risk children who have not yet received immunization and during the 2 weeks after immunization, (2) to unimmunized family members and health care professionals with close contact with high-risk unimmunized children or infants who are younger than 6 months, and (3) for control of influenza outbreaks in unimmunized staff and children in an institutional setting. Testing of current H5N1 avian influenza virus isolates, the potential agents of pandemic influenza, suggests susceptibility to oseltamivir and zanamivir. Because no prospective data exist on the efficacy of these agents in humans for H5N1 strains, the dosage and duration of therapy in adults and children may differ from those documented to be effective for epidemic influenza strains.

INTRODUCTION

Antiviral agents for treatment and prophylaxis of influenza are safe and effective in children. Annual immunization against influenza is the preferred strategy for prevention of infection, but certain situations exist in which the use of antiviral agents is beneficial.

The morbidity and mortality of epidemic influenza in unimmunized children is substantial, particularly in those younger than 2 years.¹⁻⁵ The purpose of this report is to offer guidance regarding antiviral treatment and prophylaxis to clinicians caring for children during yearly influenza epidemics and to provide resources for information on antiviral treatment in the event of an influenza pandemic, because no prospective human data currently exist on which to base recommendations for treatment of infections caused by potential H5N1 pandemic influenza virus strains.

ANTIVIRAL DRUGS FOR EPIDEMIC AND PANDEMIC INFLUENZA

Two classes of antiviral medications are currently available for treatment or prophylaxis of influenza infections: neuraminidase inhibitors (NAIs) (oseltamivir [Tamiflu; Roche Laboratories, Nutley, NJ] and zanamivir [Relenza; GlaxoSmith-Kline, Research Triangle Park, NC]) and the adamantanes (amantadine [Symme-

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words

influenza, children, influenza antiviral, oseltamivir, zanamivir, amantadine, rimantadine, ribavirin

Abbreviations

NAI—neuraminidase inhibitor

FDA—Food and Drug Administration

CNS—central nervous system

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TABLE 1 Dosing Recommendations for Antiviral Agents for Treatment and Prophylaxis of Influenza

Drug	Dosing Recommendations						
	Formulations	Treatment			Prophylaxis		
		Children	Adults		Children	Adults	
Osetamivir (Tamiflu)	75-mg capsule; 60 mg/5 mL suspension	For treatment, children ≥ 12 mo should receive ~ 4 mg/kg per d divided into 2 doses for a 5-d treatment course ≤ 15 kg >23–40 kg >40 kg 90 mg/d divided into 2 doses 120 mg/d divided into 2 doses 150 mg/d divided into 2 doses	150 mg/d divided into 2 doses for 5 d	≤ 15 kg >15–23 kg >23–40 kg >40 kg	23–40 kg >40 kg	75 mg once daily	
Zanamivir (Relenza)	5 mg per inhalation (Diskhaler)	2 inhalations (10 mg total per dose), twice daily for 5 d Children ≥ 7 y and Adults		2 inhalations (10 mg total per dose), once daily for 10 d Children ≥ 5 y and Adults			
Amantadine (Symmetrel)	100-mg tablet; 50 mg/5 mL suspension	1–9 y 5–8 mg/kg per d as a single daily dose or divided into 2 doses but not to exceed 150 mg/d ^{a,b} ; treat for 24–48 h after the disappearance of signs and symptoms 9–12 y 200 mg/d divided into 2 doses (not studied as a single daily dose) ^{a,b} ; treat for 24–48 h after the disappearance of signs and symptoms Adults 200 mg/d, either as a single daily dose or divided into 2 doses ^{a,b} ; treat for 24–48 h after the disappearance of signs and symptoms	1–9 y Same as treatment dose ^{a,b} 9–12 y Same as treatment dose ^{a,b} Adults Same as treatment dose ^{a,b}	1–9 y Same as treatment dose ^{a,b} 9–12 y Same as treatment dose ^{a,b} Adults Same as treatment dose ^{a,b}	1–9 y Same as treatment dose ^{a,b} 9–12 y Same as treatment dose ^{a,b} Adults Same as treatment dose ^{a,b}	75 mg once daily	
Rimantadine (Flumadine)	100-mg tablet; 50 mg/5 mL suspension	1–9 y Not FDA approved for treatment in children, but published data exist on safety and efficacy ⁴⁵ 6.6 mg/kg per d (maximum 150 mg/kg per d) divided into 2 doses ≥ 10 y 200 mg/d, either as a single daily dose or divided into 2 doses ^a	1–9 y 200 mg/d, either as a single daily dose or divided into 2 doses ^a ≥ 10 y 200 mg/d, either as a single daily dose or divided into 2 doses ^a	1–9 y 5 mg/kg per d once daily, not to exceed 150 mg ^{a,b} ≥ 10 y 200 mg/d, either as a single daily dose or divided into 2 doses ^{a,b}	1–9 y 200 mg/d, either as a single daily dose or divided into 2 doses ^{a,b} ≥ 10 y 200 mg/d, either as a single daily dose or divided into 2 doses ^{a,b}	200 mg/d, either as a single daily dose or divided into 2 doses ^{a,b}	

^a Amantadine and rimantadine should only be used for prophylaxis in winter seasons during which a majority of influenza A virus strains isolated are adamantane-susceptible; the adamantanes should not be used for primary therapy because of the rapid emergence of resistance. However, for those requiring adamantane therapy, a treatment course of approximately 7 days is suggested, or 24 to 48 hours after the disappearance of signs and symptoms.

^b For prophylaxis, antiviral drugs should be continued for the duration of known influenza A in the community because of the potential for repeated and unknown exposures or until immunity can be achieved after immunization.

tre]; Endo Pharmaceuticals, Chads Ford, PA] and rimantadine [Flumadine; Forest Pharmaceuticals, St Louis, MO]). Guidelines for the use of these 4 antiviral agents are summarized in Table 1. Little is currently known about the efficacy of antiviral agents against H5N1 strains of influenza A virus that may ultimately cause an influenza pandemic. Current concerns about widespread resistance to the adamantanes limit the usefulness of this class of agents for both epidemic strains and H5N1 strains of influenza A virus.

The NAIs block the action of influenza neuraminidase, an enzyme present on the viral envelope that provides for the efficient release of progeny virion particles from the surface of an infected cell. The target of the adamantanes is the viral M2 matrix protein, an ion-channel protein that spans the viral envelope's lipid bilayer and is required for viral uncoating. Detailed reviews of antiviral therapy have been published recently.⁶⁻¹²

With all antiviral medications, treatment earlier in the course of infection is likely to offer maximum benefit. Treatment starting as early as 12 hours after onset of symptoms has the greatest impact on disease resolution.¹³ Most studies have been performed in otherwise healthy children who had symptoms for less than 48 hours, with the reported improvement in outcomes being most profound in those children who were provided early therapy. Although study populations may not accurately reflect the diverse patient population seen by health care professionals, the longer symptoms extend beyond 48 hours before starting treatment, the less likely the child will benefit from antiviral therapy.

The antiviral agents discussed below that are approved for treatment and/or prophylaxis of influenza are active only against influenza viruses. Exposing children to antiviral therapy for noninfluenza infections results in unnecessary toxicity and cost and may deplete the supply of antiviral agents. Testing for influenza is encouraged if available and expected to influence clinical management, particularly at the onset of the influenza season.⁵ The sensitivity and specificity of rapid diagnostic tests for influenza have been reviewed recently.⁹

NAIs

Background

There are 2 NAIs approved by the US Food and Drug Administration (FDA): oseltamivir and zanamivir. Oseltamivir is available in tablet and liquid forms, but zanamivir is only available in an aerosol formulation.

Infection of the cell by influenza virus is initiated when viral hemagglutinin binds to sialic acid-containing glycoproteins on the cell surface. After the virus enters the cell and viral proteins and nucleic acid subsequently are produced, new viral particles assemble at the cell surface. The viral neuraminidase cleaves the virus from

the host cell membrane attachment site, thus freeing the virus to infect other cells. The NAI antiviral agents inhibit productive infection by preventing release of infectious virus from host cell membranes and promote clumping of viral particles via binding to glycoproteins that are present in respiratory mucus.^{10,12}

Oseltamivir Treatment

Oseltamivir has been investigated in a prospective, randomized, blinded, placebo-controlled study in children 1 to 12 years of age.¹⁴ A 5-day treatment course was associated with a median reduction in overall clinical illness of 36 hours and a reduction in fever of 25 hours in oseltamivir-treated children compared with placebo recipients. Furthermore, the incidence of acute otitis media (assessed by tympanometry and physician-prescribed antimicrobial therapy) was reduced by 44% compared with placebo recipients. A significant decrease in viral shedding was also noted in treated children, with few children still shedding virus on day 4 of therapy. The most common adverse drug effects noted were gastrointestinal tract disturbances, with vomiting in 14% of oseltamivir-treated children compared with 8% of children who were given placebo.

In studies of unimmunized children with asthma 6 to 12 years of age who received oseltamivir or placebo, no difference in the median time to freedom from illness was demonstrated, but a significant improvement in pulmonary function was noted on day 6 after treatment.¹⁵ For oseltamivir-treated children whose therapy was started within 24 hours of onset, a more dramatic difference in alleviation of all symptoms was noted, compared with those who were started on therapy after 24 to 48 hours of symptoms.

Although earlier therapy may lead to a more profound treatment effect, it is also possible that earlier treatment may impair the host immunologic response to influenza infection. An impaired immune response could leave the host susceptible on reexposure to the virus, as has been reported in 2 children with influenza B virus infections.¹⁶

Oseltamivir is not approved for therapy in children younger than 12 months because of concerns of central nervous system (CNS) toxicity seen in infant rats.¹⁷ Limited data on safety and efficacy of oseltamivir exist in this young age group, although no specific drug-attributable toxicities have been observed to date.^{18,19}

Oseltamivir may be taken with or without food and is eliminated entirely by glomerular filtration and tubular secretion. The dose of oseltamivir should be decreased by 50% for children with decreased renal function associated with a creatinine clearance of between 10 and 30 mL/minute.

Unpublished safety data on oseltamivir were recently reviewed by the FDA on the basis of reports of neuropsychiatric events associated with patients treated for influ-

enza with oseltamivir (www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4254b_09_01.Tamiflu%20AE%20Review%202006%20Redacted.D060309_092.pdf). Although 92% of the most recent cases were reported from Japan, a country with approximately 4 times more courses of oseltamivir prescribed than in the United States, package labeling was changed in the United States in 2006 to alert physicians to the possibility of these rare and unusual clinical findings. Accurate data on the incidence of these events are not available, but they seem to be in the range of 1 in 10 000 to 100 000 treatment courses. On the basis of the FDA review, it is not known whether the spontaneous reports of neuropsychiatric behavior reflect a true adverse event caused by oseltamivir, perhaps with a greater incidence in populations with a certain genetic background; a result of CNS infection caused by influenza virus; or a combination of both drug and virus in the CNS. There are no reports of neuropsychiatric events in adults or children receiving oseltamivir prophylaxis for influenza infection.

Zanamivir Treatment

Zanamivir is administered by aerosol twice daily for 5 days. In a study of children 4 to 12 years of age, the mean duration of symptomatic illness was reduced by 1.25 days in children who received zanamivir, compared with those who received placebo.²⁰ In 3 trials in subjects 12 years and older, zanamivir treatment decreased symptoms by 1 to 2.5 days in influenza-positive subjects.^{21–24} In a multicenter prospective study of subjects whose therapy was started within 30 hours of the onset of symptoms, resolution of major symptoms occurred 3 days earlier in the treatment group compared with that in controls.²⁴

Reported adverse effects in otherwise healthy children and adults were similar between those treated with zanamivir and those given placebo. However, concerns by the FDA regarding bronchospasm and decreased pulmonary function after inhalation of zanamivir in patients with underlying reactive airways disease, including asthma and chronic obstructive pulmonary disease, prompted warnings about use of zanamivir in this population. Potential risks and benefits should be carefully weighed before treatment of these children. Monitoring of respiratory function should be considered if treatment is given.²⁵

Zanamivir is minimally absorbed from the respiratory tract mucosa. No dosing changes are required for renal failure.

Prophylaxis With Oseltamivir and Zanamivir

Postexposure prophylaxis with oseltamivir has been reported in a multicenter study in North America and Europe for family contacts who were at least 1 year of age after identification of a documented index case within the family.²⁶ In this setting, in which the index case was also treated with oseltamivir, the protective

efficacy against proven influenza for individual contacts was 68%.²⁶ In a similar multicenter study for household contacts 12 years and older, oseltamivir was 89% effective in the prevention of laboratory-confirmed symptomatic influenza infection when used within 48 hours of contact with an index case who had not been treated.²⁷ Adverse events reported in treated subjects in this study, including gastrointestinal tract symptoms, were not different from those in controls.²⁷

Zanamivir was investigated as postexposure prophylaxis for family members 5 years and older, at a dosage of 10 mg, inhaled once daily for 10 days, with the index case also receiving treatment. After exposure to a virus-positive index case, the number of families with a clinically symptomatic member decreased 72%.²⁸

Antiviral Resistance

Development of resistance to NAIs while on therapy occurs less often than resistance to adamantanes.²⁹ In a multicenter study in the United States, only 5% of children who received oseltamivir therapy developed in vitro resistance in influenza isolates cultured during therapy.¹⁴ In contrast, a study from Japan documented resistance of 18% in isolates cultured from 50 oseltamivir-treated children.^{12,30} Fortunately, oseltamivir-resistant isolates from children do not seem to be as capable of sustaining infection as wild-type strains as assessed in animal models of influenza infection.^{31,32} However, when generated entirely in vitro, some mutants are just as capable of infectivity as the parent strain,³³ which indicates that the possibility still exists for the development and spread of oseltamivir-resistant strains among children. Zanamivir resistance was not reported in the published large-scale clinical trials.

Adamantanes

Background

Amantadine and rimantadine are approved for children 12 months and older. Amantadine, the first antiviral agent available against influenza, was approved by the FDA in 1966; rimantadine was approved in 1993. Antiviral activity is mediated by binding these agents to the M2 protein ion channels on the viral envelope, preventing acidic conditions within the virus that are required for uncoating and subsequent release of viral nucleic acid into the host cell.³⁴ Only influenza A virus contains the M2 protein. A different envelope protein that does not bind to the adamantanes provides a similar function in influenza B virus; amantadine and rimantadine are not active against influenza B. The effectiveness of adamantanes has been limited by the emergence of widespread resistance in H3N2 strains isolated in the 2005–2006 influenza season.³⁵ Recommendations for adamantane antiviral use in subsequent years will be based on the resistance patterns docu-

mented in strains circulating during those influenza seasons.

Amantadine Treatment

Placebo-controlled, randomized clinical trials have documented that amantadine treatment decreases the duration of fever and other influenza-attributable symptoms in influenza caused by adamantane-susceptible strains by approximately 1 day in children 1 year and older.³⁶⁻⁴⁰ However, many of the earlier placebo-controlled studies that included children did not report age-specific response or adverse-event rates. Adverse events have been most accurately assessed and reported in adults. The most commonly occurring (5%–10%) adverse events are nausea, lightheadedness, and insomnia. Those that occur infrequently (1%–5%) include anxiety, nervousness, irritability, dry mouth, headache, fatigue, and diarrhea.⁴¹ The incidence of CNS adverse effects noted above is twofold higher in those taking amantadine than in those taking rimantadine. Gastrointestinal adverse effects are equivalent between the 2 agents. These effects are dosage related and are usually mild, resolving when the agent is discontinued. Serious adverse effects have been reported in adults and are often associated with either high plasma drug concentrations in patients with renal insufficiency or in those with an underlying psychiatric or seizure disorder.⁴²

Although no prospective studies have been published on the treatment of children with encephalitis as a complication of influenza, data on cerebrospinal fluid concentrations of amantadine suggest a high degree of cerebrospinal fluid penetration, with concentrations that may provide antiviral activity.⁴³

Amantadine is well absorbed orally and is excreted almost entirely by the kidneys with variable metabolism before elimination. The dose should be decreased 50% in children with creatinine clearance between 30 and 50 mL/minute per 1.73 m². Additional reductions are required for more profound renal failure.

Rimantadine Treatment

Rimantadine was evaluated in prospective studies of children using acetaminophen-treated controls between 1 and 12 years of age⁴⁴ and 1 and 15 years of age.⁴⁵ In a study by Thompson et al,⁴⁴ no differences were recorded in the reduction of symptoms between the 2 groups, although the amount of virus shed was less during the first 2 days of therapy for the treatment group. Of concern, the virus shed by those who continued to have positive culture results on the fourth day of treatment was often resistant to rimantadine. Hall and colleagues⁴⁵ noted a significant reduction in severity of disease, including fever. However, a high rate of rimantadine resistance occurred in treated children, with almost half of the strains noted to be resistant when isolated from children who were still shedding virus at the end of the

7-day treatment course. In addition, it is concerning that rimantadine-treated children were more likely to be shedding virus at the end of therapy than were controls. No differences in adverse-event rates were noted between children treated with rimantadine and those treated with acetaminophen. In controlled studies in adults, no drug-attributable adverse effects occurred in more than 5% of the study subjects, with the most commonly reported events being insomnia and dizziness.⁴⁶

Rimantadine is also well absorbed orally but, unlike amantadine, undergoes extensive hepatic metabolism with subsequent renal elimination. Dose adjustment should be made for severe hepatic dysfunction or renal failure.

Prophylaxis With Amantadine and Rimantadine

Early studies on the prevention of influenza with amantadine were conducted in home or institutional settings during the influenza season using prospective, double-blind trial designs and documented a statistically significant benefit by reducing the attack rate of influenza A.⁴⁷⁻⁵⁰ However, as with the early amantadine treatment studies, age-specific data are lacking.

Studies on the use of rimantadine as prophylaxis for children within families were conducted during influenza seasons in which the predominant circulating strains were H1N1⁵¹ and H3N2.⁵² In both studies, prophylaxis reduced the number of symptomatic influenza cases in children relative to an attack rate of 15% to 20% among placebo recipients. Prophylaxis in children also reduced the number of cases of symptomatic influenza in adult family members. Of note, cases of asymptomatic influenza infection as documented by throat culture or fourfold increase in influenza antibody titers did occur in a small number of children who received rimantadine prophylaxis.

Antiviral Resistance

Amantadine or rimantadine resistance develops in approximately one third of patients who receive antiviral therapy.⁵³ The development of resistance has implications for therapeutic failure for (1) the child, if resistance develops early in therapy, (2) household or close contacts, because resistance in the index case determines which therapy is likely to be effective in those exposed to the index case, and (3) communities, in which resistance may be so widespread to a particular agent that empiric therapy with that agent may no longer be recommended.

Resistance to adamantanes occurs rapidly, often within the first 3 days of therapy. Mutations lead to structural changes at predictable, specific sites on the M2 protein. These changes are relatively stable, with little reversion to wild-type susceptible virus after stopping the adamantane. Appreciable differences in virulence or

transmissibility between resistant and susceptible viruses have not been noted.

In a recent study, nasal swabs, nasal aspirates, or throat cultures were obtained from hospitalized children before, during, and after a 3- to 5-day course of amantadine, and 80% of isolates from treated children demonstrated amantadine resistance.⁵⁴ Shedding of resistant strains was not associated with persistent or relapsing clinical disease, which is felt to reflect an adequate host immunologic response that develops as resistant strains are emerging. For the high-risk child with a poor immunologic response to infection, persistent disease or relapse is a concern.

Close contacts of an amantadine- or rimantadine-treated child who subsequently develop influenza infection are at high risk of infection caused by an adamantane-resistant influenza virus. If such patients require treatment or prophylaxis, an NAI should be used. During the 2005–2006 influenza season, data collected on widespread resistance to adamantanes in circulating influenza A strains in the United States led the Centers for Disease Control and Prevention to recommend against the use of these agents for either treatment or prophylaxis of influenza A infections.⁵⁵

Ribavirin

Ribavirin has *in vitro* activity against influenza virus but is not currently approved for treatment of influenza infection. Limited studies have been performed with aerosolized ribavirin in the treatment of influenza in children.⁵⁶ For life-threatening influenza infection requiring parenteral therapy, intravenous ribavirin may be obtained as an investigational product through the FDA, as supplied by the manufacturer. No prospective, controlled data currently exist on the safety or efficacy of parenteral ribavirin for severe, invasive influenza infection, although limited data on pharmacokinetics of parenteral ribavirin exist for adults.⁵⁷

INDICATIONS FOR THERAPY AND PROPHYLAXIS

Therapy

- Influenza infection of any severity in high-risk children (see Appendix) regardless of immunization status
- Any otherwise healthy child with moderate-to-severe influenza infection who may benefit from the decrease in duration of clinical symptoms documented to occur with therapy

Prophylaxis

- High-risk children during the 2 weeks after influenza immunization, if influenza is active in the community

- High-risk children for whom influenza vaccine is contraindicated
- Family members or health care providers who are unimmunized and are likely to have ongoing, close exposure to (1) high-risk, unimmunized children or (2) infants who are younger than 6 months
- Control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with high-risk pediatric residents (eg, extended-care facilities)
- As a supplement to immunization among high-risk children
- Postexposure prophylaxis in a family setting
- High-risk children and their family members and close contacts, as well as health care workers, when circulating strains of influenza virus in the community are not matched with vaccine strains

ANTIVIRAL THERAPY IN PANDEMIC INFLUENZA

Antiviral therapy may play a major role in both treatment and prophylaxis during a pandemic.^{58,59} Pandemic influenza is likely to occur sometime within the next decade. Recent observations document the spread of an epidemic of H5N1 strain of avian influenza A virus in both wild and domestic bird species from southeast Asia to Indonesia, Europe, and Africa, with further spread felt likely to occur. As of October 16, 2006, 256 adult and pediatric cases of H5N1 influenza infection have been documented worldwide, associated with a mortality rate of 59%.⁶⁰ These infections have occurred most often in those with close, direct contact with poultry. Efficient transmission of the virus between humans, an event that is required before a human pandemic can occur, has not been documented to date with any of the currently identified H5N1 strains.

Intense planning for the possibility of an influenza pandemic with a virulent strain of H5N1 or another influenza virus subtype is ongoing at international, national, state, and local levels. The American Academy of Pediatrics and other professional organizations and stakeholders have had important input into the Pandemic Influenza Strategic Plan of the US Department of Health and Human Services, which was released in late 2005.⁶¹ Interim priorities for antiviral therapy and vaccine are included as part of the plan and reflect a need to treat and protect those most at risk of severe and fatal influenza and to preserve critical societal infrastructure (eg, law enforcement, medical facilities, government). Efforts are currently underway to stockpile adequate supplies of antiviral drugs to address both health care and societal requirements. The Strategic National Stockpile currently includes oseltamivir and rimantadine. Although most strains of H5N1 are susceptible only to the NAIs, some are susceptible to the adamantanes. The dose

and duration of therapy for H5N1 infections may be different from those for currently circulating H3N2 or H1N1 infections. In the case of a pandemic, the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and state and local health departments will provide current recommendations for therapy and prophylaxis.

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APPENDIX: INFANTS AND CHILDREN AT HIGH RISK OF COMPLICATIONS FROM INFLUENZA INCLUDE THOSE WITH:

- Ages between 6 and 24 months (no antiviral agent is currently approved for infants younger than 12 months)

- Asthma or other chronic pulmonary diseases such as cystic fibrosis
- Hemodynamically significant cardiac disease
- Immunosuppressive disorders or therapy
- HIV infection
- Sickle cell anemia and other hemoglobinopathies
- Diseases requiring long-term aspirin therapy, such as rheumatoid arthritis or Kawasaki disease
- Chronic renal dysfunction
- Chronic metabolic disease such as diabetes mellitus
- Neuromuscular disorders, seizure disorders, or cognitive dysfunction that may compromise the handling of respiratory secretions

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