

— **INFECTIOUS DISEASES** —  
**Board Review Manual**

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**Viral Infections in the  
Immunocompromised  
Patient: Parvovirus B19,  
Respiratory Viruses,  
BK and JC Viruses,  
and Vector-borne and  
Zoonotic Viruses**

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**TYGACIL** – indicated for the treatment of adults with CABP caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*

**is a recommended monotherapy in the CMS/JCAHO\* Quality Measures for non-ICU bacterial CAP patients<sup>1</sup>**



The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established.

**An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options.**

**Reference: 1.** *Specifications Manual for National Hospital Inpatient Quality Measures*, version 3.3a, Release Notes 3.3a. [http://www.jointcommission.org/specifications\\_manual\\_for\\_national\\_hospital\\_inpatient\\_quality\\_measures/](http://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures/). Effective April 1, 2011. Accessed July 8, 2011.

**Please see brief summary of Prescribing Information on adjacent page.**

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**TYGACIL® (tigecycline) Brief Summary**

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**INDICATIONS AND USAGE**

TYGACIL is indicated for the treatment of adults with complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* gr. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*.

TYGACIL is indicated for the treatment of adults with complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* gr. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

TYGACIL is indicated for the treatment of adults with community-acquired pneumonia infections caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*.

**CONTRAINDICATIONS**

TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.

**WARNINGS AND PRECAUTIONS**

**Anaphylaxis/Anaphylactoid Reactions**

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.

**Hepatic Effects**

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

**Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia**

A study of patients with hospital acquired pneumonia failed to demonstrate the efficacy of TYGACIL. In this study, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 14/122 [11.5%]) than the comparator.

**Use During Pregnancy**

**TYGACIL may cause fetal harm when administered to a pregnant woman.** If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline [see **USE IN SPECIFIC POPULATIONS**].

**Tooth Development**

**The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown).** Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

**Clostridium difficile-Associated Diarrhea**

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

**Patients With Intestinal Perforation**

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

**Tetracycline-Class Effects**

TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL.

**Superinfection**

As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

**Development of Drug-Resistant Bacteria**

Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

**Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥2% of Patients Treated in Clinical Studies**

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators <sup>a</sup> (N=2307)
<b>Body as a Whole</b>		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
<b>Cardiovascular System</b>		
Phlebitis	3	4
<b>Digestive System</b>		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
<b>Hemic and Lymphatic System</b>		
Anemia	5	6
<b>Metabolic and Nutritional</b>		
Alkaline Phosphatase Increased	3	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	3	2
Hyponatremia	2	1
Hypoproteinemia	5	3
SGOT Increased <sup>b</sup>	4	5
SGPT Increased <sup>b</sup>	5	5
<b>Respiratory System</b>		
Pneumonia	2	2
<b>Nervous System</b>		
Dizziness	3	3
<b>Skin and Appendages</b>		
Rash	3	4

<sup>a</sup> Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.

<sup>b</sup> LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In all Phase 3 and 4 studies that included a comparator, death occurred in 4.0% (150/3788) of patients receiving TYGACIL and 3.0% (110/3646) of patients receiving comparator drugs. **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL treated patients versus comparator. The cause of this increase has not been established. This increase should be considered when selecting among treatment options.** (See Table 2.)

**Table 2. Patients with Outcome of Death by Infection Type**

Infection Type	n/N	TYGACIL %	n/N	Comparator %	Risk Difference* % (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.3, 1.7)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (-0.4, 2.0)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.0, 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.4, 6.3)
Non-VAP <sup>a</sup>	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP <sup>a</sup>	25/131	19.1	15/122	12.3	6.8 (-2.1, 15.7)
RP	11/128	8.6	2/43	4.7	3.9 (-4.0, 11.9)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)**

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.

\* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

\*\* Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

<sup>a</sup> These are subgroups of the HAP population.

Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).

In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established [see **WARNINGS AND PRECAUTIONS**].

The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.

Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%).

For comparators, discontinuation was most frequently associated with nausea (<1%).

The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies: *Body as a Whole*: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

*Cardiovascular System*: thrombophlebitis

*Digestive System*: anorexia, jaundice, abnormal stools

*Metabolic/Nutritional System*: increased creatinine, hypocalcemia, hypoglycemia

*Special Senses*: taste perversion

*Hemic and Lymphatic System*: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

*Skin and Appendages*: pruritus

*Urogenital System*: vaginal moniliasis, vaginitis, leukorrhea

**Post-Marketing Experience**

The following adverse reactions have been identified during postapproval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Anaphylaxis/anaphylactoid reactions, acute pancreatitis, hepatic cholestasis, jaundice, and severe skin reactions, including Stevens-Johnson Syndrome.

**DRUG INTERACTIONS**

**Warfarin**

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

**Oral Contraceptives**

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Teratogenic Effects—Pregnancy Category D [see **WARNINGS AND PRECAUTIONS**]**

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, <sup>14</sup>C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg-hr/mL and 6 mcg-hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

Results from animal studies using <sup>14</sup>C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman [see **WARNINGS AND PRECAUTIONS**].

**Pediatric Use**

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended [see **WARNINGS AND PRECAUTIONS**].

**Geriatric Use**

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

**Hepatic Impairment**

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see **CLINICAL PHARMACOLOGY (12.3)** and **DOSAGE AND ADMINISTRATION (2.2)** in full Prescribing Information].

**OVERDOSAGE**

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD<sub>50</sub>) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD<sub>50</sub> was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

This Brief Summary is based on TYGACIL direction circular LAB-0458-2.0, revised 01/11.



# HOSPITAL PHYSICIAN®

## INFECTIOUS DISEASES BOARD REVIEW MANUAL

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The *Hospital Physician Infectious Diseases Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in infectious diseases. Each manual reviews a topic essential to current practice in the subspecialty of infectious diseases.

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## Viral Infections in the Immunocompromised Patient: Parvovirus B19, Respiratory Viruses, BK and JC Viruses, and Vector-borne and Zoonotic Viruses

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# Viral Infections in the Immunocompromised Patient: Parvovirus B19, Respiratory Viruses, BK and JC Viruses, and Vector-borne and Zoonotic Viruses

Gregory M. Anstead, MD, PhD

## INTRODUCTION

In part I of this 2-part series on viral infections in immunocompromised hosts, infections due to the various herpesviruses were described. This part addresses viral infections due to parvovirus B19, adenovirus, the traditional respiratory viruses (respiratory syncytial virus, rhinovirus, and the influenza and parainfluenza viruses), the newly emerging respiratory viruses (human metapneumovirus, bocavirus, and the corona- and polyomaviruses), the BK and JC viruses, West Nile virus, and the zoonotic viruses (rabies and lymphocytic choriomeningitis viruses). For many of these viruses, readily accessible diagnostic testing was not available until the last decade. With the exception of influenza, these viruses differ from the common herpesviruses in that prophylaxis and treatment regimens are poorly defined. However, infection from many of these viruses can be prevented by infection control measures and careful donor selection.

## PARVOVIRUS B19

Parvovirus B19 infection occurs worldwide, and there is a high seroprevalence in adults (60%–90%).<sup>1</sup> The virus is typically transmitted by the respiratory route, although transmission by blood products and from transplanted organs also occurs.<sup>2,3</sup> The replication of parvovirus B19 requires actively dividing cells, such as erythroid precursor cells.<sup>4</sup> B19 is associated with several diseases, including hydrops fetalis, erythema infectiosum, and arthropathy. In immunocompromised patients, aplastic crisis is the most common presentation, but hepatitis, vasculitis, and myocarditis have also been reported.<sup>4</sup> In HIV patients, a diagnosis of B19 is most likely in patients with severe anemia (hematocrit <24%), a CD4 count below 100 cells/ $\mu$ L, and the absence of reticulocytes.<sup>5</sup> In a study of 98 cases of B19 infection in transplant patients, anemia, leukopenia,

and thrombocytopenia were present in 98.8%, 37.5%, and 21%, respectively. Other manifestations included: flu-like illness, rash, and arthralgia. Hepatitis, myocarditis, glomerulopathy, and pneumonitis were rarely observed. Three patients died of B19 myocarditis. The characteristics of hepatitis, pneumonitis, and myocarditis due to B19 are not well described. Allograft rejection, dysfunction, or loss occurred in 10.4% of transplant patients infected with B19.<sup>6</sup>

Thrombotic microangiopathy due to B19 has been observed in renal transplant recipients, with findings of elevated serum lactate dehydrogenase (LDH), thrombocytopenia, and hemolytic anemia.<sup>7</sup> B19 is also a contributor to transplant coronary artery disease in pediatric cardiac transplant patients.<sup>8</sup> In addition to primary infection, reactivation of latent B19 infection may occur. Because of the various modes of transmission and reactivation, the timing of B19 infection ranges from early post-transplantation to years after transplantation; however, most cases occur within the first 3 months after transplantation.<sup>3</sup>

The most sensitive test for detecting B19 infection is polymerase chain reaction (PCR) assay of blood or bone marrow specimens. A bone marrow biopsy with pure red cell aplasia is suggestive of B19 infection.<sup>6</sup> Evidence for allograft-mediated transmission includes early onset after transplantation and detection of parvovirus DNA in donor serum or tissues or high IgM antibody titers in donor sera.<sup>3</sup>

There is no specific prophylaxis against parvovirus B19. The treatment of B19 disease in transplant patients is reduction of immunosuppression and administration of intravenous immunoglobulin (IVIG) at a dose of 400 mg/kg/day for 5 days.<sup>5</sup> In transplant patients, the rate of recurrence of B19 disease after IVIG treatment was 23.2%.<sup>6</sup> In HIV patients, anemia due to B19 may dramatically improve within months after starting highly active antiretroviral therapy (HAART), obviating the need for IVIG. Nevertheless, some HIV patients with B19 infection may have persistent anemia despite HAART and may also require IVIG.<sup>9</sup>

## **VIRAL RESPIRATORY INFECTIONS**

A panoply of respiratory viruses is now recognized, with many newly discovered species in the last decade. The respiratory viruses include influenza, parainfluenza, rhinovirus, respiratory syncytial virus (RSV), adenovirus (AdV), human metapneumovirus (hMPV), bocavirus, the coronaviruses, and the polyomaviruses KI and WU. Furthermore, there has been a revolution in the availability of rapid diagnostic tests for the most common respiratory viruses. Direct fluorescent antibody (DFA) testing using nasopharyngeal aspirates or swabs is now available and provides a result in hours. The available multiplex DFA assays typically detect influenza A and B; parainfluenza 1, 2, and 3; RSV; AdV; rhinovirus; and hMPV. DFA has lower sensitivity than PCR, but this can be an advantage for the detection of only clinically relevant infections. Moreover, DFA is more rapidly performed and less expensive than PCR. The high sensitivity of PCR can be a limitation because it may detect asymptomatic infections or persistent viral shedding and not active infection.<sup>10</sup> For viruses not included in the usual DFA panels, PCR, nucleic acid amplification testing (NAT), or culture are possible methods of diagnosis.<sup>11</sup> As a result of this revolution in virus discovery and detection, much of the older literature on respiratory viruses is no longer accurate.

It is impossible to distinguish respiratory pathogens by signs and symptoms. Common symptoms of upper respiratory tract illness include malaise, sore throat, coryza, cough, and fever. Dyspnea may indicate progression to lower respiratory tract involvement or bacterial superinfection. In lower tract infection, chest radiography typically reveals diffuse interstitial infiltrates, but airspace disease may also be observed. Chest computed tomography (CT) findings may include ground-glass infiltrates, nodules, and consolidation. Immunocompromised patients infected with respiratory viruses may be superspreaders, because of the high levels of virus in their secretions and their long duration of shedding.<sup>11</sup> Protracted infection and shedding has been documented for parainfluenza, RSV, hMPV, rhinovirus, and influenza.<sup>12,13</sup>

For hematopoietic stem cell transplant (HSCT) recipients, progression of upper respiratory tract infection to lower respiratory involvement occurred in 35% and did not depend on the specific virus. Risk factors for progression to lower tract infection included an underlying diagnosis of leukemia, age greater than 65 years, neutropenia and lymphopenia, and the use of myeloablative regimens.<sup>14,15</sup> In allogeneic HSCT recipients, viral respiratory infections may predispose to the development of aspergillosis.<sup>16</sup>

The incidence of viral respiratory infections in solid organ transplant (SOT) recipients varies from 7.7% to 64%.<sup>17–19</sup> The risk of progression to lower tract disease is dependent on the time post-transplant, the intensity of immunosuppression, and the type of transplant. Lung transplant recipients are at the greatest risk.<sup>11,20</sup>

In a study of respiratory infections in lung transplant recipients in Denver (Colorado), a viral etiology was identified in 51 cases: hMPV (7 cases), RSV (13 cases), parainfluenza virus (19 cases), influenza (16 cases), and rhinovirus (3 cases). Sixteen cases had multiple pathogens, and 16% of the infections required hospitalization, including 25% of hMPV single-agent infections, 38% of RSV single-agent infections, 10% of parainfluenza single-agent infections, and 19% of the multiple-agent infections. Chronic graft rejection in the first year after a viral respiratory infection was observed in 25% of the patients and did not vary with the pathogen.<sup>21</sup> In pediatric lung transplant patients, younger age at transplant and prior cytomegalovirus (CMV) infection were risk factors for viral respiratory infections.<sup>22</sup>

There are few recent studies on viral respiratory infections in HIV patients. A South African study from 2000 compared viral infections of the lower respiratory tract in HIV-positive and HIV-negative children. The HIV-positive children were 6 times more likely to develop severe lower respiratory tract infection and had a much higher risk of death (7.5% versus 0%).<sup>23</sup>

There is a meager armamentarium of vaccines, drugs, and immunomodulators to combat the multitude of viral respiratory infections. Nevertheless, certain measures can reduce the rates of nosocomial transmission, including education and hand hygiene for health care personnel and visitors, cohorting of patients, contact isolation, and droplet precautions. Also, medical staff and visitors should be monitored for respiratory symptoms to prevent exposure to vulnerable patients.<sup>24</sup>

### **ADENOVIRUS**

The human AdVs comprise 7 species (A-G) and 52 serotypes; they usually cause self-limited respiratory, gastrointestinal, and conjunctival infections in immunocompetent persons. However, AdV can cause severe infections in the immunocompromised, including pneumonia, hepatitis, hemorrhagic cystitis, colitis, pancreatitis, meningoencephalitis, and disseminated disease. The disease manifestations depend on the species, serotype, and host factors.<sup>25</sup> In fact, patients can have coinfection or sequential infection with multiple AdV types.<sup>26</sup> AdV infection occurs in up to 40% of pediatric HSCT patients, 10% of adult HSCT patients, and 5% to 10% of SOT recipients.<sup>27</sup> AdVs are spread

person-to-person, by fomites, and by contaminated water.<sup>28</sup>

### **Clinical Manifestations**

Adenoviral involvement of the respiratory tract in immunocompromised patients takes 3 forms: (1) asymptomatic, (2) respiratory symptoms only, or (3) as a component of disseminated disease. AdV pneumonia may have a progressive, rapidly fatal course. Chest radiographs in AdV pneumonitis include heterogeneous and homogeneous opacities, mass-like consolidation, and pleural effusions.<sup>29</sup> Histopathologic specimens from the respiratory tract in AdV pneumonia reveal 2 types of intranuclear inclusions: eosinophilic “Cowdry A” inclusions and basophilic inclusions (“smudge” cells). These inclusions must be differentiated from those due to CMV and HSV infection.<sup>30</sup>

Adenoviral hepatitis is more common in pediatric transplant recipients; it presents with elevated transaminase, alkaline phosphatase, and LDH levels.<sup>31</sup> The infection can progress to hepatic failure.<sup>32</sup> CT and magnetic resonance imaging (MRI) may show multiple non-enhancing lesions in the liver.<sup>31</sup> The differential diagnosis includes hepatitis due to the hepatitis B and C viruses, the Epstein-Barr virus, HSV, and CMV.

Adenoviral hemorrhagic cystitis (HC) presents with hematuria accompanied by viruria. The differential diagnosis includes HC due to the BK virus, but adenoviral HC is more likely to have systemic manifestations and nephropathy.<sup>33</sup> Colitis due to AdV presents as diarrhea with or without life-threatening hematochezia.<sup>34</sup> Adenoviral pancreatitis has been observed most often after bone marrow transplant (BMT); the differential diagnosis in this setting includes graft versus host disease, CMV infection, and medication adverse effect.<sup>35</sup> Adenoviral meningoencephalitis is uncommon; there are no specific neurologic presentations and no consistent findings on imaging studies of the central nervous system (CNS). The diagnosis is made by performing PCR for AdV in the cerebrospinal fluid (CSF), even if PCR of blood samples is negative.<sup>36</sup>

In BMT and HSCT patients, risk factors for AdV infection include younger age, allogeneic transplantation, T-cell-depleting conditioning regimens, HLA-mismatched grafts, whole body irradiation, and low T-cell count after transplantation.<sup>37</sup> Severe lymphopenia is a risk factor for disseminated disease and a fatal outcome.<sup>38</sup>

AdV is usually detected in the first 100 days after BMT or HSCT.<sup>39</sup> Definitions of the extent of AdV disease include: asymptomatic infection (virus detection, no signs or symptoms), probable disease (virus detection with signs and symptoms), and definite disease

(signs and symptoms arising from the appropriate organ, plus virus detection and/or histopathologic evidence). Disseminated disease refers to involvement of at least 2 sites. In BMT and HSCT patients, diarrhea is the most common presentation;<sup>40</sup> hemorrhagic cystitis and detection of AdV in the blood predict dissemination.<sup>41</sup> In SOT, more severe AdV infections occur in pediatric patients, in those with liver and lung allografts, and in patients who received anti-lymphocyte antibodies and have D+/R– AdV status. It is common for AdV infection to involve the transplanted organ, suggesting reactivation of latent donor infection.<sup>27</sup>

In HIV patients, the most common manifestation of AdV infection is gastroenteritis; other presentations include pneumonitis, hepatitis, encephalitis, nephritis, parotitis, pancreatitis, and neuritis.<sup>39</sup> In a prospective study from the United Kingdom, the risk of AdV infection in patients with HIV at 1 year was 28%: 17% if CD4 is greater than 200/μL versus 38% if CD4 is less than 200/μL.<sup>42</sup> In this study, in which cultures were obtained monthly, stool AdVs were isolated in 30% of patients, but AdV was the causative organism for acute diarrhea in only 12% patients. Persistent shedding of AdV may occur, especially with lower CD4 counts.<sup>42</sup> Attributable death from AdV is difficult to ascertain in HIV patients because multiple other pathogens are often present simultaneously.<sup>39</sup>

### **Diagnosis**

Diagnosis of AdV infection is achieved by culture, antigen testing, histopathologic exam, and PCR. Serologic methods are not useful and growth of the virus in culture is slow and insensitive. Antigen testing can be performed on respiratory and stool samples and has moderate to high sensitivity versus cultures. PCR-based assays can be conducted on stool, respiratory, urine, and ocular biopsy specimens, bronchoalveolar lavage fluid, CSF, and blood. For blood, a quantitative viral load can be obtained; there is no specific threshold that determines severity of infection and so it is more useful to follow the viral load over time.<sup>25</sup> Although PCR is the most sensitive test to detect AdV, it also identifies patients with latent non-active viral infections and thus may lead to overdiagnosis of AdV allograft infection. Immunohistochemical staining and in situ hybridization using tissue from biopsy specimens are the most useful tests to detect AdV infection because these methods are sensitive and specific.<sup>43</sup>

### **Prophylaxis and Treatment**

There is no prophylaxis available against AdV and there are no randomized controlled trials to guide treat-

ment, but data from case series suggest that cidofovir may be effective. In a trial of 29 HSCT patients with adenovirus disease treated with cidofovir, success was achieved in 69%.<sup>44</sup> Some centers perform periodic assessment of the blood viral load, with initiation of cidofovir therapy if virus is detected; such preemptive therapy may decrease mortality.<sup>45</sup> Unlike the extensive studies that have been done for the prevention and treatment of infections due to HSV and CMV, adequate trials for the management of AdV infections are sorely lacking.<sup>46</sup>

### **RESPIRATORY SYNCYTIAL VIRUS**

RSV commonly causes bronchiolitis in infants and young children. In the immunocompromised patient, RSV infection typically begins in the upper respiratory tract, with most patients reporting cough, rhinorrhea, and sinus congestion.<sup>24</sup> However, in the immunocompromised, RSV can cause severe lower respiratory tract disease and is probably the most important cause of morbidity and mortality of all the respiratory viruses in this population.<sup>11</sup> RSV infection affects between 0% and 49% of HSCT recipients.<sup>47</sup> Factors that increase the risk of RSV infection after HSCT include male sex, allogeneic transplant, CMV seropositivity, and pre-engraftment status. Risk factors for RSV pneumonia in allogeneic recipients include receiving a mismatched transplant or a myeloablative regimen. During the first 3 months after HSCT, patients with RSV infection and persistent lymphopenia are at high risk of progression to pneumonia. HSCT patients with RSV infection often have delayed engraftment or graft failure, and the infection often progresses to respiratory failure, with a mortality rate up to 50%.<sup>48</sup>

For the prevention of RSV pneumonia, about half of U.S. pediatric SOT centers use RSV prophylaxis, mostly palivizumab, for infants up to age 24 months.<sup>49</sup> RSV infection in immunocompromised hosts has been treated with systemic (oral or IV) or aerosolized ribavirin.<sup>48</sup> Immunomodulators that have been combined with ribavirin include IVIG, RSV immunoglobulin (no longer available), and palivizumab (a monoclonal antibody against RSV).<sup>50</sup> The most studied therapy is aerosolized ribavirin 2 g given 3 times a day or 6 g over 18 hours. An analysis of the trials of aerosolized ribavirin concluded that RSV patients with pneumonia who were not treated had a higher mortality rate (89% versus 50%).<sup>48</sup> However, cost and logistical issues with aerosolized ribavirin hamper its use, including the availability of a small-particle nebulizer and equipment to limit health care worker exposure to the aerosolized drug, which is teratogenic and irritating.<sup>24</sup> RSV patients with pneumonia treated with aerosolized ribavirin and an immunomodulator had a lower mortality rate than those

treated with aerosolized ribavirin alone or with systemic ribavirin with or without an immunomodulator (24% vs 50% vs 54%, respectively).<sup>48</sup> Mortality rates in more recent studies of RSV infections were lower than in older studies. This may be due to better care, such as earlier identification of infection and initiation of treatment and improved management of concomitant infections and respiratory therapy.<sup>48</sup> Also, early treatment of RSV infection with ribavirin and IVIG at the upper respiratory stage may abort the progression to pneumonia.<sup>24</sup>

### **INFLUENZA VIRUS**

Influenza should be suspected in any patient presenting with fever, rhinorrhea, myalgias, and headache, especially during the fall and winter months.<sup>24</sup> Progression to influenza pneumonia is more likely in lung transplant and HSCT recipients. Complications of influenza are more common in the HSCT and SOT populations. In addition to pneumonia, these complications include secondary bacterial pneumonia, myocarditis, and myositis.<sup>51</sup> Severe disease has been commonly reported in HSCT recipients, with attributable mortality rates as high as 43%.<sup>52</sup> In a review of HSCT recipients with influenza, risk factors for the development of pneumonia included earlier onset post-transplant and lymphopenia. In patients not treated with antiviral agents, 18% progressed to pneumonia.<sup>53</sup> However, in a recent series of 19 HSCT patients with influenza, none progressed to lower tract infection, although 86% received oseltamivir.<sup>54</sup> The absence of progression to lower tract disease in this series may be due to the utilization of rapid diagnostics and oseltamivir.<sup>54</sup> HIV infection does not increase susceptibility to influenza. However, AIDS is associated with greater influenza-associated morbidity and mortality.<sup>55</sup>

An annual influenza vaccine is recommended for all transplant recipients, transplant candidates, their household contacts, and health care workers in contact with immunocompromised patients. The immunogenicity of the vaccine is dependent on the immune system status of the particular patient. For HSCT recipients it is recommended to wait 6 months to administer the vaccine, whereas for SOT recipients vaccine administration is recommended 3 to 6 months post-transplant. The live, attenuated intranasal preparation is not recommended for immunocompromised persons.<sup>11</sup> Prophylactic oseltamivir may be considered during influenza season for those expected to have poor response to the vaccine or those who cannot receive the vaccine because of egg allergy.<sup>24</sup>

With the recent widespread resistance of the influenza virus to amantadine and rimantadine, oseltamivir and zanamivir are the drugs of choice. For immuno-

suppressed patients, oseltamivir should be started at any time during the course of the illness, with a recommended dose of 150 mg twice a day and a treatment duration of 10 days for those remaining symptomatic after 5 days.<sup>11</sup> Alternatively, inhaled zanamivir is available and has been used successfully in HSCT recipients;<sup>56</sup> the dose is 2 puffs twice daily for 5 days. Although resistance to oseltamivir or zanamivir has been reported, surveillance data for the 2010/2011 flu season indicate that 99% of isolates have retained susceptibility.<sup>57</sup>

### **PARAINFLUENZA VIRUS**

Infection with the parainfluenza viruses occurs year-round and can cause croup, bronchiolitis, the common cold, and pneumonia. In transplant recipients, parainfluenza causes a range of illness, from asymptomatic infection to fatal pneumonia.<sup>11</sup> Cough is the predominant symptom of parainfluenza infection; rhinorrhea is typically absent and fever is present in only 17% to 35% of patients.<sup>24</sup> Other complications include Guillain-Barré syndrome, encephalomyelitis, and parotitis.<sup>58-60</sup> In lung transplant recipients, parainfluenza infection occurs in 5.3% of patients, with lower tract involvement in 10% to 60%.<sup>61</sup> Bronchiolitis obliterans can be a long-term sequela.<sup>62</sup> The estimated frequency of parainfluenza infections following HSCT is 2% to 7%, with mortality rates from 18% to 33%.<sup>63</sup> There is no prophylaxis or immunization; ribavirin has been used in the treatment of parainfluenza in transplant recipients with uncertain efficacy.<sup>64,65</sup>

### **RHINOVIRUS**

Rhinoviruses are the most common viruses isolated from immunocompetent persons with acute respiratory illness. These patients usually experience the common cold, a self-limited syndrome of coryza, nasal obstruction, sneezing, and pharyngeal discomfort. Although upper respiratory tract symptoms predominate in rhinovirus infection, lower tract involvement has been increasingly recognized.<sup>66</sup> Although information on the specific manifestations of rhinovirus lower respiratory tract infection is limited, patchy, diffuse ground-glass opacities have been observed in the chest CT scans of adult HSCT patients who suffered a fatal outcome.<sup>67</sup> In the United Kingdom, the records of 626 adult patients with BMT or HSCT were examined for episodes of viral respiratory infections. There were 27 patients with 29 confirmed viral respiratory infections. The viruses present were rhinovirus (40%), RSV (22.2%), influenza A (18.5%), parainfluenza (14.8%), and enteroviruses (7.4%). Of the 27 patients, there were 3 deaths attributable to the viral respiratory infections, 2 from rhinovirus and 1 from parainfluenza.<sup>68</sup> In a study from

Houston, TX, 32% of BMT patients with rhinovirus infection developed fatal pneumonia.<sup>66</sup> Unfortunately, no prophylaxis or antiviral treatment is available.

### **THE NOVEL RESPIRATORY VIRUSES**

Several novel respiratory viruses have been described in the last decade, including the hMPV, the human bocavirus, the human coronaviruses NL63 and HKU1, and KI and WU polyomaviruses. hMPV has been found to cause upper and lower respiratory tract infection in HSCT and SOT patients.<sup>69</sup> In SOT, cases of hMPV infection have been reported in lung transplant patients. In a study comparing hMPV with RSV infection in lung transplant patients, both viruses caused graft dysfunction, but only RSV caused chronic rejection.<sup>70</sup> The presentation of hMPV infection in transplant recipients varies from asymptomatic infection to mild upper respiratory symptoms to fatal pneumonia.<sup>69</sup> In a series of 5 HSCT patients with hMPV pneumonia, signs and symptoms at disease onset included a low-grade fever (80%), cough (60%), nasal congestion (60%), wheezing (60%), and sore throat (80%). Sinusitis, otalgia, otitis media, conjunctivitis, and rashes were absent. Once pneumonia developed, there was rapid progression of pulmonary infiltrates, often accompanied by hypotension and/or septic shock. Alveolar hemorrhage was common. Four of the 5 cases were fatal. In these HSCT patients, disease due to hMPV was detected within 40 days after transplantation and between January and April in Seattle (Washington).<sup>71</sup> By contrast, Debiaggi and colleagues in Italy found that HSCT recipients may harbor hMPV asymptotically for prolonged periods.<sup>13</sup>

In a series of Canadian HIV patients with fever and respiratory symptoms who were on antiretroviral therapy, hMPV was the most common infection after influenza. Compared to patients with influenza, HIV patients with hMPV infection had higher CD4 counts at the time of diagnosis and were more likely to present with wheezing.<sup>72</sup> In a study from South Africa comparing children with and without HIV infection, hMPV infection was more common in non-HIV-infected children. However, in the HIV-infected children, hMPV was more likely to lead to prolonged hospitalization or death, and was often accompanied by bacterial and *Pneumocystis* infections.<sup>73</sup>

No prophylactic measures are available for hMPV. Also, there are no adequate trials to guide the treatment of hMPV infection, although ribavirin is active in vitro and in animal models. The use of IVIG has been advocated for the treatment of severe hMPV infections.<sup>70,74</sup>

The respiratory coronaviruses typically cause mild community-acquired infections in children, with rhinorrhea, cough, and fever.<sup>75</sup> Four lower respiratory syn-

dromes caused by human coronaviruses have also been reported: community-acquired pneumonia, acute tracheobronchitis, acute exacerbations of chronic obstructive pulmonary disease, and acute asthma exacerbation. The coronaviruses have also emerged as important causes of respiratory tract infection in transplant patients. Previously, the incidence of these infections was underestimated because of limitations in diagnostic testing. With the advent of NAT, multiple strains of coronaviruses have been described in transplant recipients, including OC43, 229E, NL63, and HKU1. In prospective studies of lung transplant recipients, coronaviruses comprised 16.7% to 24% of specimens positive for respiratory viruses.<sup>18,62</sup> However, there is limited data on the clinical presentation of the coronavirus in the immunocompromised host. Several fatal cases of coronavirus HKU1 pneumonia have been described in immunosuppressed patients.<sup>76</sup> The diagnosis of coronavirus infection is based on NAT, viral culture, or serology.<sup>11</sup> At present, there is no standard prophylaxis therapy for coronavirus infection.<sup>11,77</sup>

Bocavirus infection is uncommon in immunocompetent adults, and its significance in immunocompromised patients remains unknown. In a series of 66 transplant patients from Italy, bocavirus was detected in 4 patients with respiratory symptoms.<sup>78</sup> Disseminated bocavirus infection has been observed in a child with CMV infection after HSCT.<sup>79</sup> Bocavirus was found to be uncommon in a group of HIV patients presenting with suspected pneumocystosis.<sup>80</sup> There is no specific prophylaxis or treatment for bocavirus infection.

Exposure to the KI and WU polyomaviruses (KIPyV and WUPyV) is common, with seroprevalence rates of 67% and 89% in healthy blood donors, respectively.<sup>81</sup> These viruses have been associated with both upper and lower respiratory tract disease, especially in children. However, 70% to 80% of patients with these polyomaviruses are coinfecting with another respiratory virus, making it difficult to discern the clinical significance of a positive finding. The importance of these viruses for transplant recipients is unknown. In a study of 200 hospitalized patients, KIPyV was found with a greater frequency in HSCT recipients (17.8 vs 5.1%).<sup>82</sup> There is no specific prophylaxis or treatment.

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## **NONRESPIRATORY POLYOMA VIRUSES: JC AND BK**

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### **JC VIRUS**

Exposure to the JC virus is widespread and is transmitted by respiratory secretions.<sup>83</sup> The most common manifestation of JC virus is progressive multifocal leu-

koencephalopathy (PML), which is characterized by the histopathologic triad of (1) multiple demyelinating lesions; (2) oligodendrocytes with enlarged nuclei with viral inclusions; and (3) abnormal astrocytes.<sup>84</sup> PML has been observed in patients with hematologic malignancies, transplant recipients, those receiving immunomodulator therapy, and in persons with AIDS. PML presents as progressive dementia, apraxia, visual changes, and motor deficits; 18% of patients also experience seizures.<sup>85</sup> Initially, MRI in PML shows patchy areas of demyelination in the subcortical white matter; without edema, contrast enhancement, or mass effect. PML can be tentatively diagnosed by the characteristic MRI findings in an immunocompromised host. A definitive diagnosis is established by brain biopsy. PML is also diagnosed by detection of JC virus in the CSF using PCR in the setting of consistent clinical and radiologic findings.<sup>83</sup>

In addition to PML, the JC virus can cause granule cell neuronopathy, meningitis, and encephalopathy.<sup>83</sup> The granule cells are abundant neurons in the cerebellum; in JC virus granule cell neuronopathy (JVC GCN), the patient presents with ataxia, dysarthria, and other signs and symptoms of cerebellar dysfunction. MRI shows cerebellar atrophy. JVC GCN may occur as an isolated syndrome, or may accompany 5% of PML cases.<sup>84</sup>

The use of natalizumab, a monoclonal antibody directed against CD49a (used in the treatment of multiple sclerosis and Crohn's disease), also increases the risk of PML.<sup>86</sup> There have also been reports of PML in patients treated with other immunosuppressive agents.<sup>83</sup>

There is no prophylaxis for PML and therapy with either cidofovir or cytarabine has not been effective.<sup>85</sup> In HIV patients, HAART may result in clinical improvement; however, worsening symptoms are possible due to immune reconstitution syndrome.<sup>87</sup> During the immune reconstitution process, lymphocytes infiltrate the CNS lesions, which will be seen as enhancement on a contrasted MRI scan. A mass effect can occur, and corticosteroid administration may be beneficial.<sup>83</sup> Patients diagnosed with PML while on immunomodulating agents with a long half-life, such as natalizumab, benefit from removal of the agent by plasma exchange.<sup>88</sup>

### **BK VIRUS**

Infection with the BK virus is widespread, affecting about 60% to 80% of adults in Europe and the United States.<sup>89,90</sup> Transmission occurs via oral or respiratory secretions, and usually occurs asymptotically in childhood. The virus then settles into latency at various sites, including leukocytes, kidney, lung, liver, brain, and eye. However, in an immunocompromised host, primary or reactivation disease can occur.<sup>91</sup> In kidney

transplant recipients, BK virus infection can present as nephropathy, ureteral stricture, or hemorrhagic cystitis.<sup>92</sup> BK viremia occurs in 10% to 60% of renal transplant recipients, with nephropathy occurring in 1.5% to 20%. BK virus nephropathy (BKVN) typically manifests as tubulointerstitial nephritis, with a progressive decline in creatinine clearance occurring 9 to 13 months post-transplant, which may ultimately result in renal allograft loss. Typical signs of infection such as fever, malaise, and cytopenias are absent. The urinalysis of patients with BKVN is compatible with interstitial nephritis (hematuria, sterile pyuria).<sup>91</sup>

BK viremia is a sensitive, but not specific, marker for nephropathy. The presence of urinary decoy cells (epithelial cells with large nuclei and basophilic ground-glass inclusions) carries a positive predictive value for nephropathy of about 20%. Urinary BK DNA testing has a high negative predictive value but a poor positive predictive value. However, if detection of BK DNA is sustained and the level of viremia significantly increased ( $>10^7$  copies/mL), the positive predictive value for the diagnosis of nephropathy improves up to 67%.<sup>92</sup> A definitive diagnosis of BK virus nephropathy is established by kidney biopsy.<sup>93</sup> There is no widely accepted prophylaxis for BK viral infection. The accepted treatment of BKVN in transplant recipients is reduction of immunosuppression.<sup>93</sup>

The BK virus has also been rarely reported to cause tubulointerstitial nephritis, pneumonitis, hemorrhagic cystitis, retinitis, and encephalitis in HIV patients with CD4 cell counts below 100 cells/ $\mu$ L.<sup>2,94</sup> Other than immune reconstitution with HAART, there is no specific treatment in this population.

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## OTHER VIRAL INFECTIONS

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### LYMPHOCYTIC CHORIOMENINGITIS VIRUS

The lymphocytic choriomeningitis virus (LCMV) and related arenaviruses are rodent-borne and are found worldwide. Humans are usually infected through exposure to rodent excreta, but transmission has occurred through donor organs. Infection with LCMV is typically asymptomatic or associated with a mild, transient illness; however, LCMV can cause meningitis and encephalitis in immunocompetent persons. The fatality rate is low ( $<1\%$ ) in the immunocompetent host.<sup>95</sup> However, immunosuppressed patients can develop a fatal hemorrhagic fever-like disease, with abdominal pain, altered mental status, thrombocytopenia, elevated transaminase levels, coagulopathy, graft dysfunction, and either fever or leukocytosis within 3 weeks after transplantation.<sup>95,96</sup>

Transmission of LCMV and an LCMV-like arenavirus via organ transplantation has been documented in 4 clusters.<sup>96,97</sup> Of 13 organ recipients described in those clusters, 12 died of multisystem organ failure, with hepatitis as a prominent feature. Death occurred within 9 to 76 days after organ transplant.<sup>97</sup> The diagnosis of the LCMV cases was achieved by electron microscopy of Vero cells inoculated with CSF, followed by indirect fluorescent antibody testing and immunohistochemical analysis of brain tissue of mice inoculated with the CSF. In one of the clusters, an investigation revealed that a member of the donor's household had obtained a pet hamster 3 weeks before the donor died. LCMV was isolated from the hamster and this isolate was identical to the isolates of the 4 patients involved in the cluster.<sup>104</sup> The one transplant patient that survived was treated with ribavirin and reduction of immunosuppressive therapy.<sup>96</sup> There is no test for screening organ donors for LCMV infection. Thus, donors with meningitis or encephalitis pose a risk for transmitting infections that may well be fatal to recipients. Therefore, the risks and benefits to transplant recipients in accepting organs from such donors should be carefully weighed.<sup>95</sup> There is no accepted prophylaxis for LCMV infection.

### WEST NILE VIRUS

WNV is a mosquito-borne virus that typically causes asymptomatic infection, a febrile illness, or encephalitis. WNV infection is usually mild or even asymptomatic in non-elderly immunocompetent persons. For every case of WNV neuroinvasive disease, there are approximately 140 infections; about 20% of infected persons develop nonneuroinvasive disease.<sup>98</sup> However, SOT recipients have 40 times the risk of the general population for developing neuroinvasive disease.<sup>99</sup> WNV infections in transplant patients have occurred from the mosquito-borne route, blood products, and transplanted organs. Donor-derived WNV infection may arise in 2 ways. First, the donor may be naturally infected prior to transplant and may have mild or asymptomatic disease so that WNV infection in the donor is not suspected. Second, many donors are trauma victims, and these donors may have received blood products contaminated with WNV prior to transplant. However, blood products in the United States are now screened for the presence of WNV. Although the screening methods for WNV in blood products are quite sensitive, current methods still do not detect all WNV-infected blood donations, and organ donors are not routinely screened.<sup>100</sup>

In 2002, the first cases of WNV infection transmitted through donor organs were reported. An organ donor in Georgia (US) transmitted WNV infection through

kidney, heart, and liver transplantation to 4 recipients. Three of the recipients developed WNV encephalitis (with one fatal outcome) and the fourth recipient developed a febrile illness. The organ donor had a negative serological test for WNV, but he had received multiple blood products prior to donation. The organ donor's WNV infection was traced to a unit of plasma. The plasma donor recalled a "viral illness" a few weeks prior to plasma donation. In June 2003, blood collection agencies in the United States implemented WNV screening by NAT, which detects WNV viremia.<sup>101</sup>

Screening of organ donors by WNV NAT is currently not being done because of logistical issues. The Health Resources Services Administration (HRSA) published recommendations in 2004 advising consideration of WNV in the appropriate epidemiologic setting and to withhold transplantation for 28 days if the living donor has a positive NAT. For deceased donors, the HRSA advised to proceed with transplantation only if the recipient's condition is life-threatening and to inform the prospective organ recipient of the potential risk.<sup>102</sup> As of March 2011, there have been 5 episodes of WNV infection transmitted by donor organs involving 11 organ recipients (2 clusters of 4 recipients, and 3 individual cases). Thus, clinicians should maintain a high index of suspicion for WNV disease in any transplant recipient who develops fever and neurologic symptoms (especially tremor and flaccid paralysis), particularly in regions with significant WNV activity. In an immunocompromised patient, diagnosis of WNV infection is best achieved by NAT or reverse transcription PCR on serum or CSF.<sup>103</sup> There are no antiviral agents with proven efficacy in the prevention or treatment of WNV infection. The administration of IVIG for severe WNV infection has been advocated, based on anecdotal reports of clinical improvement with this treatment.<sup>104</sup> The problem of WNV transmitted in donated organs illustrates the difficulties of screening the organ and blood supply for novel pathogens in the midst of an outbreak of an emerging infection.

## **RABIES**

Rabies has also been transmitted by donor organs. In a case series from 2004, 4 recipients of organs from a common organ donor died of encephalitis. The donor had died of subarachnoid bleeding of unknown cause. In the investigation that followed, Negri bodies were observed in the brains of all recipients. Interviews with persons who had known the donor reported that the donor said that he had been bitten by a bat.<sup>105</sup> This case series highlights the difficulty of screening for uncommon pathogens in organ donors and the dire consequences that can result. There is no effective treatment

for rabies, so prevention in organ recipients depends on careful donor selection.

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## **CONCLUSION**

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Viral infections exact a tremendous toll in terms of morbidity and mortality in immunocompromised patients. The methodology for the diagnosis of many viral infections has greatly improved in the past 10 years. However, our therapeutic armamentarium against viral infections is woefully lacking, and many immunocompromised patients who suffer a viral infection have a poor prognosis. Nevertheless, careful donor screening, immunization for influenza, rigorous infection control measures, post-transplant surveillance, and adjustment of a patient's immunosuppressive regimen can lessen the impact of these infections. In HIV patients, HAART has dramatically decreased the incidence and severity of infections due to opportunistic viruses.

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**ZYVOX®** linezolid injection, tablets and for oral suspension  
Brief summary of prescribing information.

**INDICATIONS AND USAGE** ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see **PRECAUTIONS, Pediatric Use**). **Vancomycin-Resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia. **Nosocomial pneumonia** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multidrug-resistant strains (MDRSP<sup>\*</sup>)). **Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis**, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers. **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*. **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multidrug-resistant strains (MDRSP<sup>\*</sup>)), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS** ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressor agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT<sub>1</sub> receptor agonists (triptans), meperidine, or buspirone.

**WARNINGS** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression. In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed. **Mortality imbalance in an Investigational Study in Patients With Catheter-related Bloodstream Infections, Including Those With Catheter-site Infections.** ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. In an open-label investigational study in seriously ill patients with intravascular catheter-related infections, an imbalance in mortality was seen in patients treated with ZYVOX compared with vancomycin/dicloxacillin/oxacillin. While causality has not been established, mortality was higher in patients treated with ZYVOX who were infected with Gram-negative organisms alone, with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study. Patients with Gram-positive infections had no difference in mortality. ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. *Clostridium difficile*-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

**PRECAUTIONS** General Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation. Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see **PRECAUTIONS, Drug Interactions**). Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms). Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmologic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks. Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported. The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials. Prescribing ZYVOX in the absence of a proven or

strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients** Patients should be advised that: ZYVOX may be taken with or without food. They should inform their physician if they have a history of hypertension. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants. They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants. **Phenylethanolamines:** Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist. They should inform their physician if they experience changes in vision. They should inform their physician if they have a history of seizures. Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible. Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future. **Drug Interactions** **Monoamine Oxidase Inhibition:** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. **Adrenergic Agents:** Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. **Serotonergic Agents:** Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the **PRECAUTIONS, General Section, Drug-Laboratory Test Interactions**. There are no reported drug-laboratory test interactions. **Pregnancy Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.5-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Non-teratogenic Effects** In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantation embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternbrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE**); nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C<sub>max</sub> and the volume of distribution (V<sub>ss</sub>) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults. Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 40 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h. Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC

values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

**ADVERSE REACTIONS Adult Patients** The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators<sup>1</sup> (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events<sup>2</sup> were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators<sup>3</sup> (n=1464) with at least 1 drug-related adverse event were 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events<sup>2</sup> was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections<sup>1</sup> with ZYVOX (n=248) or cefadroxil (n=251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications<sup>1</sup> with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocytopenia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 1.0; generalized edema 2.3 and 1.0; loose stools 2.3 and 3.0; localized pain 0.9 and 0.0; and skin disorder 0.9 and 1.0. The percent of pediatric patients treated for uncomplicated skin and skin structure infections<sup>1</sup> with either ZYVOX (n=248) or cefadroxil (n=251) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 19.2 and 14.1, respectively. The percent of pediatric patients discontinuing due to a drug-related adverse event was 1.6 and 2.4 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 5.7 and 5.2; nausea 3.3 and 2.0; headache 2.4 and 0.8; loose stools 1.2 and 0.8; vomiting 1.2 and 2.4; generalized abdominal pain 1.6 and 1.2; localized abdominal pain 1.6 and 1.2; eosinophilia 0.4 and 0.4; rash 0.4 and 1.2; vertigo 1.2 and 0.4 and pruritus at non-application site 0.4 and 0.0 respectively. The percent of pediatric patients treated for all other indications<sup>1</sup> with either ZYVOX (n=215) or vancomycin (n=101) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 18.8 and 34.3 respectively. The percent of patients discontinuing due to a drug-related adverse event were 0.9 and 6.1 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 3.8 and 6.1; nausea 1.4 and 0.0; loose stools 1.9 and 0.0; thrombocytopenia 1.9 and 0.0; vomiting 1.9 and 1.0; anemia 1.4 and 1.0; eosinophilia 1.4 and 0.0; rash 1.4 and 7.1; oral moniliasis 0.9 and 4.0; fever 0.5 and 3.0; pruritus at non-application site 0.0 and 2.0; and anaphylaxis 0.0 and 10.1<sup>4</sup> respectively. **Laboratory Changes** ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were

identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The percent of adult patients with at least one substantially abnormal hematologic<sup>5</sup> value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: hemoglobin (g/dL) 0.9 and 0.0; platelet count (x 10<sup>3</sup>/mm<sup>3</sup>) 0.7 and 0.8; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 0.2 and 0.6; neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 0.0 and 0.2 respectively. The percent of adult patients with at least one substantially abnormal hematologic<sup>5</sup> value in patients treated with ZYVOX 600 mg q12h or a comparator<sup>6</sup> were as follows: hemoglobin (g/dL) 7.1 and 6.6; platelet count (x 10<sup>3</sup>/mm<sup>3</sup>) 3.0 and 1.8; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 2.2 and 1.3 and neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 1.1 and 1.2 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry<sup>7</sup> value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: AST (U/L) 1.7 and 1.3; ALT (U/L) 1.7 and 1.7; LDH (U/L) 0.2 and 0.2; alkaline phosphatase (U/L) 0.2 and 0.2; lipase (U/L) 2.8 and 2.6; amylase (U/L) 0.2 and 0.2; total bilirubin (mg/dL) 0.2 and 0.0; BUN (mg/dL) 0.2 and 0.0; and creatinine (mg/dL) 0.2 and 0.0 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry<sup>7</sup> value in patients treated with ZYVOX 600 mg q12h or a comparator<sup>8</sup> were as follows: AST (U/L) 5.0 and 6.8; ALT (U/L) 9.6 and 9.3; LDH (U/L) 1.8 and 1.5; alkaline phosphatase (U/L) 3.5 and 3.1; lipase (U/L) 4.3 and 4.2; amylase (U/L) 2.4 and 2.0; total bilirubin (mg/dL) 0.9 and 1.1; BUN (mg/dL) 2.1 and 1.5; and creatinine (mg/dL) 0.2 and 0.6 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic<sup>5</sup> value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections<sup>1</sup> were as follows: hemoglobin (g/dL) 0.0 and 0.0; platelet count (x 10<sup>3</sup>/mm<sup>3</sup>) 0.0 and 0.4; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 0.8 and 0.8; neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 1.2 and 0.8 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic<sup>5</sup> value in patients treated with ZYVOX or vancomycin for any other indication<sup>1</sup> were as follows: hemoglobin (g/dL) 15.7 and 12.4; platelet count (x 10<sup>3</sup>/mm<sup>3</sup>) 12.9 and 13.4; WBC (x 10<sup>3</sup>/mm<sup>3</sup>) 12.4 and 10.3 and neutrophils (x 10<sup>3</sup>/mm<sup>3</sup>) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry<sup>7</sup> value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections<sup>1</sup> were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry<sup>7</sup> value in patients treated with ZYVOX or vancomycin for any other indication<sup>1</sup> were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

<sup>1</sup> MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

<sup>2</sup> Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

<sup>3</sup> The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

<sup>4</sup> Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

<sup>5</sup> Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

<sup>6</sup> Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

<sup>7</sup> These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

<sup>8</sup> <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

<sup>9</sup> >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 x baseline for values abnormal at baseline.

<sup>10</sup> <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

<sup>11</sup> >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

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» With proven efficacy, excellent tissue penetration, clear and consistent dosing, and a 100% bioavailable oral formulation, count on **ZYVOX** to treat cSSSI\* due to MRSA† in patients whose conditions are complicated by diabetes and renal insufficiency.<sup>1-3</sup>

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ZYVOX is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers.

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*.

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

ZYVOX use is contraindicated in patients with known hypersensitivity to linezolid or any of the other product components.

ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following: directly and indirectly acting sympathomimetic, vasopressive, and dopaminergic agents.

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT<sub>1</sub> receptor agonists, meperidine, or buspirone.

Spontaneous reports of serotonin syndrome have been reported with the coadministration of ZYVOX and serotonergic agents. If signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination occur, discontinuation of one or both agents should be considered.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters returned to pretreatment levels. Complete blood counts should be monitored weekly, particularly in patients who receive ZYVOX for longer than 2 weeks.

ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

*Clostridium difficile* associated diarrhea has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis.

Lactic acidosis has been reported with the use of ZYVOX. Patients receiving ZYVOX who develop recurrent nausea, vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation.

Peripheral and optic neuropathy have been reported primarily in patients treated with ZYVOX for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.

Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported.

The most commonly reported adverse events in adults across phase 3 clinical trials were diarrhea, nausea, and headache.

\*Complicated skin and skin structure infection.  
†Methicillin-resistant *Staphylococcus aureus*.

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Please see brief summary on adjacent pages.



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