Experience with Ribavirin for Treatment and Postexposure Prophylaxis of Hemorrhagic Fever Viruses: Crimean Congo Hemorrhagic Fever, Lassa Fever, and Hantaviruses

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Abstract

The increase in research laboratories with biosafety level 4 (BSL-4) capabilities may be associated with increased research with hemorrhagic fever (HF) viruses. The yellow fever vaccine and an investigational formalin-inactivated Rift Valley fever vaccine are the only vaccines for at-risk laboratory workers available in the United States against HF viruses. Ribavirin is a nucleoside analogue that has been demonstrated to have antiviral activity against a wide range of viruses, including many HF viruses. While intravenous (IV) ribavirin is not FDA-approved and oral ribavirin is approved only for treatment of hepatitis C in the United States, ribavirin has been used for treatment and postexposure prophylaxis for Crimean Congo hemorrhagic fever (CCHF), Lassa fever (LF), and hantaviruses, based mainly on in vitro sensitivity testing and efficacy studies in animals, but only on a limited number of studies and/or anecdotal experience in humans. The literature on both IV and oral ribavirin for treatment and postexposure prophylaxis for CCHF, LF, and hantaviruses is reviewed to aid occupational healthcare providers in the evaluation and recommendation of ribavirin to laboratory workers with exposures or illness from these HF viruses, which are associated with a significant morbidity and mortality.

Keywords
Ribavirin, treatment, prophylaxis, hemorrhagic fever with renal syndrome, hantavirus pulmonary syndrome, Lassa fever, CCHF

Introduction

Recent interest and increased investment in biodefense research have resulted in construction of new research laboratories with biosafety level 4 (BSL-4) capabilities that may involve work with hemorrhagic fever (HF) viruses. Laboratory research with certain HF viruses, such as Crimean Congo hemorrhagic fever (CCHF) and Lassa fever (LF) viruses, is recommended to be performed exclusively under BSL-4 conditions (U.S. Department of Health and Human Services, 2007). Other HF viruses (i.e., hantaviruses) may be studied under lower BSL conditions, depending on the risk of the research (CDC, 1994). While personal protective measures and current engineering controls, particularly under BSL-4 conditions where class III biosafety cabinets (BSC) or full-body, air-supplied positive-pressureized suits are utilized and make the occurrence of an aerosol exposure unlikely, exposures from percutaneous injury remain a concern (i.e., contaminated needles or equipment, bites and scratches of infected animals). In the United States (U.S.), the yellow fever vaccine is the only FDA-approved vaccine and a formalin-inactivated Rift Valley fever vaccine the only investigational new drug (IND) vaccine available against HF viruses for at-risk laboratory workers (Rusnak et al., 2011). No antiviral chemotherapy is approved by the U.S. Food and Drug Administration (FDA) for treatment or prophylaxis to HF viruses.

Ribavirin is a nucleoside analogue that has been demonstrated to have in vitro antiviral activity in cell cultures and efficacy in animal models against a large range of viruses, including many HF viruses (Kirs et al., 1983; Sidwell et al., 1979). Studies in humans have demonstrated a decrease in morbidity and mortality with IV ribavirin for treatment of hemorrhagic fever with renal syndrome (HFRS) in China and both IV and oral ribavirin for LF in Africa (Huggins et al., 1991; McCormick et al., 1986). Anecdotal experience from small CCHF cohorts suggests a possible increase in survival with ribavirin if administered within 72 hours after the onset of illness (Butenko et al., 2007; Izadi et al., 2009; Sharifi-Mood et al., 2009b; Tasdelin-Fsigin et al., 2009). Based on these limited studies, ribavirin has become a standard of care in many areas of the world for treatment of CCHF, LF, and HFRS. Oral ribavirin has also been recommended and used for postexposure prophylaxis in healthcare and laboratory workers following high-risk exposure to certain hemorrhagic fever viruses (mainly CCHF and LF) (Bausch et al., 2010; CDC 1988; ECDC, 2008; Hadi et al., 2010; Kortepeter et al., 2008; Saleem et al., 2009). However, ribavirin is FDA-approved only for treatment of hepatitis C (oral ribavirin) and severe respiratory syncytial virus in children (aerosolized ribavirin) in the U.S., and intravenous (IV) ribavirin is available only as an investigational new drug (IND) product. Ethical issues have prevented conducting clinical trials with a placebo group to further evaluate ribavirin for treatment or postexposure prophylaxis to these HF viruses, due to the significant morbidity and mortality associated with disease.

The experience in treatment and postexposure prophylaxis of hantaviruses, CCHF virus, and LF virus
with ribavirin is reviewed and may be helpful to occupational healthcare providers in managing laboratory workers with exposures to these agents. The decision to recommend off-label use of oral ribavirin or IND use of IV ribavirin for these HF viruses must consider the currently available data supporting a possible benefit from ribavirin as well as the morbidity and mortality from disease and side effects from the drug.

Ribavirin

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a synthetic purine nucleoside analogue with antiviral activity against several families of both ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) viruses. The wide range of antiviral activity and the rare development of resistance to ribavirin have been attributed to the multiple mechanisms of antiviral activity (Crotty et al., 2000; Leyssen et al., 2005, 2006; Maag et al., 2001; Sidwell et al., 1980). However, the precise mechanism of antiviral activity effect is still unclear against many viruses.

Ribavirin is converted intracellularly to ribavirin 5’ monophosphate (RBV-MP) by adenosine kinase, and then successively phosphorylated to form ribavirin 5’ diphosphate and then triphosphate (RBV-TP), the main intracellular metabolite (Smith et al., 1984; Snell, 2001; Sun et al., 2007). Antiviral activity may occur due to inhibition of inosine-5’-monophosphate (IMP) dehydrogenase by RBV-MP, resulting in decreased intracellular guanosine triphosphate (GTP) pools (that can adversely affect viral protein synthesis and replication of viral genomes) (Cameron et al., 2001; Durr et al., 1975; Leyssen et al., 2006; Tam et al., 2002; Wray et al., 1985a). However, a change in GTP pool size alone does not completely explain the full antiviral effect of ribavirin (Cameron et al., 2001; Sun et al., 2007). A primary antiviral mechanism of ribavirin in many RNA viruses is attributed to RNA mutagenesis, via incorporation of RBV-TP into the viral RNA genome (either as a base analogue of adenine or guanine triphosphate). The resulting hypermutations may result in replication and translation errors that can reduce the infectivity of the virus (even without reduction of viral titers) and result in lethal mutagenesis to the virus (Cameron et al., 2001; Chung et al., 2007, 2008; Crotty et al., 2000, 2001, 2002; Sun et al., 2007; Tam et al., 2002). Antiviral activity of ribavirin has also been attributed to: 1) inhibition of RNA polymerase complex by RBV-TP (resulting in inhibition of viral translation and transcription, and a reduction in quantity or quality of viral RNA) (Dixit et al., 2006; Eriksson et al., 1977; Investigator’s Brochure, 2004; Wray et al., 1985b); 2) inhibition of GTP dependent 5’ capping of mRNA by RTP; and 3) serving as an immunomodulatory agent. Specific immunomodulatory responses reported with ribavirin include promotion of T-cell mediated immunity via CD4 helper and CD8 cytotoxic lymphocytes; induction of type 1 cytokine responses such as interferon-γ, tumor necrosis factor-α, and interleukin-2; and suppression of interleukin (IL)-4 and IL-10 responses (Cameron et al., 2001; Liu et al., 2007; Tam et al., 1999, 2002).

In vitro sensitivity to ribavirin, for many reasons, may not always translate into effectiveness of the drug in vivo. In vitro antiviral activity may vary with the cell culture line used (particularly with DNA viruses) and has been attributed to differences in absorption and metabolism of ribavirin by the various cell lines that affect intracellular drug concentrations (Huggins, 1989; Ibarra et al., 2009; Jahrling et al., 1980; Sidwell et al., 1979, 1980; Stephen et al., 1980). Subsequent ineffectiveness of the drug in animal models may be attributed to specific disease manifestations (i.e., short incubation period combined with a rapid onset of death) or low drug levels (Chapman et al., 2002; Stephen et al., 1980). In particular, the inability to achieve effective concentrations of drug in the central nervous system (CNS) may limit use of ribavirin to treat infections that cause a primary encephalitis (Canonico et al., 1984; Huggins et al., 1984b; McKee et al., 1988; Stephen et al., 1980). For example, ribavirin given to guinea pigs infected with Junin virus (sensitive in vitro to ribavirin) resulted in a delay in the onset of viremia and decreased viral titers but did not prevent death (Huggins et al., 1984b). The ineffectiveness of ribavirin was attributed most likely to the inefficiency of ribavirin in crossing the blood-brain barrier, as viral replication in the treated guinea pigs was almost exclusively in the brain. Similar results were noted in nonhuman primates (NHPs) infected with Junin virus, where late initiation of ribavirin at day 6 postinfection (after the onset of viremia and clinical symptoms) resulted in resolution of viremia and symptoms, but death occurred later in 3 of 4 NHPs due to CNS infection (McKee et al., 1988). However, ribavirin was protective in all NHPs if given as prophylaxis (30 minutes after challenge with Junin virus); the NHPs developed only minimal symptoms and had either normal CNS histopathology (N=3) or mild, multi-focal perivascular cuffing (N=1). Therefore, while ribavirin may not be potentially effective for treatment of Junin virus infection, it may be potentially effective for postexposure prophylaxis (Enria et al., 1984; 1994; Maiztegui et al., 1979).

A concern raised in using ribavirin for postexposure prophylaxis is that it may only delay the onset of illness or prevent development of the humoral response to infection (Borio et al., 2002). Ribavirin given immediately postchallenge to NHPs infected with LF virus did not result in a delay of antibody response compared to non-ribavirin-treated control NHPs; antibodies were detected on day 10 in both groups (Jahrling et al., 1980). While a slight suppression of antibody titers initially was noted at days 10 and 14 postchallenge, similar responses were observed at day 21 and later. Also, a placebo-controlled study of ribavirin prophylaxis in humans showed that oral ribavirin (1,200 mg/day for 8 days) initiated 24 hours before IV challenge with dilute human plasma con-
Hantaviruses

Hantaviruses are in the genus of the family Bunyaviridae. Old World hantaviruses in Asia and Europe may cause hemorrhagic fever with renal syndrome (HFRS), whereas New World hantaviruses in the Americas may cause hantavirus pulmonary syndrome (HPS) or cardiopulmonary syndrome (HCPS) (Peters et al., 1999). The pathogenesis of HFRS and HPS are similar in that most symptoms are due to vascular leak, attributed to the immune response of the host to infected endothelial cells. CDB+ cytotoxic lymphocytes recognize epitopes on infected endothelial cells; the subsequent interaction is felt to result in the release of cytokines and chemokines that then alter vascular permeability (Borges et al., 2008). The clinical presentation of predominantly renal failure in HFRS versus pulmonary failure in HPS is attributed to the predilection of Old World hantavirus for endothelial cells in the kidney/reteperitoneum versus New World hantavirus predilection for endothelial cells in the lung. Disease in humans is most commonly acquired by inhalation of excreta (mainly urine) of chronically infected rodents. Laboratory workers may be exposed to hantaviruses via inhalation of aerosolized cultures or infected rodent excreta (urine, saliva, or feces) or via percutaneous injury (i.e., bites of infected animals, contaminated needles) (Douron et al., 1984; Kulagin et al., 1962; Tsai et al., 1987). Person-to-person spread of disease has been reported only with Andes virus (a hantavirus causing HCPS in South America) (Ferre et al., 2007; Martinez et al., 2005; Padula et al., 1996; Vitek et al., 1996).

**Hemorrhagic Fever with Renal Syndrome (HFRS)**

**HFRS Background**

Four hantaviruses are known to cause HFRS (Table 1). Hantaan, Dobrava, and Seoul viruses are generally associated with more severe forms of disease than Puumula virus (Antoniadis et al., 1989; Lee, 1991; Mustonen et al., 1994; Park et al., 1989). However, as disease severity may depend upon the exposure dose, viral strain, and major histocompatibility complex of the host, severe disease may occur with all four hantaviruses (Huggins et al., 1991; Kompanets et al., 2007; Kru-ger et al., 2001; Mustonen et al., 1998).

HFRS is most commonly manifested as a febrile illness with mild manifestations of hemorrhage and renal insufficiency. There are five phases of illness in HFRS: the febrile, hypotensive, oliguric, diuretic, and convalescent phases. After an incubation period of 2 to 3 weeks (range 4 to 42 days), nearly all individuals present with a febrile phase of illness, characterized by an abrupt onset of fever, headache, malaise, myalgia, and nausea and/or vomiting (Lee, 1989; Kulagin et al., 1962; Peters et al., 1999). Other signs and symptoms that may differentiate HFRS from a nonspecific febrile illness include the presence of abdominal, flank, or back pain (may be severe and mimic an acute abdomen or renal pathology), evidence of vascular fragility (i.e., pete-

**Table 1**

Demographics and Severity of Illness from Hantaviruses Causing HFRS

<table>
<thead>
<tr>
<th>Hantavirus</th>
<th>Host1</th>
<th>Mortality2</th>
<th>Dialysis2</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hantaan</td>
<td>Field mouse</td>
<td>2-15%</td>
<td>40%</td>
<td>Rural Asia, Russia3</td>
</tr>
<tr>
<td>Seoul</td>
<td>Urban rat</td>
<td>1%</td>
<td>20%</td>
<td>Urban SE Asia, worldwide (mainly seaports)</td>
</tr>
<tr>
<td>Dobrava</td>
<td>Field mouse</td>
<td>5-15%</td>
<td>37%</td>
<td>Europe (Balkans), Russia4</td>
</tr>
<tr>
<td>Puumala</td>
<td>Bank vole</td>
<td>&lt;0.5%</td>
<td>&lt;5%</td>
<td>Europe (including Scandinavia), Russia</td>
</tr>
</tbody>
</table>

1 Hantaan virus host—striped field mouse (Apodemus agrarius), Seoul virus hosts—urban rat (Rattus norvegicus and Rattus rattus), Dobrava virus host—yellow-necked field mouse (Apodemus flavicollis), and Puumala virus host—bank vole (Clethrionomys glareolus).
2 Mortality and dialysis without IV ribavirin treatment (Antoniadis et al., 1989; Lee et al., 1991; Mustonen et al., 1994).
3 Russia, east of the Ural Mountains. 4 Russia, west of the Ural Mountains.
chiae, subconjunctival hemorrhage), or evidence of vascular instability (i.e., facial or periorbital edema; flushing of the face, neck, or chest). The presence of thrombocyto-
topenia and proteinuria, known to occur early in illness,
may help differentiate HFRS from a nonspecific febrile
illness (Rusnak et al., 2009). A diagnosis of HFRS in the
febrile phase is suggested by a history of possible expo-
sure to hantavirus with a clinical syndrome of 1) fever,
2) at least two of the following clinical symptoms—
headache; pain in the back, flank, and/or abdomen; and
nausea or vomiting, 3) at least one physical exam finding
suggestive of vascular fragility or instability (facial or per-
orbital edema, facial flushing, conjunctival injection, or
petechiae), and 4) at least one of the following abnormal
laboratory tests—thrombocytopenia, ≥ +1 proteinuria, or
elevated serum creatinine (Rusnak et al., 2009). A hypo-
tensive phase may subsequently occur in only 11% to
40% of patients (generally lasting a few hours to a few
days) and the oliguric phase in approximately 40% to
60% of patients (generally lasting 3 to 7 days) in HFRS
The onset of diuresis indicates recovery and is followed by a
convalescent phase. The duration of illness is gen-
erally 3 weeks with improvement observed during the
second week of illness (the rise in platelet count general-
ly heralds improvement in serum creatinine within the
next few days). Death is most commonly from pulmonary
edema, complications of renal insufficiency, shock, or
hemorrhage.

**In Vitro and Animal Ribavirin Studies (HFRS)**

The main mechanism of antiviral activity of ribavirin
against Hantaan virus is attributed to RNA mutagenesis
that results in lethal mutagenesis (resulting in an
“extinction catastrophe” error) (Chung et al., 2007; Sev-
erson; et al., 2003; Sun et al., 2007). *In vitro* testing has
demonstrated that hantaviruses are highly sensitive
to ribavirin (Table 2), with plaque reduction EDso (50% 
effective dose) values for Hantaan virus ranging from
15 μg/ml to 40 μg/ml in Vero E6 cells (Huggins et al.,
1984a; IB, 1989; Kirsi et al., 1983). The 50% inhibitory
dose (IDso) of 12 isolates of Hantaan, Seoul, and Puumu-
la viruses from various locations showed similar sensitiv-
ity, with IDso ranging from 7 μg/ml to 50 μg/ml in Vero
E6 cells. Dose-dependent protection of ribavirin against
Hantaan virus was observed in suckling mice (decreased
viremia, decreased severity of illness, and increased
survival) when initiated at the onset of viremia (day 6) or
later with appearance of viral antigen in tissues (day 10)
(Huggins et al., 1986). By days 18-20 of illness, viral
titers in organs of ribavirin-treated mice were a 100-fold
lower than untreated controls.

**HFRS Human Studies**

A double-blinded, randomized placebo-control trial
in China conducted between 1985 and 1987 in a popu-
lation where dialysis was not available noted that IV riba-
virin (if initiated within 7 days of onset of illness) result-
ed in 1) a statistically significant reduction of mortality
(8.5% in treatment versus 2.5% in placebo group), 2) a
decrease in the occurrence and duration of oliguria, 3) a
decrease in the severity of renal failure, 4) a decrease in
hemorrhagic manifestations, and 5) an earlier resolution
of renal failure and onset of polyuria (Table 2) (Huggins
et al., 1991). Maximum protection was observed if riba-
virin was given by day 4 of illness. The mechanism by

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**Table 2**

**In Vitro and In Vivo Ribavirin Studies on Hantaviruses**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Cells Culture</th>
<th>Antiviral Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vitro Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hantaan virus¹</td>
<td>Vero cells</td>
<td>EDso 15-40 μg/ml</td>
</tr>
<tr>
<td>SNV²</td>
<td>Vero cells</td>
<td>ICso 1-6 μg/ml</td>
</tr>
<tr>
<td><strong>In Vivo Studies</strong></td>
<td>Animal Model</td>
<td>Effect</td>
</tr>
<tr>
<td>Hantaan virus³</td>
<td>Suckling mice</td>
<td>Decreased viremia and severity of illness; increased survival</td>
</tr>
<tr>
<td>SNV⁴</td>
<td>Deer mice</td>
<td>Prevented seroconversion; decreased viral load in heart, lung, liver, spleen, and kidneys</td>
</tr>
<tr>
<td><strong>Humans Trials</strong></td>
<td>Country</td>
<td>Effect</td>
</tr>
<tr>
<td>Hantaan virus⁵</td>
<td>China</td>
<td>IV ribavirin associated with a decrease in mortality, occurrence of oliguria, severity of renal failure, and risk of hemorrhage, and an earlier onset of oliguria and polyuria.</td>
</tr>
<tr>
<td>SNV⁶</td>
<td>U.S.</td>
<td>IV ribavirin not felt to decrease mortality in two trials; attributed possibly to late administration of drug in the cardiopulmonary phase of illness.</td>
</tr>
</tbody>
</table>

¹ Hantaan, Seoul, and Puumala viruses with mean IDso 7-50 μg/ml (IB, 1989; Huggins et al., 1984; Kirsi et al., 1983). ² Medina et al., 2007. ³ Ribavirin given on day 6 (onset of viremia) or on day 10 (appearance of viral antigen in tissue) (Huggins et al., 1986). ⁴ Ribavirin given 100 mg/kg intraperitoneally at day 0 (Medina et al., 2007). ⁵ Double-blinded, placebo-controlled, clinical trial conducted in medical setting without dialysis capability (Huggins et al., 1991). ⁶ One trial (open label) compared IV ribavirin treatment to nonrandomized, nonribavirin -treated HPS cases; the other trial (double-blinded, placebo-controlled trial) was discontinued early due to slow accrual of subjects (Chapman et al., 1999; Mertz et al., 2004).
which ribavirin prevented death was attributed most likely to the prevention of oliguria, as 12 of the 13 deaths were associated with prolonged oliguria.

Based on the results of this study in China, the IV ribavirin treatment protocol for HFRS was made available in 1987 at a U.S. Department of Defense (DoD) medical facility in Seoul, Korea, using the same 7-day dosing regimen as in the China study (loading dose of 33 mg/kg, followed by 16 mg/kg q6h on days 1-4, and then 8 mg/kg q8h on days 5-7) (Rusnak et al., 2009). In the 34 subjects with serological confirmed HFRS (from 1987 to 2005) in this study who received at least four doses of the drug, HFRS disease was milder compared to non-ribavirin-treated historical controls. Oliguria was present in one subject before initiation of ribavirin; no subjects subsequently developed oliguria or required dialysis (compared to 39% to 60% oliguria and 40% dialysis requirement historically in nonribavirin-treated subjects infected with Hantaan virus) (Kim et al., 2006; Lee, 1991; Rusnak et al., 2009).

Ribavirin has been used for treatment of HFRS mainly in Southeast Asia. While dialysis may prevent many of the deaths that ribavirin may have prevented in the China study (mortality generally <5% in settings with dialysis capability), ribavirin may potentially still decrease morbidity (i.e., decrease in dialysis requirement or hemorrhagic manifestations) (Huggins et al., 1991; Rusnak et al., 2009). Ribavirin has not generally been recommended or used for treating the less severe form of HFRS due to Puumala virus.

**Hantavirus Pulmonary Syndrome (HPS)**

**HPS Background**

Mortality from HPS may vary among the various New World hantaviruses, but a 40% mortality is commonly observed in HPS due to Sin Nombre virus (SNV) (responsible for most HPS cases in North America) and to Andes virus in South America (Dietl et al., 2007; Padula et al., 2000; Verity et al., 2000; Vial et al., 2006; Young et al., 2000). Similar to HFRS, hantapulmonary syndrome also has phases of illness (febrile, shock/ pulmonary edema, diuretic, and convalescent phases). After an incubation period of a median of 14-17 days (range 9-33 days), individuals with HPS caused by SNV have an abrupt onset of a febrile illness prograde, generally associated with severe myalgia, headache, and malaise, that usually lasts from 3 to 5 days (Young et al., 2000). Symptoms of nausea, vomiting, abdominal pain, and diarrhea may be seen later in the febrile phase of illness. Cough may not occur until later in the febrile phase and may precede the onset of the pulmonary edema. Upper respiratory tract infection (URTI) symptoms of sinusitis, ear pain, and rhinorrhea are uncommon in HPS (Moolenar et al., 1995; Verity et al., 2000). A decreased platelet count may be helpful in distinguishing HPS from other nonspecific febrile illnesses (a follow-up platelet count should be repeated within 12 or 24 hours if a diagnosis of HPS is considered and the initial platelet count is normal, especially during an outbreak or known high-risk activity for hantavirus exposure).

Most individuals with HPS are hospitalized at the time they are entering the cardiopulmonary phase (individuals at this time often have cough, tachypnea, tachycardia, and postural hypotension). The onset of noncardiogenic pulmonary edema is generally abrupt and associated with copious, amber-colored, nonpurulent secretions (as high as 1 L/hour in severe cases). Pulmonary edema (due to vascular leak) and shock (due to acute myocardial failure) may progress rapidly, often over 4 to 24 hours. Ventilator support may be required in as few as 4 hours. Individuals may then develop lactic acidosis and oliguria, with death occurring within 1 to 3 days in severe cases. The cardiopulmonary phase in survivors generally lasts 3 to 6 days and is followed by rapid improvement after the onset of diuresis. The presence of thrombocytopenia, immunoblastic lymphocytes (≥10%), and immature polymorphonuclear cells (myelocytes, metamyelocytes, or promyelocytes) in the cardiopulmonary phase supports a clinical diagnosis of HPS.

Unlike HPS from SNV that is not generally associated with hemorrhagic manifestations or multiorgan failure, HCPS from Andes virus commonly has many features of HFRS such as severe renal failure (10% may require dialysis), multiorgan failure, hemorrhage (81% of the cases in Chile with hemorrhagic manifestations), and myopericarditis (Castillo et al., 2001; Saggioro et al., 2007). Also, severe liver involvement (hepatic enzymes elevation 5 to 10 times normal or hepatic necrosis) and myositis may be associated more commonly with HCPS due to Andes virus (Lazaro et al., 2000).

**In Vitro and Animal Ribavirin Studies (HPS)**

*In vitro* studies in Vero cells demonstrated SNV to be susceptible to ribavirin (Table 2), with a 50% inhibitory concentration (IC50) ranging from 1 μg/ml to 6 μg/ml (Medina et al., 2007). Antiviral activity from ribavirin was demonstrated in SNV-infected deer mice (prevented secondary conversion and decreased viral load in the heart, lung, liver, spleen, and kidney).

**HPS Human Studies**

An open-label trial using IV ribavirin for treatment of HPS due to SNV (1993-1994) did not show a decrease in mortality (47% mortality compared to a 50% mortality in nonrandomized, untreated HPS cases not enrolled in the study) (Chapman et al., 1999) (Table 2). A subsequent placebo-controlled, double-blinded trial with IV ribavirin (1996-2001) for treatment of HPS in North America was terminated prematurely due to the slow accrual of subjects. The number of subjects enrolled was too small to draw conclusions, but a statistically signifi-
cant decrease in death was not observed (death in 3 of 10 (30%) ribavirin-treated cases versus 5 of 13 (38%) cases in the placebo group) (Mertz et al., 2004). One possible reason for the lack of an observed drug benefit was the late administration of ribavirin in the cardiopulmonary phase, giving minimal time for the ribavirin to have an effect. A median time of only 4 hours (range 3-15 hours) was reported from ribavirin initiation to death or to initiation of extracorporeal membrane oxygenation support (ECMO) in the latter study. Ribavirin is not recommended for treatment of HPS.

Ribavirin Postexposure Prophylaxis for Hantaviruses

While ribavirin postexposure prophylaxis was effective against both Old and New World hantaviruses in animal studies, there are no data in humans concerning the efficacy of ribavirin postexposure prophylaxis against hantaviruses (Huggins et al., 1986; Jonson et al., 2008; Medina et al., 2007). Ribavirin postexposure prophylaxis has been considered only in the research laboratory setting, where a laboratory worker may have a defined exposure to a known high concentration of virus. A laboratory worker at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) was exposed to 7 ml of cell culture supernatant containing a high concentration of SNV (after a filter cracked and resulted in the spray of supernatant outside the BSC and onto her scrub tops) and received oral ribavirin (400 mg tid for 20 days) (Rusnak et al., 2004). Oral ribavirin postexposure prophylaxis was also initiated in a laboratory worker (600 mg bid) after a potential aerosol exposure to Andes virus. Both individuals remained asymptomatic and RT-PCR and specific IgM ELISA assays remained negative.

Any decision to offer off-label use of ribavirin as postexposure prophylaxis after a hantavirus laboratory exposure must consider the risk of developing disease, the morbidity and mortality of the disease, and the potential benefit from ribavirin against the adverse effects. The patient needs to be informed of the risks and any potential benefits, and the lack of controlled trials in humans to assess ribavirin efficacy as postexposure prophylaxis. Postexposure prophylaxis may be considered particularly after a high-risk exposure to the more virulent New World hantaviruses (i.e., SNV, Andes virus) with a 40% mortality. In high-risk exposures to Old World hantaviruses, one may decide to not recommend ribavirin for postexposure prophylaxis or for treatment if disease should occur, as mortality from HFRS is generally <5% if dialysis is available. However, one may consider IV ribavirin for treatment if symptoms of HFRS should occur or if subsequent hantavirus-specific RT-PCR or serologies become positive (except for HFRS due to Puumala virus that is associated with a milder disease), as ribavirin may potentially decrease the severity of renal failure (including dialysis requirement) and risk of hemorrhage. A third option may be to recommend postexposure prophylaxis with oral ribavirin, in an attempt to possibly ameliorate or prevent disease altogether (based on prophylaxis data in animal studies). Ribavirin dosage regimens and adverse events are reviewed under the Dosing Regimens and Adverse Events sections.

Lassa Fever

Lassa fever is an Arenavirus that is endemic in West Africa. Disease in humans is most commonly acquired in the natural setting by inhalational or contact with infected rodent excreta. Nosocomial and laboratory-acquired LF have been reported from contact with infected blood or body secretions (saliva, vomitus, stool, or urine) or cultures, but the source of exposure was unclear in one laboratory worker (lethal case) who did not work directly with LF virus (Bausch et al., 2004; Carey et al., 1972; CDC, 1970; Fisher-Hoch et al., 1995; Leifer et al., 1970; Monath et al., 1973; WHO, 2005). Case fatality rates of hospitalized cases generally range from 15% to 25% (but reported as high as 71% in nosocomial outbreaks) (Carey et al., 1972; Fisher-Hoch et al., 1995; Frame et al., 1989; McCormick et al., 1987; Monath et al., 1973; Peters, 2010; WHO, 2005). However, most cases of Lassa fever (approximately 90%) are associated with only mild or no symptoms (Peters, 2000). The estimated overall fatality rate for all cases is from 1% to 5% (McCormick et al., 1987).

After an incubation period of generally 7 to 18 days, individuals generally experience a gradual onset of fever, weakness, and fatigue (McCormick et al., 1987). At approximately day 3 to 4 of illness, patients may experience arthralgias (mainly large joints), back pain, a nonproductive cough, and severe retrosternal or epigastric pain (most commonly a sharp or burning pain that is aggravated by leaning forward), that is then followed in the ensuing few days with severe headache, severe sore throat, and gastrointestinal symptoms (abdominal cramping, diarrhea, nausea, and vomiting). Individuals with mild disease generally recover within 8 to 10 days. Individuals with moderate or severe disease may have rapid disease progression at days 6 to 10 of illness, that may result in respiratory distress or stridor due to laryngeal edema, hypovolemia, encephalopathy, and bleeding (usually mucosal and not frank hemorrhage). Poor prognostic factors are 1) presence of fever, sore throat, and vomiting that has a 5.5 relative risk factor of death, 2) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 150 IU/ml (55% fatality for AST ≥ 150 IU/ml), 3) high serum viral burden, or 4) bleeding. Individuals in the third trimester of pregnancy have been reported to have a poor prognosis (mortality in 12/40 patients, with an odds ratio for death of 5.57 compared to first two trimesters) (Price, 1988).
Lassa Fever In Vitro and Animal Ribavirin Studies

The specific mechanism of ribavirin's antiviral activity against LF has not been evaluated. In vitro testing demonstrated antiviral activity against LF virus in Vero cell cultures at ribavirin concentrations as low as 5 µg/ml to 50 µg/ml (IC50 of 9 µg/ml) (Günther et al., 2004; Jarhling et al., 1980; Stephen et al., 1980). The mean inhibitory concentrations (MIC) have ranged from 1 µg/ml to 10 µg/ml (Connor et al., 1984).

Ribavirin was demonstrated to have efficacy in guinea pigs and NHPs infected with LF virus (Allen et al., 1980; Jarhling et al., 1980). Rhesus NHPs treated with ribavirin were protected against death and the development of severe disease when treatment was initiated either on day 0 or day 5. After subcutaneous challenge with Lassa virus; ribavirin was continued through day 18 (Jarhling et al., 1980; Stephen et al., 1979). All 8 ribavirin-treated NHPs survived, compared to 60% mortality (6/10) in untreated controls. Initiation of ribavirin on day 0 also resulted in a delay of viremia to day 7 and lower peak viremia levels. The ribavirin treatment dose in this study was estimated to provide drug serum levels of 1.2 µg/ml to 4.5 µg/ml and liver tissue levels of 30 µg/g to 50 µg/g.

A subsequent study in cynomolgus NHPs showed ribavirin to be protective against death in all NHPs if combined with high-titered immune serum to LF, even if initiated as late as day 7 or day 10 post-challenge (7/7 and 6/6 survival, respectively, compared to death in 13 of 14 untreated NHP controls) (Jarhling et al., 1984). Immune serum, while protective alone if initiated at day 0 after challenge, only resulted in temporary suppression of viremia after subsequent infusions were given on days 3 and 6, with titers rebounding to levels observed in untreated controls (attributed to immune serum suppressing only viremia and not viral replication in infected tissues).

Lassa Fever Human Studies

Both IV and oral ribavirin have been associated with a reduction in mortality in subjects with LF who had either an AST ≥ 150 IU/ml or increased serum viral titers (McCormick et al., 1986). However, currently no clinical indicators are able to predict which individuals will develop severe versus mild disease that would allow for stratification of therapy. In severe LF cases (AST ≥ 150 IU/ ml), death was observed in 19% of IV ribavirin-treated and 14% or oral ribavirin-treated subjects, compared to 55% of nonribavirin-treated subjects (Table 3). Initiation of IV ribavirin within 6 days of the onset of fever had a greater effect than if initiated at day 7 or later (Table 3). Based on this study, ribavirin has been recommended by the WHO and CDC for treatment of LF and is used in countries where LF is endemic.

Ribavirin Postexposure Prophylaxis for Lassa Fever

The CDC has recommended consideration of ribavirin for postexposure prophylaxis after high-risk exposures to LF virus (CDC 2005 guidelines did not address prophylaxis) (CDC, 1988, 2005). High-risk exposure was defined as direct exposure to blood, tissues, or other potentially infectious body fluids (i.e., urine, vomitus, stool) either by penetration of intact skin, contact with broken skin, or direct exposure to mucosal surfaces (i.e., percutaneous injuries with a contaminated needle, gross contamination of ungloved hands with vomitus or blood, kissing, sexual contact, or contact of eyes with infected droplets) (CDC, 1988). Decisions to recommend ribavirin postexposure prophylaxis must consider 1) the risk and severity of disease and 2) the potential benefit against the risk of adverse effects from ribavirin.

Most of the experience with ribavirin postexposure prophylaxis for LF has involved healthcare workers (HCW) with nosocomial exposures. Secondary transmission of LF in HCWs has been attributed mainly to contact

Table 3

Mortality in Patients with Severe Lassa Fever (AST ≥ 150 IU/mL) in Sierra Leone who were given either treatment with a) IV ribavirin, b) oral ribavirin, c) immune plasma, or d) no therapy. Analysis is listed for all patients with AST ≥ 150 IU/mL, as a subanalysis based on day of illness of ribavirin initiation, and for patients with an AST ≥ 150 IU/mL but < 10^3.6 TCID/ml serum viral burden. Data in table adapted from McCormick, et al. (1986).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All subjects with AST ≥ 150 IU/ml</th>
<th>Ribavirin given ≤ 6 days fever onset</th>
<th>Ribavirin given ≥ day 7 fever onset</th>
<th>Only subjects with &lt; 10^3.6 viral burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ribavirin</td>
<td>12/63 (19%)</td>
<td>1/20 (5%)</td>
<td>11/34 (26%)</td>
<td>3/32 (9%)</td>
</tr>
<tr>
<td>Oral Ribavirin</td>
<td>2/14 (14%)</td>
<td>1/5 (20%)</td>
<td>1/9 (11%)</td>
<td>2/29 (7%)</td>
</tr>
<tr>
<td>Plasma</td>
<td>14/28 (50%)</td>
<td>6/16 (38%)</td>
<td>8/12 (66%)</td>
<td>5/32 (16%)</td>
</tr>
<tr>
<td>No Therapy</td>
<td>33/60 (55%)</td>
<td>11/18 (61%)</td>
<td>22/43 (52%)</td>
<td>31/111 (28%)</td>
</tr>
</tbody>
</table>

1 Increased survival compared to no therapy (p=0.00003) and plasma (p=0.003). 2 Increased survival compared to no therapy (p=0.006). 3 Increased survival if ribavirin initiated ≤ 6 days after onset of fever (p=0.049). 4 Increased survival compared to no therapy (p=0.02). 5 Increased survival compared to no therapy (p=0.01).
with contaminated body fluids or equipment (particularly during surgeries and before implementation of improved infection control practices in hospitals) (Bausch et al., 2004; Carey et al., 1972; CDC, 1995; Fisher-Hoch et al., 1995; Monath et al., 1973; WHO, 2005). LF virus is present in the blood at varying concentrations (may vary by at least three orders of magnitude), and virus may be sporadically recovered from throat washings and urine of patients (recovered up to 15 days from throat washings and 32 days from urine after the onset symptoms) (Johnson et al., 1990; Liefer et al., 1970; Monath, 1975). The risk of transmission by aerosol, respiratory droplets, or casual contact is felt to be low and standard barrier precautions are recommended (CDC, 1995). Respiratory droplet or aerosol spread has been implicated in some cases where the exact route of transmission was unclear, particularly in earlier outbreaks (Carey et al., 1972; Monath, 1975). Nosocomial transmission (from a single index case) to 7 healthcare workers and 3 patients without known percutaneous exposures (specific mode of transmission could not be defined) was associated with both prolonged contact and heavy or moderate contact to the index case (frequent or infrequent direct patient care such as changing IV lines, measuring urine, emptying emesis basins) (Monath et al., 1973). Use of barrier infection control measures and discontinued use of contaminated multidose vials have been associated with a decrease in secondary cases in nosocomial outbreaks (Fisher-Hoch, 1995; Tarentola et al., 2007; WHO, 2005). Mortality from nosocomial LF has ranged from 36% to 71% (Carey et al., 1972; Fisher-Hoch et al., 1995; Monath et al., 1973; WHO, 2005).

No controlled clinical studies have been performed in humans to assess the effectiveness of oral ribavirin postexposure prophylaxis for LF. Of 20 LF cases hospitalized in developed countries, secondary transmission of disease has not been confirmed in over 1,000 persons with various degrees of contact with the index cases (Crowcroft et al., 2004; Haas et al., 2003; Hadi et al., 2010; Holmes et al., 1990; Johnson et al., 1990; Macher et al., 2006; Tarentola et al., 2007). The absence of secondary cases has been primarily attributed to barrier infection control measures, but many individuals with high-risk exposure to LF virus had also received postexposure prophylaxis with oral ribavirin. While not a confirmed LF case, an elevated LF IgG titer of 1:320 was observed in an asymptomatic physician (no history of travel to Africa) who provided invasive care to a patient without wearing gloves or a protective mask and who had also received ribavirin postexposure prophylaxis (Haas et al., 2003; Tarentola et al., 2007). As the IgM serology was negative and no early serum sample was available to demonstrate seroconversion, recent asymptomatic infection could not be confirmed. However, the IgG response was specific for Lassa virus strain AV that was isolated from the index patient and supported the index case as the source. In a subsequently published retrospective study, 25 persons in Sierra Leone who received oral ribavirin postexposure prophylaxis within 2 days of the incident did not develop clinical symptoms of LF (Hadi et al., 2010). While LF virus-specific IgG serology was positive 3 months after the incident in 3 subjects, previous infection could not be excluded (Bausch et al., 2000; Johnson et al., 1987).

**Crimean Congo Hemorrhagic Fever**

CCHF is a Bunyavirus that is endemic in Africa, Eastern Europe and the Balkan Peninsula, the Middle East, Russia, and China. Infection is generally acquired in the natural setting by the bite of an infected tick or contact with infected animals. Individuals may also acquire disease by nosocomial transmission or in the laboratory setting (Gaidamovish et al., 2000; van Eeden et al., 1985). Fatality rates from CCHF have generally ranged from 15% to 30% (range 1% to 73%) (Ergönlü et al., 2007; Kartİ et al., 2004). Variation in mortality has been attributed in part to differences in virulence of the viral strains in various geographic areas (Papa et al., 2002).

After an incubation period of 2 to 7 days (range 2-14 days), individuals generally experience an abrupt onset of high fever and chills, often associated with a severe headache, neck pain or stiffness, and photophobia. The disease rapidly progresses to involve mental status changes (confusion or aggression) within the initial 2 days of the illness, as well intense lower back pain and myalgia, gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrheea), and sore throat (Swanpoel et al., 1989). Hemorrhagic manifestation and disseminated intravascular coagulopathy (DIC) are observed generally by day 3 to 5 of illness. Petechiae and purpura (particularly located on the axillae, upper extremities, and antecubital fossae) are common, as well as bleeding from the mucosa (epistaxis, hemoptysis, hematemesis, melena, and hematuria) and phlebotomy sites. Signs of vascular instability (facial flushing, facial edema, injected conjunctiva) are common. Approximately 50% of individuals have hepatic enlargement, with hepatorenal failure occurring as early as day 5 of illness. Death generally occurs between days 5 to 14 of illness and is due to multi-organ failure, cerebral hemorrhage, severe anemia, dehydration/shock, myocardial infarction in predisposed patients, pulmonary edema, and/or pleural effusions. Lab results in the initial 5 days of illness that were associated with a 90% mortality are leukocytosis ≥10,000 cells/mm³, platelet count ≤20,000/mm³, AST ≥200 U/L, ALT ≥150 U/L, partial thromboplastin time (PTT) ≥60 seconds, and fibrinogen ≤110 mg/dL. Increased serum viral load (≥1 x 10⁹ copies/ml) was also associated with increased mortality (Cevik et al., 2007).

**CCHF In Vitro and Animal Ribavirin Studies**

In vitro ribavirin sensitivity testing demonstrated inhibition of CCHF virus (at ribavirin concentrations as low as 3 μg/mL) that was dependent on cell culture type.
(Berezina et al., 1983; IB, 1989; Watts et al., 1989). Seven CCHF isolates from different geographic locations were uniformly sensitive to ribavirin (ED$_{50}$ range 3 µg/ml to 16 µg/ml) (IB, 1989; Watts et al., 1989). Concentrations as low as 12.5 µg/ml completely inhibited CCHF growth in chick embryo fibroblast cultures, and lower ribavirin concentrations partially inhibited viral growth (Berezina et al., 1983).

Ribavirin resulted in decreased morbidity and mortality in suckling mice if administered early after CCHF viral challenge. In non-ribavirin treated suckling mice challenged with CCHF, virus was noted initially in the liver, followed by a viremia and virus in the spleen, and then virus in the heart and brain by day 6 and 7 (100% mortality) (Tignor et al., 1993). In ribavirin-treated mice (administered at days 0, 5, and 9), all mice survived intraperitoneal CCHF viral challenge. Virus was isolated at days 6 to 13 from the liver and serum but not from the brain, heart, or spleen. However, delay of treatment until day 5 postchallenge (earliest time of onset of symptoms) did not decrease or delay death, suggesting ribavirin treatment of CCHF would need to be initiated early in illness to be effective (due to CNS involvement). A second study in white mice demonstrated ribavirin was most effective if given 2 hours prior to infection (40% to 60% survival versus death in all untreated animals), but not if ribavirin initiation was delayed to 24 hours postchallenge (Berezina et al., 1983). The protective effect of ribavirin was also demonstrated to be dependent on the challenge dose of CCHF virus (Bente et al., 2010).

**CCHF Human Studies**

Placebo-controlled trials in humans to assess efficacy of ribavirin for treatment of CCHF have not been performed. Recommendations to offer ribavirin treatment of CCHF are based on in vitro sensitivity and animal studies. Reports of ribavirin’s reduction of CCHF mortality in humans in uncontrolled clinical trials have varied (results summarized in Table 4).

Multiple studies (primarily from Iran) suggest a decrease in CCHF mortality if ribavirin is given within 72 hours after the onset of illness compared to subjects not given ribavirin or subjects given ribavirin > 72 hours after illness onset (Metanat et al., 2006; Sharif-Mood et al., 2009a, 2009b) (Table 4). CCHF patients in Iran who survived illness had ribavirin initiated approximately 24 hours earlier than nonsurvivors (Izadi et al., 2009). In this same cohort, survivors who did not develop hemorrhage had received ribavirin approximately 2 days earlier than survivors with hemorrhage. However, most reports in Turkey note ribavirin to be associated with either a minimal or no reduction in CCHF mortality, compared to non-ribavirin-treated patients (mainly historical controls) (Cevik et al., 2008; Elaldi et al., 2009; Ergönül et al., 2004; Karti et al., 2004) (Table 4). The differences in study results from these two countries may be attributed to confounders such as 1) differences in virulence of CCHF virus strains, 2) variation in the severity of illness, 3) the number of days after onset of illness when the ribavirin was initiated, and 4) bias due to the nonrandomization of subjects. The most important variable reported on a multivariate analysis for increased survival from CCHF in Iran was the time interval between disease onset and ribavirin initiation (particularly if ribavirin was initiated within 4 days of illness onset) (Izaldi et al., 2009). Many studies in Turkey did not report an analysis of the effectiveness of early administration of ribavirin, and some reports noted early ribavirin administration within 4 days of illness onset in Turkey was less common, particularly before 2007 (Tasdelen Fisgin et al., 2009; Ozkurt et al., 2006) (Table 4). The lower mortality of 5% in Turkey (different viral strain than in Iran) may also make a statistically significant decrease in mortality more difficult to demonstrate, compared to Iran where >50% mortality has been reported without ribavirin treatment (Ergönül et al., 2006a; Koskal et al., 2010). However, preliminary analysis of a recent nonrandomized study in Turkey assessing early use of ribavirin (initiated ≤ 4 days of illness onset) was associated with a lower mortality (5%) compared to no ribavirin given (27% fatality), but these values have not yet reached statistical significance (p=0.067) (Tasdelen Fisgen et al., 2009) (Table 4). In this study, higher mean platelet counts were observed in the 21 patients in the early use of ribavirin (EUR) group than in the later ribavirin use group or no use of ribavirin group, and lower AST and ALT levels at day 9 were observed with EUR compared to no ribavirin use.

Without a placebo-controlled trial, the effectiveness of ribavirin in treating CCHF remains unclear. Clinical trials with ribavirin for treatment and prophylaxis of CCHF are promoted under coordination with the WHO to better assess the efficacy of ribavirin against CCHF, but randomized controlled trials involving a placebo arm are considered unethical (ECDC, 2008). A recent meta-analysis of ribavirin for treatment of CCHF (21 pooled studies that included mostly historical control trials and only two randomized trials) reported a 44% reduction in mortality compared to no use of ribavirin, but also noted that the observational data were heavily confounded and a randomized trial with quality supportive care was needed to assess a benefit (Soares-Weiser et al., 2010). Given the high morbidity and mortality in CCHF, ribavirin has been recommended by the WHO for treatment of CCHF, and continues to be used in countries where CCHF is endemic. As the greatest effect on mortality has been reported with early drug administration, ribavirin treatment may be considered (particularly if within 4 days from the onset of illness) until further studies suggest otherwise.

**Ribavirin Postexposure Prophylaxis for CCHF**

The CDC has noted postexposure prophylaxis with oral ribavirin after high-risk exposure to CCHF virus may be justified, based on the significant morbidity and mor-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Survival with Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swaneepoel, 1990</td>
<td>S. Africa</td>
<td>7/7 survival if given ≤ 4 days after onset illness; 2/5 survival if given ≥ 5 days after onset illness</td>
</tr>
<tr>
<td>Avsic-Zupanc, 2007</td>
<td>Kosovo</td>
<td>6/6 survival</td>
</tr>
<tr>
<td>Cevik, 2008*</td>
<td>Turkey</td>
<td>4/9 (44.5%) survival versus 9/16 (56%) survival without Ribavirin*</td>
</tr>
</tbody>
</table>

**IV Ribavirin**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year(s)</th>
<th>Day of Illness of Ribavirin Initiation</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher-Hoch, 1995</td>
<td>1994</td>
<td>Day 4, Day 5, Unknown</td>
<td>3/3 (all severe cases)</td>
</tr>
<tr>
<td>Smego, 2004</td>
<td>2000</td>
<td>Unknown</td>
<td>4/9 (44%)</td>
</tr>
</tbody>
</table>

**Oral Ribavirin**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year(s)</th>
<th>Day of Illness of Ribavirin Initiation</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pakistan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mardani, 2003</td>
<td>1999-2001</td>
<td>Mean day 4 illness No Ribavirin</td>
<td>61/69 (88.4%) 5/12 (11.7%)</td>
</tr>
<tr>
<td>Alavi-Naini, 2006*</td>
<td>1999-2004</td>
<td>Unknown No Ribavirin</td>
<td>199/236 (84.3%); p&lt;0.001 7/19 (36.8%)</td>
</tr>
<tr>
<td>Metanat, 2006*</td>
<td>1999-2004</td>
<td>≤ 72 hours No Ribavirin</td>
<td>75/89 (84%); p=0.06 71/95 (75%)</td>
</tr>
<tr>
<td>Sharifi-Mood, 2009a*</td>
<td>1999-2003</td>
<td>≤ 72 hours No Ribavirin</td>
<td>58/60 (97%) 15/31 (49%)</td>
</tr>
<tr>
<td>Izadi, 2009*</td>
<td>2000-2006</td>
<td>≤ 4 days No Ribavirin</td>
<td>32/38 (84.2%) 15/25 (60%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 4 days No Ribavirin</td>
<td></td>
</tr>
</tbody>
</table>

**Turkey**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year(s)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergonul, 2004</td>
<td>2002-2003</td>
<td>Mean 5.5 days No Ribavirin</td>
</tr>
<tr>
<td>Elaldi, 2009*</td>
<td>2004</td>
<td>Mean 4.4 days in survivors No Ribavirin</td>
</tr>
<tr>
<td>Ozkurt, 2006*</td>
<td>2002-2004</td>
<td>Most ≥ 5 days (mean day 6) No Ribavirin</td>
</tr>
<tr>
<td>Koksal, 2010*</td>
<td>2004-2007</td>
<td>Unknown No Ribavirin</td>
</tr>
<tr>
<td>Tasdelen Fisgin, 2009*</td>
<td>2004-2007</td>
<td>≤ 4 days No Ribavirin</td>
</tr>
<tr>
<td>Bodur, 2010*</td>
<td>2006-2008</td>
<td>Mean 4.3 days No Ribavirin</td>
</tr>
</tbody>
</table>

**Russia**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year(s)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butenko, 2007*</td>
<td>Unknown</td>
<td>&lt; 4 days in 18 cases</td>
</tr>
</tbody>
</table>

---

1 Cevik et al., 2008. All CCHF cases were severe (in 2006). No statistically significant difference in survival was noted between the groups (p = 0.571). The study did not report data concerning day of illness of ribavirin initiation. 2 Alavi-Naini et al., 2006. A statistically significant increase in survival with ribavirin treatment was observed compared to non-ribavirin-treated historical controls. 3 Metanat et al., 2006. A trend for an increase in survival was observed with ribavirin treatment compared to non-ribavirin-treated historical controls (p=0.06). 4 Sharifi-Mood et al., 2009a. A statistically significant increase in survival was observed if ribavirin was initiated ≤ 72 hours of onset of illness compared to later initiation of ribavirin. 5 Izadi et al., 2009. Multivariate analysis showed the time interval between disease onset and ribavirin initiation to be one of the most important variables on multivariate analysis for increased survival (p=0.0004), particularly with ribavirin initiation ≤ 4 days of disease onset. Survivors received ribavirin approximately 24 hours earlier than nonsurvivors (p=0.033) and approximately 2 days earlier in non-blooding survivors than bleeding survivors (p=0.013). 6 Elaldi et al., 2009. The author also noted no statistically significant survival difference observed among subjects who received ribavirin ≤ 72 hours after onset of symptoms versus later initiation of ribavirin (p=0.14), but the data were not provided (i.e., number of cases with early initiation of ribavirin) (Ergonul, 2009). 7 Ozkurt et al., 2006. No difference in survival was observed in ribavirin-treated subjects compared to non-ribavirin-treated historical controls (p=0.226). Only 5 of 22 cases had initiation of ribavirin before day 5 of illness (initiated on days 5 to 10 of illness (as late as day 12) in most cases). Patients were not admitted until mean day 6 to 6.5 of illness. The mean recovery time was shorter in ribavirin-treated cases compared to non-ribavirin-treated cases. 8 Koskal et al., 2010. Prospective randomized cohort study showed no increased survival with ribavirin treatment compared to non-ribavirin-treated CCHF controls (also no decrease in the duration of hospitalization or liver function tests), but the study did not analyze the effect of early use of ribavirin or note the day of illness that ribavirin was initiated (no information concerning details of randomization policy). 9 Tasdelen Fisgin et al., 2009. Nonrandomized study. A trend for decreased death rate was observed with early use of ribavirin (EUR) compared to no use of ribavirin (NUR)(p=0.067). No statistically significant difference was observed in preliminary observations with EUR compared to late use of ribavirin (LUR (p=0.52) or with LUR compared to NUR (p=0.317). Most LUR and NUR cases occurred between 2004 to 2006, and most EUR cases (76%) in 2007. Mean platelet counts were statistically significantly higher (days 5 to 10) and mean AST and ALT levels lower (day 9) in the (EUR) group compared to the (NUR) group. 10 Bodur et al., 2010. No statistically significant difference in survival or RTPCR or disease progression between ribavirin and nonribavirin-treated patients. No analysis was performed on early use of ribavirin (initiated ≤ 72 h after onset of symptoms). Hospital admission in the two groups occurred at a mean of 4.3 to 4.4 days after onset of symptoms. 11 The yearly case fatality rate in Russia ranges from 1.7% to 11.1% (rate of 3.2% from 2002-2008) [European CDC, 2008].
tality of disease, even though data concerning its efficacy are limited (CDC, 1988; ECDC, 2008). Most experience with ribavirin postexposure prophylaxis in CCHF has involved nosocomial transmission of CCHF (frequency of disease transmission in exposures given ribavirin postexposure prophylaxis compared to similar-risk exposures not given ribavirin prophylaxis) (Table 5).

Approximately 4% (5/129) of exposed HCWs in Iran had positive CCHF serology compared to none of 94 unexposed workers (Mardani et al., 2007). In South Africa, 7 of 459 HCWs (1.5%) developed nosocomial CCHF during an outbreak (van de Wal et al., 1985). Transmission was reported to be highest after percutaneous exposures (i.e., contaminated needles), but disease has also occurred after mucosal and intact skin exposures to blood or blood-containing secretions, particularly involving emergency operations on undiagnosed CCHF cases (Burney et al., 1980; Naderi et al., 2010; van de Wal et al., 1985). Low disease transmission to family members in Iran (only 1 of 57 relatives with close contact to the index case) suggests cutaneous contact (intact skin) with blood or contaminated body fluids to be low risk (Izadi et al., 2008). However, nosocomial CCHF is still reported sporadically from blood contact on intact skin or without a clear source of transmission (Gürbüz et al., 2009; Mardani et al., 2007; Naderi et al., 2010; Papa et al., 2002; Tutuncu et al., 2009). Implementation of barrier infection control measures has been associated with a decrease in secondary infections in HCWs (Athar et al., 2005; Celikbaş et al., 2005; Ergönül et al., 2007; Jauréguiberry et al., 2005; van Eeden et al., 1985).

Postexposure prophylaxis with IV ribavirin after six needlestick exposures was associated with only one case of CCHF (mild disease) compared to two cases of severe disease occurring after three needlestick exposures and 4 of 46 (9%) other contacts not given ribavirin in South Africa (van de Wal et al., 1985) (Table 5). In Pakistan, CCHF occurred after 2 of 4 needlestick exposures (no CCHF in the two persons who received ribavirin postexposure prophylaxis) and 1 of 5 cutaneous exposures not given ribavirin prophylaxis (Atta et al., 1998).

While symptomatic disease has not been reported in most cases given ribavirin prophylaxis, ribavirin postexposure prophylaxis potentially may have prevented clinical disease in one case after a needlestick exposure in Turkey (sera positive for PCR, CCHF IgM was negative) and in two HCWs without known percutaneous exposure in Germany (seroconversion of CCHF) (Bangash et al., 2003; Pool, 2010; Tutuncu et al., 2009) (Table 5). The decision to recommend postexposure prophylaxis should be based on the 1) risk and severity of disease, 2) potential benefit from ribavirin, and 3) risk of drug effects. Subjects should be informed of the lack of clear evidence in humans regarding a benefit with ribavirin for treatment or postexposure prophylaxis of CCHF.

### Dosing Regimens and Adverse Events
As ribavirin is not FDA-approved for treatment or for postexposure prophylaxis of HF viruses, there is no specific dose or duration of treatment but only a range of suggested dosage regimens (Table 6). The antiviral activity of ribavirin is dependent on the dose and plasma concentration (Dixit et al., 2006). Studies and anecdotal experience suggest the greatest effect in treatment of HFRS, LF, and CCHF is observed when ribavirin is initiated early in the illness.

### IV Ribavirin Treatment Dose
The recommended duration of treatment with ribavirin is 7 days for HFRS and 10 days for LF and CCHF

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### Table 5
Experience with Ribavirin Postexposure Prophylaxis (PEP) for CCHF

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Experience with Ribavirin PEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van de Wal, 1985</td>
<td>S. Africa</td>
<td>33% (3/9) needlesticks versus 9% (4/46) other contacts with CCHF. Mild disease in 1 of 6 persons with needlesticks who received ribavirin versus severe CCHF in 2 of 3 not given ribavirin.¹</td>
</tr>
<tr>
<td>Fisher-Hoch, 1995</td>
<td>Pakistan</td>
<td>0/2 persons with needlesticks given ribavirin developed disease²</td>
</tr>
<tr>
<td>Tutuncu, 2009</td>
<td>Turkey</td>
<td>No symptoms after a needlestick in those who received ribavirin PEP (had a positive PCR in the second week after exposure but negative CCHF IgM). Illness after blood contact (did not wear gloves; refused ribavirin).³</td>
</tr>
<tr>
<td>Bangash, 2003</td>
<td>Pakistan</td>
<td>8 healthcare workers and 4 attendants with contact to infected case given oral ribavirin PEP.³ One attendant developed CCHF symptoms 24 hours later and was given IV ribavirin (improved after 4 days and survived).</td>
</tr>
<tr>
<td>Saleem, 2009</td>
<td>Pakistan</td>
<td>28 healthcare workers exposed to blood and secretions of infected CCHF patient given PEP with oral ribavirin; no secondary cases (barrier infection control precautions used).⁴</td>
</tr>
</tbody>
</table>

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¹ IV ribavirin initially given at dosage of 45 mg/kg, followed by 17 mg/kg q6h x 4 days and then 8 mg/kg q8h x 6 days, but later changed to 30 mg/kg in divided doses. ² Oral ribavirin 500 mg po q6h x 7 days. ³ Oral ribavirin loading dose of 2 g, then 4 g/day x 4 days, and 2 g/day x 6 days. ⁴ Oral ribavirin loading dose of 1,600 mg, then 400 mg tid x 5 days.
(CDC, 1988; Huggins et al., 1991; McCormick et al., 1986). IV ribavirin has been most commonly administered as a loading dose of approximately 30 mg/kg, followed by 16 mg/kg q6h for 4 days, and then 8 mg/kg q8h for 6 days (only 3 days in HFRS), with the exception that the WHO recommends a lower 17 mg/kg loading dose for treatment of CCHF and LF (Table 6). No dosage adjustment is required with hepatic failure as the liver is

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Source/Country</th>
<th>Loading Dose</th>
<th>Subsequent Doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV Ribavirin</strong></td>
<td>Huggins (HFRS)(^1)</td>
<td>33 mg/kg(^1)</td>
<td>16 mg/kg q6h x 4 days, then 8 mg/kg q8h x 3 days(^1)</td>
<td>If given ≤ 7 days of illness onset (greater effect if ≤ 4 days of illness onset).</td>
</tr>
<tr>
<td></td>
<td>WHO (HFRS only)(^2)</td>
<td>33 mg/kg</td>
<td>16 mg/kg q6h x 4 days, then 8 mg/kg q8h x 6 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>McCormick (LF)(^3)</td>
<td>2 g</td>
<td>1 g q6h x 4 days, then 500 mg q6h x 6 days</td>
<td>Decreased death if AST ≥ 150 IU/ml or high viral burden(^3).</td>
</tr>
<tr>
<td></td>
<td>CDC(^4)</td>
<td>30 mg/kg</td>
<td>16 mg/kg q6h x 4 days, then 8 mg/kg q8h x 6 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WHO (LF, CCHF)(^2)</td>
<td>17 mg/kg</td>
<td>17 mg/kg q6h x 4 days, then 8 mg/kg q8h x 6 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bichat Guidelines(^5)</td>
<td>30 mg/kg</td>
<td>15 mg/kg q6h x 4 days, then 7.5 mg/kg q8h x 6 days, OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 g</td>
<td>1 g q6h x 4 days, then 500 mg q8h x 6 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borio(^6)</td>
<td>30 mg/kg</td>
<td>16 mg/kg (max 1 g) q6h x 4 days, then 8 mg/kg (max 500 mg) q8h x 6 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DoD (CCHF and LF)(^7)</td>
<td>33 mg/kg(^1)</td>
<td>16 mg/kg q6h x 4 days, then 8 mg/kg q8h x 6 days(^1)</td>
<td></td>
</tr>
<tr>
<td><strong>Oral Ribavirin</strong></td>
<td>McCormick (LF)(^3)</td>
<td>None</td>
<td>1 g/day (given q8h) x 10 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borio (VHF)(^8)</td>
<td>2 g</td>
<td>600 mg q12h if &gt; 75 kg x 10 days (400 mg qAM; 600 mg qPM if &lt; 75 kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Russia (CCHF)(^8)</td>
<td>30 mg/kg</td>
<td>600 mg q12h x 5-10 days (500 mg q12h if &lt; 75 kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WHO(^9) Bichat (VHF)(^5)</td>
<td>2 g</td>
<td>1 g q6h x 4 days, then 500 mg q6h x 6 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Turkey(^10)</td>
<td>None</td>
<td>4 g/day x 4 days, then 2.4 g/day x 6 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iran(^11)</td>
<td>30 mg/kg</td>
<td>15 mg/kg q6h x 4 days, then 7.5 mg/kg q8h x 6 days</td>
<td>Greater effect if given ≤ 3 days onset of illness.</td>
</tr>
</tbody>
</table>

\(^1\) Maximal loading dose 2.64 g; maximal dose 1.28 g q6h; maximal dose 0.64 g q8h (Huggins et al., 1991). \(^2\) The WHO application notes that the 17 mg/kg IV ribavirin loading dose for treatment of LF and CCHF (not HFRS) is lower than recommended in other reports. Maximal dose of 1 g IV q6h and 500 mg q6h. (WHO application). IV ribavirin treatment regimen used by Cevik (Cevik et al., 2008). \(^3\) McCormick, 1986. Greater effect also observed if ribavirin was initiated on day 6 or earlier after onset of fever. \(^4\) CDC, 1988. \(^5\) Bichat Guidelines were written by a task force on biological and chemical agent threats, European Commission, Luxembourg for viral hemorrhagic fevers. \(^6\) Dosing regimen recommended in the Working Group on Civilian Biodefense consensus statement for viral hemorrhagic fevers for a bioterrorist event (Borio et al., 2002). The oral ribavirin 600 mg bid treatment dose was based on the 1,000 mg/day treatment dose in the LF treatment study in Sierra Leone, the availability of oral ribavirin most commonly as 200 mg capsules, and difficulty in giving 3 doses per day. \(^7\) Dosing regimen used in the Department of Defense IV ribavirin protocol for treatment of CCHF or LF (maximum loading dose of 2.64 g, maximal doses of 1.28 g q6h and 0.64 g q8h). \(^8\) Treatment was generally given within 72 hours after the onset of illness. \(^9\) WHO oral ribavirin dosing regimen for children is 30 mg/kg, followed by 15 mg/kg q6h x 4 days, then 7 mg/kg q6h x 6 days (WHO application). This is the oral dosing regimen used in many countries in the Mideast for treatment of CCHF and is the dosage recommended by the European CDC (Alavi-Naini et al., 2006; Altab et al., 2003; Bossi et al., 2004; European CDC, 2008; Izadi et al., 2009; EIC, 2005; Ozkurt et al., 2006; Saleem et al., 2009). \(^10\) Dosing regimen used for CCHF treatment in Pakistan and Turkey (Bodur et al., 2010 [Turkey]; Ergonul et al., 2004 [Turkey]; Celikbas et al., 2005 [Turkey]; Fisher Hoch et al., 1995 [Pakistan]). \(^11\) Same as the WHO oral ribavirin dosing regimen recommended for children (based on weight) (Elaldi et al., 2009; Mardani et al., 2003).
not a major site of metabolism (Glue, 1999). Approximately 27% of IV ribavirin and 16% of oral ribavirin are renally excreted; the drug should be used in caution in individuals with severe renal failure (Catlin et al., 1980; Glue et al., 1999; Preston et al., 1999). Of note, IV ribavirin has been given to HFRS patients with moderate and severe renal failure without a dose reduction and no increase in adverse events (Huggins et al., 1991).

Higher serum levels are achieved with IV ribavirin (compared to oral ribavirin). The peak serum concentration of ribavirin after a 33 mg/kg IV loading dose is predicted to be approximately 40 μg/ml. Levels are then maintained between 3 μg/ml (trough) and 26 μg/ml (peak) with doses of 15 mg/kg q6h and between 3.7 μg/ml (trough) and 17 μg/ml (peak) with doses of 8 mg/kg q8h (IB, 1989; Laskin et al., 1987). The mean ribavirin level in the LF clinical trial was 94 μM (range 91 μM to 99 μM) in eight subjects while receiving IV ribavirin 1 g IV q6h, and 69 μM (range 5 μM to 83 μM) in 11 subjects while receiving 500 mg q6h (above the 4 μM to 40 μM MIC range for Lassa virus) (Connor et al., 1984; McCormick et al., 1986).

**Oral Ribavirin Treatment Dose**

Oral ribavirin has also been used for treatment of CCHF or LF, as IV ribavirin is costly and may not be readily available in many countries where disease is endemic. Treatment regimens recommended for LF and CCHF most commonly involve a loading dose of approximately 2 grams (in order to achieve earlier and higher serum drug levels), followed by total daily doses generally ranging from 2 g/day to 4 g/day (given at intervals of every 6, 8, or 12 hours) for 10 days (Table 6) (Bassi et al., 2004; ECDC, 2008; WHO, Reference A). However, oral ribavirin without a loading dose was effective in decreasing LF mortality in Sierra Leone; the mean serum ribavirin concentration in four subjects receiving oral ribavirin (1,000 mg/day, given in three divided doses) was 3.1 μM/L (range 1.7 μM/L to 5.3 μM/L) (Conner et al., 1984; McCormick et al., 1986).

The bioavailability of oral ribavirin is approximately 50% (may be increased with food); hematemesis may potentially impair absorption of oral ribavirin (Glue, 1999; Ergönül et al., 2006b; Preston et al., 1999). The mean peak serum drug level in six healthy volunteers was 638 ng/ml after a single 400 mg oral dose and 782 ng/ml after a 600 mg oral dose, compared to 4,187 ng/ml after a single 150 mg IV dose (Glue, 1999; Preston et al., 1999). A linear dosing relationship between the area under the concentration-time curve (AUC) was reported after single oral ribavirin doses ranging from 200 to 1,200 mg (Fernandez et al., 1986; Glue, 1999; Laskin et al., 1987). Steady state is generally achieved within 2 to 4 weeks, with a reported mean steady state serum concentration of 2,200 ng/ml with a 600 mg bid dosing regimen (Glue, 1999; Lertora et al., 1991).

**Postexposure Prophylaxis Dosing Regimen**

No controlled trials have determined the optimal dose and duration of oral ribavirin for postexposure prophylaxis. Dosing regimens have ranged from 1 g to 4 g daily, given in 2 to 4 divided doses (Table 7). As the steady state for oral ribavirin is not achieved until 2 to 4 weeks, one may consider a loading dose of approximately 2 grams, particularly in CCHF that has a shorter incubation period or if there is a delay in initiation of prophylaxis. A higher loading of 35 mg/kg (maximum dose of 2.5 g) was suggested in a recent publication for postexposure prophylaxis in LF in order to achieve higher serum ribavirin levels above the MIC range for LF (Table 7) (Bausch et al., 2010). As the oral ribavirin LF treatment regimen in Sierra Leone demonstrated a decrease in mortality without giving a loading dose, the added benefit of a loading dose for LF postexposure prophylaxis is unknown (McCormick et al., 1986). The CDC had recommended a prophylaxis regimen of 500 mg q6h (without a loading dose) for 7 days for LF, but these recommendations were not included in the most recent guidelines (CDC, 1988, 2005) (Table 7).

The duration of postexposure prophylaxis is generally related to the maximum range of the incubation period and has generally ranged from 7 to 10 days for LF and CCHF (Table 7). As hantaviruses have a longer incubation period, prophylaxis regimens for 3 to 4 weeks may be considered. Individuals with exposures should be followed for symptoms of infection. Acute and convalescent serology may provide insight to the frequency of asymptomatic infection with ribavirin prophylaxis.

**Adverse Events**

The frequency and severity of adverse events from ribavirin are dependent on the dose and duration of ribavirin therapy. Thereby, adverse events with oral ribavirin are generally less frequent and milder than with IV ribavirin.

**Anemia**

A reversible hemolytic anemia is a common side effect of ribavirin and is dependent on the dose and duration of ribavirin therapy. A 25% or greater reduction in hematocrit was observed in 1/3 of subjects receiving IV ribavirin in the HFRS treatment study in China and in 75% of subjects in an HFRS treatment study in South Korea (Huggins et al., 1991; Rusnak et al., 2009). A progressive anemia was observed in 27% of severe acute respiratory syndrome (SARS) patients receiving IV ribavirin, but no increased requirement for blood transfusions was observed compared to nonribavirin-treated SARS patients (12% versus 10%) (Muller et al., 2007). While the anemia is reversible and tolerated in young adults, the anemia may be severe and require transfusion. IV ribavirin should be used with caution in individuals with conditions where anemia may be poorly tolerated.
(i.e., preexisting severe anemia, cardiac disease). Oral ribavirin for postexposure prophylaxis (600 mg qid for 10 days) is generally only associated only with a mild anemia (approximately a 2% mean decrease in hematocrit); a mild increase in the indirect bilirubin due to hemolysis may be observed (Canonica et al., 1985; Haas et al., 2003; Holmes et al., 1990).

**Chemistries**

It is unclear if IV ribavirin is associated with hypocalcemia, hypomagnesemia or an increase in pancreatic enzymes/pancreatitis as these abnormalities occur commonly in viral hemorrhagic fevers (Rusnak et al., 2009). A multivariate analysis (retrospective study) of SARS patients receiving IV ribavirin suggested ribavirin-treated SARS patients were more likely to develop hypomagnesemia than non-ribavirin treated SARS patients, but not increased amylase levels or hypocalcemia (Muller et al., 2007). While hyperuricemia was commonly reported (uric acid as high as 27 mg/dl) in HFRS patients treated with IV ribavirin, the subjects were asymptomatic and the hyperuricemia readily resolved near the time of diuresis onset and ribavirin dose reduction to 8 mg/kg q8h (Rusnak et al., 2009).

**Other Adverse Events**

Symptoms from viral hemorrhagic fevers may mask many adverse events associated with IV ribavirin. Oral ribavirin is commonly associated with gastrointestinal symptoms (nausea, vomiting, abdominal cramps, or diar-

<table>
<thead>
<tr>
<th>Virus</th>
<th>Incubation Period</th>
<th>Therapy Duration Recommended or Used</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNV</td>
<td>Median 14-17 days (range 9-33 days)</td>
<td>21-28 days¹</td>
<td>No data in humans, but 400 mg q8h and 600 mg q12h used after two exposures¹</td>
</tr>
<tr>
<td>Andes Virus</td>
<td>Median 18 days (range 7-39 days)</td>
<td>21-28 days¹</td>
<td></td>
</tr>
<tr>
<td>HFRS</td>
<td>2-3 weeks (range 4-42 days)</td>
<td>No data in humans¹</td>
<td></td>
</tr>
<tr>
<td>LF²</td>
<td>Median 7-18 days</td>
<td>7 days³</td>
<td>500 mg q6h</td>
</tr>
<tr>
<td></td>
<td>5-8 days⁴</td>
<td></td>
<td>10 mg/kg qid</td>
</tr>
<tr>
<td></td>
<td>10 days⁵</td>
<td></td>
<td>600 mg 4 times daily (adults)</td>
</tr>
<tr>
<td></td>
<td>10 days⁶</td>
<td></td>
<td>35 mg/kg LD (max 2.5 g); then 15 mg/kg tid</td>
</tr>
<tr>
<td></td>
<td>10 days⁷</td>
<td></td>
<td>400 mg bid (range 400-1,200 mg/day)</td>
</tr>
<tr>
<td>CCHF²</td>
<td>2-7 days (range 2-14 days)</td>
<td>7 days³</td>
<td>500 mg q6h</td>
</tr>
<tr>
<td></td>
<td>10 days⁸</td>
<td></td>
<td>2 g LD, 1 g q6h x 4 days, 500 mg q6h x 6 days</td>
</tr>
<tr>
<td></td>
<td>5 days⁹</td>
<td></td>
<td>LD 1600 mg, then 500 mg tid x 5 days</td>
</tr>
<tr>
<td></td>
<td>14 days¹⁰</td>
<td></td>
<td>600 mg bid</td>
</tr>
</tbody>
</table>

LD = Loading Dose

¹ No data exist in humans to support postexposure prophylaxis for hantaviruses. The dosing regimen is based on dosing regimens used for LF and CCHF postexposure prophylaxis. The duration of 21 to 28 days has been used only after two New World hantavirus exposures and was based on the longer incubation period of hantaviruses (Rusnak et al., 2004). ² In a bioterrorism event, the Working Group on Civilian Biodefense consensus statement for viral hemorrhagic fevers does not recommend postexposure prophylaxis with ribavirin, but to consider treatment with ribavirin if symptoms of infection develop (Borio et al., 2002). ³ CDC and Bichat Guidelines. CDC recommended consideration of ribavirin postexposure prophylaxis for LF and also notes use may be justified but unstudied for CCHF (postexposure prophylaxis not addressed in recent CDC VH guidelines). CDC does not currently recommend use of convalescent plasma for prophylaxis for LF. Bichat Guidelines dosage applies for VHFs in addition to LF and CCHF (Bosset et al., 2004; CDC, 1988, 2005). ⁴ Dosage regimen used in 16 subjects assessed as high-risk exposure (Haas et al., 2003). ⁵ Dosage regimen used as postexposure prophylaxis for high-risk contacts to two imported cases of LF virus (Crowcroft et al., 2004; Holmes et al., 1990). ⁶ Proposed dosing regimen for postexposure prophylaxis for LF virus. Maximum loading dose of 2.5 g and maximum dose of 1 g tid (approximately 2.4 g loading dose followed by 1 g tid in a 70 kg person) (Bousch et al., 2010). ⁷ Dosage regimen of 400 mg bid for 10 days used in most subjects (dosage ranged from 400 mg to 1,200 mg/day for a mean duration of 8 days (range 1 to 14 days). Only 43% compliance in completing a 10-day course (Hadi et al., 2010). ⁸ CCHF postexposure prophylaxis dosage regimen in Pakistan is the same as for treatment (EIC, 2005). ⁹ Loading dose of 1,600 mg, then 400 mg tid x 5 days. Prophylaxis dose was lower and shorter duration than generally recommended, due to limited availability and delay in acquisition of oral ribavirin. A total of 38 individuals were exposed to blood and secretions of CCHF patient before implementation of effective barrier infection control measures and given ribavirin postexposure prophylaxis (Saleem et al., 2009). ¹⁰ Two asymptomatic seroconversions of CCHF observed (Pool, 2010).
rhea). Antiemetics may be considered, particularly if an oral loading dose is recommended. Other adverse events reported include fatigue, myalgia, headache, irritability, mood swings, nightmares, floating sensation, skin rash, itching, metallic taste, and insomnia (Crowcroft et al., 2004; McEvoy, 2004; Haas et al., 2003). Of note, compliance with postexposure prophylaxis in 23 subjects in developed countries was only 43% for completing a 10-day course (mean duration of 8 days (range 1-14 days) (Hadi et al., 2010). As ribavirin is teratogenic, the drug should not be used in pregnancy and individuals should be cautioned not to become or cause pregnancy for 7 months after cessation of ribavirin. However, limited experience of ribavirin in pregnancy (i.e., life-threatening illnesses, unknown pregnancy) has not demonstrated evidence of teratogenicity in newborns (Dizbay et al., 2009; Hegenbarth et al., 2001).

**Ribavirin Postexposure Prophylaxis for Laboratory Exposures to HF Viruses**

Deaths from laboratory-acquired infections (LAIs) historically have been more frequently associated with viral agents, including HF viruses (CDC, 1970; Gaimovish et al., 2000; Liefer et al., 1970; Miller, 2004; Mirza et al., 2005; Pike, 1976, 1979; Sulkin et al., 1949). High virulence and lack of treatment or a protective vaccine may have contributed to deaths.

The infrequency of reported LAIs from CCHF and LF may be due to the low number of at-risk subjects working with these agents and to protection provided by BSL-4 working conditions (Gaidamovish et al., 2000; Mirza et al., 2005; Risi et al., 2010). While unlikely to occur today, three laboratory outbreaks in Russia (1958 to 1967) were responsible for 144 HFRS cases, with the largest outbreak (113 laboratory workers and visitors to the laboratory) attributed to inhalation of airborne virus from excreta of rodents collected from the field (Gaidamovish et al., 2000; Kulagin et al., 1962). In the U.S. Biodefense Program, eight laboratory workers assessed with a significant risk exposure to HF viruses received postexposure prophylaxis with immune sera prepared from recovered patients in virus-endemic areas (5 LF, 2 Machu, and 1 Junin virus potential exposures; all remained asymptomatic). Three laboratory workers have received postexposure prophylaxis with ribavirin (LF, SNV, and Andes virus potential exposures); no individuals developed illness or seroconverted (Kortepeter et al., 2008; Rusnak et al., 2004) (Table 7). No conclusions can be made as to the effectiveness of ribavirin in these cases.

**Summary**

Recommendations to use ribavirin for treatment or postexposure prophylaxis for HF viruses must consider the risk of disease, the morbidity and mortality from the disease, and the potential benefit of ribavirin against the side effects from therapy. IV ribavirin is not FDA-approved and must be administered under an investigational protocol in the United States. Use of oral ribavirin for treatment or postexposure prophylaxis of HF viruses is an off-label use of the drug, and subjects must be educated concerning the risks and potential benefits of ribavirin in these circumstances. If ribavirin is given after a high-risk occupational exposure, RT-PCR and acute/convalescent serology to document infection or seroconversion should be considered. Due to ethical issues of a control group, it is unlikely that placebo-control trials to further assess ribavirin efficacy in humans to these HF viruses will be performed.

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