Rodney Dangerfield lamented that he “got no respect” but was a good comedian. This thought is analogous to West Nile virus (WNV). This mosquito-borne virus has proved itself to be a capable pathogen, causing an epidemic in the United States despite the US health care system being theoretically prepared to prevent a bioterrorism attack. I would like to make the case that the WNV epidemic was the result of bioterrorism. The epidemic illustrated how poorly prepared we are to meet the challenges posed by this and other agents that may not get the respect they deserve.

WNV first appeared in the United States in 1999. This infection “got no respect” even though it caused significant morbidity and mortality while crossing the United States unabated for the past 9 years. Patients died mainly of neuroinvasive complications such as encephalitis and a polio-like paralysis. The lack of respect became a reality to clinicians in Phoenix in 2004 when they found themselves poorly prepared to manage the many acutely ill patients affected by WNV. That there was a lack of practical information about how to manage WNV became readily apparent to these clinicians.

Challenges included (1) inability to adequately prepare for the uniqueness of the disease or seriousness of the illness, (2) inability to diagnose the infection in a timely way, (3) lack of adequate information on how to treat the infection, and (4) lack of information about coordination regarding prevention measures. These and other problems support the idea that there was a lack of preparedness at the grassroots level. It is not that nothing was done but that the threat of WNV was not given due respect politically and in the scientific community compared with avian influenza virus and Bacillus anthracis, 2 agents that so far have caused comparatively minimal damage in the United States.

I am in a reasonable position to raise issues about how the WNV epidemic has been handled in the United States. I have both research and clinical experience in arboviruses, having worked in arbovirology in my early career with the NIH, and being in private practice for more than 25 years. Most of the early information on WNV infections came from clinicians turned arbovirologists and arbovirologists turned clinicians.

Arboviruses have not been a serious problem in the United States, and this may partly be why WNV has not received the attention it should. Bioterrorism, however, has received a lot of attention. Was the WNV epidemic the result of bioterrorism? Using relatively simple techniques in a low-tech laboratory, enormous numbers of mosquitoes can be infected with WNV. Of interest is that the strain of WNV that caused the epidemic in the United States originated in the Middle East.

To get an idea of some of the problems clinicians faced in caring for critically ill patients, picture diagnostic laboratory tests taking 6 or more days before the results become known, as detailed in our article in this issue of Infections in Medicine. An aggravating problem was the knowledge that diagnostic tests for WNV infection were available but not readily accessible and did not allow for rapid turnaround time at the community hospital level. The years between 1999 and 2004 should have been enough time to establish rapid diagnostic tests and an algorithm on how best to deal with critically ill patients with WNV.

Most clinicians might know that WNV is an RNA virus and thus is resistant to acyclovir. However, they may be unaware that WNV, like hepatitis C virus (HCV), belongs to the genus Flavivirus. Most clinicians know that interferon and ribavirin have been used successfully in the treatment of HCV infection. Thus, it seemed reasonable to use these drugs for the critically ill patient with WNV infection. We postulated that these would be better alternatives than ceftriaxone or acyclovir. Faced with critically ill patients on a ventilator who were unable to move against...
Prevention of Opportunistic Infections in the Solid Organ Transplant Recipient

Christopher L. Vinnard, MD and Emily A. Blumberg, MD

The successful management of immunosuppression following solid organ transplant requires a delicate balance between preventing allograft rejection and minimizing the risk of infection. Strategies that may reduce the risk of de novo opportunistic infection and emergence of latent infection during the early posttransplant period—specifically infection caused by Cytomegalovirus, opportunistic fungi such as Aspergillus and Candida, and bacteria such as Pneumocystis jiroveci and Mycobacterium tuberculosis—are presented in this review. [Infect Med. 2008;25:403-415]

Key words: Opportunistic infection ■ Solid organ transplant

Opportunistic infections that occur early after solid organ transplant (SOT) may be de novo or may represent reactivation of latent infection (Figure). Common opportunistic infections include those caused by Cytomegalovirus (CMV), fungal pathogens such as Aspergillus and Candida, and bacterial pathogens such as Pneumocystis jiroveci and Mycobacterium tuberculosis. Knowing this, clinicians can institute preventive strategies in the setting of SOT (Table).

CMV infection

CMV infection in the SOT recipient is a cause of significant morbidity and mortality.1 Disease is characterized by a febrile illness with or without direct end-organ damage. The term “CMV syndrome” refers to this febrile illness and may be the first sign of CMV infection in the SOT recipient. In addition, diverse effects, mediated by CMV infection, impact immune response. These effects may increase the risk of infection with other opportunistic pathogens during the posttransplant period.2 They also may increase the risk of acute and chronic allograft injury.2

CMV infection is usually transmitted to the SOT recipient from the organ donor rather than it being a reactivation of a latent CMV infection in the organ recipient. Presence of CMV may represent isolated viremia (infection) or viremia associated with end-organ damage (disease). The serostatus of the donor and recipient will predict the risk of viremia posttransplant, which, in turn, will correlate with the risk of CMV disease.3 Infection risk is highest in a CMV-seronegative recipient of an organ from a CMV-seropositive donor; however, even seropositive recipients are at increased risk for infection if the donor is also seropositive.

The level of risk for CMV disease—as defined by serological status—depends on the type of allograft received. Lung, pancreas, and small-bowel transplant recipients are at highest risk; liver and heart transplant recipients are at intermediate risk; and kidney transplant recipients are at lower risk. This may be related both to an increased risk of acquisition of CMV from donor organs with a potentially higher burden of latent virus and to the greater degree of immunosuppressive therapy used in some of these recipients. For any transplant recipient, risk will be significantly augmented by the use of specific immunosuppressive agents, which may increase the potential for reactivation of latent virus. These agents include antilymphocyte therapies (eg, antithymocyte globulin), muromonab-CD3, and alemtuzumab. In addition, rejection and its treatment may be linked to the development of CMV disease.4

Prevention of CMV disease has

Dr Vinnard is a fellow and Dr Blumberg is professor of medicine in the division of infectious disease, University of Pennsylvania, Philadelphia.
been shown to have a significantly positive effect on outcomes in SOT recipients. Two strategies have emerged: prophylaxis and preemptive therapy. Prophylaxis requires administration of antiviral agents to all at-risk SOT recipients before the development of detectable CMV infection. Preemptive therapy requires regular surveillance for CMV infection, with initiation of antiviral therapy for any patient in whom the virus is detected. Quantitative testing for CMV DNA by nucleic acid (ie, polymerase chain reaction) assay has replaced CMV antigen testing as the most common surveillance method because of its advantages in test characteristics and ease of use. In centers in which nucleic acid testing is not available, antigenemia can be used to monitor patients for the development of CMV infection.

Each strategy has advantages and disadvantages. Prophylactic therapy may be logistically simpler to follow, particularly outside the clinical trial environment. However, universal prophylaxis carries a potential risk of development of ganciclovir-resistant CMV. It also may prevent antibody formation and may delay the presentation of CMV infection. In addition, antiviral therapies may not be well tolerated; adverse effects include significant cytopenias. Preemptive therapy carries less risk of drug-related toxicities, but it leads to higher rates of asymptomatic CMV infection. Potentially, more virus-mediated modulation of the immune system could occur.

A number of agents have proved to be effective for the prevention of CMV infection and disease. Acyclovir, valacyclovir, ganciclovir, and valganciclovir have all shown efficacy in prevention of CMV disease in select populations. Before the release of valganciclovir, ganciclovir was the drug most frequently administered to the highest-risk patients. Ganciclovir is available in both intravenous and oral formulations; the oral formulation was often preferred despite the high pill burden and poor oral bioavailability.

Valganciclovir is a valine ester prodrug of ganciclovir with significantly improved oral bioavailability. In a prospective, randomized, double-blind trial comparing ganciclovir with valganciclovir for CMV prophylaxis among high-risk (donor-positive/recipient-negative) SOT recipients, similar rates of CMV disease were seen in both groups at 6 and 12 months of follow-up. Valganciclovir has replaced ganciclovir for most prophylactic indications because of its increased bioavailability and the absence of associated resistance. However, in analysis of the liver transplant recipient subset of this trial, more tissue-invasive CMV disease was seen in the valganciclovir arm (14% vs 3%). As a result, valganciclovir was not approved by the FDA for the prevention of CMV disease in liver transplant recipients, although some centers have continued to use it.

Regardless of the agent used for prophylactic therapy, the duration of antiviral administration is not standardized. In most cases, prophylaxis is administered for a minimum of 100 days posttransplant. However, longer durations of prophylaxis also have been used, especially for the highest-risk recipients, and a comparative trial of 3 versus 6 months of prophylaxis is currently ongoing. Reintroduction of prophylaxis should be considered following treatment of rejection, especially when cytoytic therapies are used.

Although most transplant centers use prophylaxis rather than preemptive therapy for prevention of CMV disease, few prospective trials compare these strategies. In a meta-analysis of 3 trials that included 151 patients and compared either oral acyclovir or ganciclovir prophylaxis with either oral or intravenous (5 mg/kg twice daily) ganciclovir preemptive therapy, no difference was seen in rates of CMV disease, acute rejection, or all-cause mortality.

In a recent trial, 98 kidney transplant recipients were randomly selected to receive either valganciclovir prophylaxis (900 mg/d) or preemptive therapy (900 mg twice daily). No difference was seen in rejection, allograft function, or mortality, although there was a trend toward increased symptomatic CMV disease in the prophylaxis group. In another trial, 70 kidney transplant recipients were randomly selected to receive prophylactic valacyclovir (2 g 4 times daily) or preemptive valganciclovir (900 mg twice daily). Although there was also no difference in allograft function or mortality, a higher rate of acute rejection was seen in the preemptive therapy group. Based on the findings from these relatively small single-center trials, the optimal strategy for the prevention of CMV disease has not been defined, and additional comparative trials are ongoing.

The use of immunoglobulin for the prevention of CMV disease has declined with the development of specific antiviral therapies for CMV. Initial studies of CMV immunoglobulin supported its use in limited populations, but drawbacks include cost and inconvenience of administration. A recent meta-analysis found no additional benefit of antiviral therapy combined with immunoglobulin, compared with antiviral therapy alone. At some transplant centers, immunoglobulin may still be used, primarily in conjunction with antiviral therapies for those patients at highest risk.

Other viruses
The SOT recipient is also at risk for infection with or reactivation of her-
Changing timeline of infection after organ transplantation

**Opportunistic Infections and SOT**

Donor-derived infection

**Nosocomial, technical**

(1 donor or recipient)

Activation of latent infection

(1 relapsed, residual, opportunistic)

Community-acquired

Transplant

Dynamic assessment of risk of infection

Recipient-derived infection

Common infections in solid organ transplant recipients

**< 1 Month**

Infection with antimicrobial-resistant species: MRSA, vancomycin-resistant Enterococcus, *Candida* (non-albicans)

Aspiration

Catheter infection

Wound infection

Anastomotic leaks and ischemia

Clostridium difficile colitis

Donor-derived infection (uncommon) with:

HSV, LCMV, rhabdovirus, West Nile virus, HIV, *Trypanosoma cruzi*

Recipient-derived infection (colonization) with:

Aspergillus, *Pseudomonas*

**1 - 6 Months**

Infections with PCP and antiviral (CMV, hepatitis B virus) prophylaxis:

Polyomavirus BK infection, *C. difficile* colitis, hepatitis C virus infection, adenovirus infection, Cryptococcus neoformans infection, *Mycobacterium tuberculosis* infection

Anastomotic complications

Infections without prophylaxis:

*Pneumocystis* infection; infection with herpes viruses; hepatitis B virus infection; infection with *Listeria, Nocardia, Toxoplasma, Strongyloides, Leishmania, T cruzi*

**> 6 Months**

Community-acquired pneumonia and urinary tract infection; infection with *Aspergillus, atypical moulds, and Mucor species*

Infection with *Nocardia* and *Rhodococcus* species

Late viral infections:

CMV infection (colitis, retinitis), hepatitis (B or C virus), HSV encephalitis, community-acquired infection (ie, SARS, West Nile virus infection, JC polyomavirus infection, skin cancer, lymphoma (ie, PTLD)

Figure – Infections occur in a generally predictable pattern after solid organ transplant. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug-related toxicities that may cause leukopenia, or immunomodulatory viral infections such as those caused by CMV, hepatitis C virus, or Epstein-Barr virus. At the time of transplant, a patient’s short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent allograft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust both prophylaxis and immunosuppressive therapy. (MRSA, methicillin-resistant *Staphylococcus aureus*; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; PCP, *Pneumocystis pneumonia*; CMV, *Cytomegalovirus*; SARS, severe acute respiratory syndrome; PTLD, posttransplant lymphoproliferative disease.) (Adapted from Fishman JA. *N Engl J Med.* 2007.37 Used with permission.)
OPPORTUNISTIC INFECTIONS AND SOT continued

Table – Guidelines for prophylaxis at the University of Pennsylvania

<table>
<thead>
<tr>
<th>Indication</th>
<th>Patient population</th>
<th>Medication</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>CMV D+/R—</td>
<td>IV ganciclovir</td>
<td>6 mg/kg/d</td>
<td>100 days</td>
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<td>CMV D—/R+, D+/R+</td>
<td>PO ganciclovir</td>
<td>1 g tid</td>
<td>100 days</td>
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<tr>
<td></td>
<td></td>
<td>Acyclovir</td>
<td>800 mg tid</td>
<td></td>
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<tr>
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<td>CMV D—/R—</td>
<td>Acyclovir a</td>
<td>400 mg tid</td>
<td>100 days</td>
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<tr>
<td>Kidney</td>
<td>CMV D+/R—</td>
<td>Valganciclovir</td>
<td>900 mg daily</td>
<td>100 days</td>
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<td>CMV D—/R+, D+/R+</td>
<td>Valganciclovir</td>
<td>450 mg daily</td>
<td>90 days</td>
</tr>
<tr>
<td></td>
<td>CMV D—/R—</td>
<td>Acyclovir a</td>
<td>400 mg bid</td>
<td>90 days</td>
</tr>
<tr>
<td>Heart</td>
<td>CMV D+/R—, D+/R+</td>
<td>Valganciclovir</td>
<td>900 mg daily</td>
<td>100 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Ganciclovir</td>
<td>1000 mg tid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMV D—/R—, D—/R+</td>
<td>Acyclovir a</td>
<td>400 mg bid</td>
<td>100 days</td>
</tr>
<tr>
<td>Lung</td>
<td>CMV D+/R—</td>
<td>IV ganciclovir</td>
<td>5 mg/kg q12h</td>
<td>2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>followed by</td>
<td>Valganciclovir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or valganciclovir</td>
<td>900 mg daily</td>
<td>10 weeks</td>
</tr>
<tr>
<td></td>
<td>CMV D+/R+, D—/R+</td>
<td>Valganciclovir</td>
<td>900 mg daily</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>CMV D—/R—</td>
<td>Valacyclovir a</td>
<td>500 mg daily</td>
<td>12 months</td>
</tr>
</tbody>
</table>

continued

directly through the prevention of CMV disease.14

The clinical significance of HHV6, HHV7, and HHV8 viremia in the SOT recipient remains uncertain.15
For patients receiving ganciclovir or valganciclovir, infection with HHV7 may be relatively more common than infection with HHV6. In a comparison with infections in historical controls, infections with VZV, HHV6, and EBV may have declined with the use of ganciclovir or valganciclovir for prophylaxis against CMV infection.16 HHV8 viremia may be a consequence of reactivation of latent infection or donor-derived infection. There is no consensus on the role of donor screening or monitoring of SOT recipients for HHV8 infection.17

Fungal infection
Strategies for the prevention of fungal infections after transplant are less universally agreed on. In general, lung transplant recipients are at highest risk, followed by liver, pancreas, and small-bowel transplant recipients. Kidney and heart transplant recipients are at comparatively lower risk. There are few randomized trials that compare antifungal regimens, and many strategies have been developed based on observational data.18
Liver transplant recipients are at risk for both invasive aspergillosis and invasive candidiasis. Specific factors have been used to identify patients at high risk for invasive candidiasis. In an observational study of risk for invasive fungal infections in liver transplant recipients, high-risk patients were defined as having at least 2 of the following criteria: choledochojunostomy anastomosis, retransplant, intraoperative administration of more than 40 units of blood products, return to the operating room for intra-abdominal bleeding, return to the operating room for anastomotic leak or vascular insufficiency, preoperative serum creatinine level greater than 2 mg/dL, and perioperative Candida colonization. Low-risk patients—ie, those with no more
than 1 of these criteria—may not require antifungal prophylaxis.\textsuperscript{19,20}

In a meta-analysis of prophylaxis for fungal infections in liver transplant recipients, prophylaxis with fluconazole decreased the incidence of invasive fungal infections by 75% but had no effect on total mortality.\textsuperscript{21} The decision to use fluconazole prophylaxis for high-risk patients also may depend on the prevalence of disease at an individual transplant center. Prophylaxis is usually not continued beyond 4 weeks post-transplant. It is uncertain whether there is a role for prophylaxis against invasive aspergillosis in the liver transplant recipient, and there is no established regimen that is recommended at this time.\textsuperscript{22}

Although lung transplant recipients are at increased risk for fungal infections, there are not yet universally agreed-on risk factors to guide the use of antifungal prophylaxis in this population. Observational studies have suggested a role for both aerosolized amphotericin B and itraconazole, but no prospective trials have evaluated individual regimens.\textsuperscript{23,24} A recent survey of centers performing lung transplantation found significant variation in the type of antifungal prophylaxis regimen used.\textsuperscript{25} The appropriate duration of prophylaxis is also not well

### Table – Guidelines for prophylaxis at the University of Pennsylvania

<table>
<thead>
<tr>
<th>Indication</th>
<th>Patient population</th>
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<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungal</td>
<td>Liver, kidney, heart</td>
<td>Nystatin</td>
<td>5 mL swish and swallow</td>
<td>90 days</td>
</tr>
<tr>
<td>Liver</td>
<td>Patients with 1 of the following: Renal failure, Re-operation, Prolonged operative course, Roux-en-Y anastomosis, Preoperative fungal colonization, Massive blood transfusions intraoperatively</td>
<td>Fluconazole</td>
<td>400 mg daily</td>
<td>At least 1 week posttransplant</td>
</tr>
<tr>
<td>Lung</td>
<td>Donor or recipient with cultures of respiratory secretions positive for fungi</td>
<td>Voriconazole</td>
<td>200 mg q12h</td>
<td>May depend on bronchoscopic findings</td>
</tr>
<tr>
<td>Pneumocystis infection</td>
<td>Liver, kidney, heart, lung</td>
<td>TMP/SMX SS or DS</td>
<td>Once daily</td>
<td>Liver, heart: 1 year; kidney: 180 days; lung: lifelong</td>
</tr>
<tr>
<td>Not sulfa-allergic</td>
<td>TMP/SMX SS or DS</td>
<td>3 times weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfa-allergic</td>
<td>Atovaquone or Dapsone or Aerosolized pentamadine</td>
<td>1500 mg daily</td>
<td>Same</td>
<td></td>
</tr>
</tbody>
</table>

CMV, Cytomegalovirus; D+, donor-positive; D—, donor-negative; R+, recipient-positive; R—, recipient-negative; TMP/SMX, trimethoprim/sulfamethoxazole; SS, single-strength; DS, double-strength.

\textsuperscript{a} For herpes simplex virus prophylaxis.

\textsuperscript{b} Longer duration may be used in high-risk patients maintained on higher doses of immunosuppression, or in the setting of rejection.
defined. Continuing prophylaxis for 4 to 6 months has been suggested to allow for suture healing and reduction of net immunosuppression. There may be a subset of patients who would benefit from extending prophylaxis to 1 year or beyond. The presence of *Aspergillus* in cultures of respiratory tract secretions should prompt investigation for invasive aspergillosis, with an institution of the appropriate treatment based on those results.

Recipients of a pancreas allograft (whether pancreas alone, simultaneous kidney-pancreas, or pancreas after kidney transplant) also are at high risk for invasive fungal infection. This risk approximates what is seen in liver transplant recipients. Specific risk factors include older age of donor or recipient, enteric drainage, and vascular graft thrombosis. The majority of infections in these patients are caused by *Candida* species. Fluconazole prophylaxis should be considered in high-risk patients. Duration of prophylaxis is not defined and may vary with the degree of ongoing risk.

Guidelines on antifungal prophylaxis in other transplant recipients have not been established. Small-bowel transplant recipients are at considerable risk for invasive *Candida* infection, and although no controlled trials have been performed, experience with liver transplant and nontransplant small-bowel surgery has led to the common use of fluconazole prophylaxis.

The period of greatest risk is the first 2 months posttransplant. Prophylaxis in kidney transplant recipients should be limited to those with candiduria. Although patients with ventricular assist devices are at increased risk for invasive fungal infections, antifungal prophylaxis has not been systematically studied in this population and is not consistently recommended.

**P. jiroveci pneumonia**

Before trimethoprim/sulfamethoxazole (TMP/SMX) was routinely used in the SOT recipient, there was a high incidence of *Pneumocystis pneumonia* (PCP) posttransplant, especially between months 2 and 6 following transplant. The risk of PCP in the SOT recipient is also increased during periods of prolonged neutropenia and increased immunosuppression. It has been suggested that prophylaxis with TMP/SMX be limited to centers in which the incidence of PCP is greater than 3% to 5% or to any patient previously infected with *Pneumocystis*. In practice, most centers continue to provide prophylaxis for all SOT recipients for at least a limited time after transplant.

For patients who are intolerant to TMP/SMX, alternative prophylactic agents include dapsone, atovaquone, pentamidine, and clindamycin with pyrimethamine. Activity of the glucose-6-phosphate dehydrogenase (G6PD) enzyme should be measured before the use of dapsone. Even in patients with normal G6PD activity, a risk of dapsone-related hemolytic anemia and methemoglobinemia is present. None of these alternative agents will have the additional antimicrobial activity of TMP/SMX, which includes activity against *Toxoplasma*, as well as activity against many community-acquired bacterial pathogens of the respiratory and urinary tracts. This may be particularly significant for heart transplant recipients, who are at increased risk for toxoplasmosis and in whom TMP/SMX is highly effective for toxoplasmosis prophylaxis.

In a review of 596 heart transplant recipients who received TMP/SMX prophylaxis for PCP for a minimum of 1 year posttransplant, no cases of toxoplasmosis were found. As prophylaxis for PCP, TMP/SMX may be given 3 times weekly or once daily; it is unknown which of these dosing schedules is preferable.

Duration of prophylaxis for PCP will depend on the ongoing risk of infection. This risk is based on the patient’s level of immunosuppression along with any history of previous *Pneumocystis* infection. For kidney, heart, and liver transplant recipients maintained on low levels of immunosuppression, prophylaxis may be discontinued at 1 year posttransplant. A longer duration of prophylaxis may be beneficial for lung transplant recipients, and lifelong prophylaxis is commonly used.

A retrospective review of 28 cases of PCP in lung transplant recipients at a single center identified 10 that occurred more than 1 year posttransplant. No cases of PCP were identified in patients receiving prophylaxis for *Pneumocystis* infection. All patients with a history of *Pneumocystis* infection and those patients who require significant ongoing immunosuppression—as in the treatment of chronic allograft rejection—should be evaluated for lifelong prophylaxis for *Pneumocystis* infection.

**Latent tuberculosis**

Although donor-derived tuberculosis infection may occur, most cases of tuberculosis following transplant represent reactivation of latent infection in the context of immunosuppression. The incidence of tuberculosis in SOT recipients, based on a review of published reports, is estimated to range from 0.35% to 15%, depending on the background prevalence of tuberculosis at the various study sites. In one large review, most cases (437 of 511) of tuberculosis were in kidney transplant recipients, and the median time to onset was 9 months posttransplant. To identify latent infection before transplant, patients should undergo tuberculin skin testing. A positive skin test result is defined as induration greater than 5 mm. Two-step
testing should be considered for all patients with initial negative results, with a repeat of the skin test approximately 2 weeks later.33

Living donors who are related to the recipient also should be tested and treated for latent infection as indicated. All patients with positive skin test results should receive preventive therapy with isoniazid after active disease has been excluded. The treatment for latent tuberculosis in the SOT recipient, as in the general population, is isoniazid 300 mg/d for 9 months.34 Because many transplant candidates may have cutaneous anergy, nonresponders should also receive isoniazid if they have any of the following: radiographic evidence of previous active tuberculosis without prior treatment or prophylaxis, a history of inadequately treated tuberculosis, close contact with an infectious patient or receipt of an allograft from a donor with previous inadequately treated tuberculosis.32 There are no data on the use of γ-interferon tests for the diagnosis of latent tuberculosis in the SOT recipient.

Among kidney transplant candidates, and possibly lung transplant candidates, it may be best to complete treatment before the transplant is performed. Among liver transplant recipients, treatment may be deferred until hepatic function has stabilized.35 Although the risk of isoniazid toxicity may be greater in a liver transplant recipient, abnormal liver enzyme levels after transplant may not be related to isoniazid. Liver transplant patients should undergo liver biopsy to check for enzyme abnormalities. It may be difficult to differentiate rejection, recurrent viral infection, and drug toxicity.33

For patients intolerant to isoniazid, rifampin 600 mg/d for 4 months is an alternative therapy; however, caution should be used with rifampin in the SOT recipient. It affects the metabolism of many other agents, including the calcineurin inhibitors and target of rapamycin (TOR) inhibitors, which may result in suboptimal immunosuppression, allograft rejection, and possible loss of the organ; careful monitoring is critical.36

Conclusion
Skillful prevention of opportunistic infection in the SOT recipient allows for the successful maintenance of immunosuppression and a much lower risk of complications related to allograft rejection. Because of a growing population of potential recipients, strategies for expanding the donor pool are being evaluated. These include the use of expanded criteria for donors to include those who may be a source of donor-derived infections and the use of more potent immunosuppressive strategies to minimize the risk of rejection in higher-risk transplant recipients. Ultimately, prophylactic measures may require adaptation to provide enhanced protection from both new and established pathogens in this evolving patient population.

Therapeutic agents mentioned in this article

<table>
<thead>
<tr>
<th>Antiviral</th>
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**REFERENCES**


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Critical Views continued from page 402

gravity, therapy with interferon and ribavirin seemed a more reasonable approach than “supportive” care.2 If desperate clinicians could come to this conclusion in less than 5 years after the initial WNV outbreak, why was more information about this therapeutic option not available?

I give the response of the NIH and CDC in assigning the WNV epidemic a failing grade. The slow response has allowed WNV to go from epidemic to endemic status. Now we will be faced with WNV infections every year wherever there are mosquitoes in the United States. My analysis is that more resources were being put into the study of other infectious threats, such as smallpox and avian influenza, than into the study of WNV infection, for politically rather than medically expedient reasons. Unfortunately, the NIH and CDC may lose objectivity when nonmedical governmental purse strings are influencing their decisions.

The United States has enough resources, experience, and knowledge to deal with and identify to deal with infectious disease problems uninfluenced by politics, media, and government funding pressures. A retrospective look at the WNV epidemic offers the chance to reexamine and improve efforts on how to deal with such epidemics.

Food for thought: $100,000 should be awarded to any physician who first recognizes a bioterrorism agent. The astute physician who recognized the first case of anthrax deserved such an award. Also, an independent advocacy group, such as the Infectious Diseases Society of America, should be engaged to generate the expertise needed and a more rapid response to suspected infectious bioterrorist threats.

REFERENCES

Brief, critical editorial reviews by experts in the field are welcome.

Please query the editor first before submitting materials (denise.rapposelli@cmpmedica.com).

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Further Evidence That HTLV Protects Against HIV Progression

Farshad Bagheri, MD, Kashyapkumar Patel, MD, Edward Samourjian, BS, Naveen Pathak, MD, Vyacheslav Shamalov, MD, Jonas Gintautas, MD, PhD, and Thomas Santucci, MD

Previous case reports have suggested an association between human T-cell lymphotropic virus (HTLV) types 1 and 2 infection and chronic nonprogressive HIV infection. Evidence is lacking about the specifics of how the two are related. We report 2 cases of chronic nonprogressive HIV infection (of 9 and 13 years’ duration, respectively) in women in whom HTLV coinfection was diagnosed. These cases provide clinical support that HTLV coinfection may serve as a protective factor against progression of HIV infection. Possible reasons for this relationship and potential future research are discussed.


Key words: HIV ■ Human T-cell lymphotropic virus

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uman T-cell lymphotropic virus type 1 (HTLV-1), human T-cell lymphotropic virus type 2 (HTLV-2), and HIV-1 were among the first human retroviruses to be identified (in 1979, 1981, and 1982, respectively). To date, debate persists concerning the effects of coinfection with HTLV-1 and HIV-1 or coinfection with HTLV-2 and HIV-1. This is partially because of the paucity of data that has been published and also because of conflicting results in the reports that do exist. Some evidence suggests that HIV-1/HTLV-1 coinfection can accelerate the progression of HTLV-1 infection while it has no effect on the progression of HIV-1 infection. Other reports have indicated that coinfection with HTLV-1 may attenuate the progression of HIV-1 infection.2 Some studies on HTLV-2/HIV-1 coinfection have reported that the progression of HIV-1 infection to AIDS is neither accelerated nor suppressed.4 Other studies, however, have reported slowed progression of HIV infection to AIDS in patients coinfected with HTLV-2.25

HTLV-2 infection may be associated with higher rates of neurological abnormalities in patients coinfected with HIV-1.6 HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a disabling disease that occurs in approximately 2% of those with HTLV-1/2 infections.7 It has a slow onset, and its characteristic manifestations are lower lumbar pain and spastic paraparesis of the lower extremities, including ankle clonus and positive Babinski sign. Evidence indicates that HAM/TSP may be more likely to develop in patients coinfected with HTLV-1/2 and HIV-1 than in patients infected with HTLV-1/2 alone.8 Very few systematic studies have been conducted to clarify any of these associations, however.

Two cases of chronic, nonprogressive HIV infection in women, both of whom were coinfected with HTLV-1/2 and one of whom had HAM/TSP, are reported. These cases lend support to the theory that HTLV-1/2 infection may be a protective factor against progression of HIV infection even in patients with co-occurring HAM/TSP.

Case report 1
A 66-year-old African Jamaican woman presented to the emergency department (ED) with leg weakness
and a tingling sensation that had persisted for 3 months. The patient’s medical history was significant for HIV infection, which was diagnosed 13 years ago; colon cancer, for which colectomy was performed 13 years ago; and hypertension. It was suspected that HIV infection occurred through contact with her husband, who was HIV-positive and had died 7 years earlier of an HIV-related infection. The patient had never received antiretroviral therapy (ART), and the HIV infection was considered to be chronic nonprogressive.

On physical examination, the patient’s lower extremities had decreased strength. Movement against gravity was possible only on dorsiflexion and plantar flexion of the foot, with flexion and extension of the leg, and with flexion and extension of the thigh. Patellar, Babinski, and Achilles reflexes were hyperactive. The head and neck displayed choreiform movements, which are signs of HAM/TSP.

MRI of the spine without contrast showed no evidence of cord compression but rather mild cervical and lumbar degenerative changes. MRI of the brain without contrast showed moderate to severe white matter abnormalities involving the cerebral hemisphere and pons. Considering the limited display of thoracic spinal degeneration, characteristic of HAM/TSP, the inflammatory process affecting the thoracic spine was considered to be in an early phase.

One year before the patient was admitted, a quantitative polymerase chain reaction (PCR) analysis demonstrated an HIV-1 RNA level of 9160 copies/mL. Four months later, another PCR analysis showed an HIV-1 RNA level of 5116 copies/mL, which is a clinically significant decrease. The CD4+ cell count 1 year before admission was 486/µL; repeated CD4+ cell counts 1 month and 4 months later were 583/µL and 390/µL, respectively. A serum test for HTLV-1/2 antibodies was reactive, supporting the diagnosis of an HTLV infection. Tests for HTLV-1/2 in cerebral spinal fluid using enzyme-linked immunosorbent assay were also positive, supporting the diagnosis of HAM/TSP.

Because of lack of symptom progression, ART was not started. Since there is no effective treatment thus far for TSP/HAM, the patient was given baclofen 10 mg PO q24h as a supportive measure. After 35 months of follow-up, the patient’s HIV infection continues to be chronic nonprogressive. Highly active antiretroviral therapy was begun because of the possible coexistence of HIV/AIDS myelopathy. To date, the patient has tolerated the treatment well. The CD4+ cell count remains high but has not significantly increased since assessments performed 5 months previously. The viral load is undetectable, there is less paresthesia, and the patient’s muscular rigidity has subsided.

Case report 2
A 46-year-old African American woman presented to the ED with lower back pain and excessive dry cough of 2 weeks’ duration and a 20- to 30-lb weight loss occurring over the course of 2 to 3 months. The lower back pain was in the vicinity of the L2 and L3 vertebrae and was diffuse, moderate to severe in intensity, and unremitting. The patient’s past medical history was significant for HIV infection, which was diagnosed 9 years earlier, and latent syphilis and hepatitis C virus infection, both diagnosed 1 year before the current presentation to the ED.

The patient had been a habitual cocaine, injection drug, and alcohol user and smoked a half-pack of cigarettes per day for approximately 24 years. She stated that she was indigent and sexually active. She had never received ART and denied ever experiencing chest pain, fever, night sweats, or hemoptysis.

On physical examination, bibasilar rales and bilateral wheezing were noted in the patient’s lungs. Her upper and lower extremities had strength of movement against gravity with some resistance with all motion; reflexes were normal. The patient’s lumbar area was tender to palpation; skin was intact and very loose from the excessive weight loss over such a short period. A CT scan of the chest displayed significant mediastinal and retrocrural lymphadenopathy and mild axillary lymphadenopathy. Results of a tuberculin skin (ie, purified protein derivative) test were negative.

A lymphocyte subset panel revealed a CD4+ cell count of 583/µL, which is high for a patient who has been HIV-positive for nearly a decade. Results of previous laboratory tests, conducted 2 years earlier, revealed a CD4+ cell count of 1008/µL. HTLV-1/2 infection was suspected because of the patient’s chronic nonprogressive HIV infection and the excessive mediastinal and retrocrural lymphadenopathy, indicative of possible lymphoma. Results of a serum analysis for HTLV-1/2 antibodies were positive.

ART was not initiated because of a lack of symptom progression. After 3 months’ follow-up, HIV infection in this patient continues to be chronic nonprogressive and the patient is not receiving ART.

Discussion
HTLV-1 is endemic to distinct geographical areas, including Japan, the Caribbean basin, West Africa, Melanesia, South America, and the Middle East. Whereas HTLV-1 infection is most often diagnosed in patients of African American descent in North America, HTLV-2 infection is mainly diagnosed in American Indians. Both HTLV-1 and HTLV-2...
infections mostly occur in high-risk groups, such as injection drug users. In the United States, large-scale blood supply screening in the general population has documented rates of HTLV-1/2 infection of 0.043%. In a significant proportion of HTLV-1 infections, the patient either has links to an area where the virus is endemic or has a history of risk-related behaviors, such as injection drug use.

Rates of HTLV-1/2 infection are higher among patients infected with HIV-1 than among the general population. HAM/TSP-associated myelopathy is rarely reported in the United States (ie, less than 20 cases). Among HTLV-1– or HTLV-2–infected persons who are HIV-negative, the estimated lifetime risk of HAM/TSP is less than 2%. However, as mentioned, it has been suggested that HIV/HTLV coinfection may increase the risk of HAM/TSP development. One of the patients had a history of injection drug use. The patient with HAM/TSP also had a link to an area (Jamaica) where HTLV is endemic.

These cases provide clinical support for the hypothesis that HTLV-1/2 coinfection with HIV-1 may be protective against transition to AIDS. One potential mechanism for attenuation of HIV infection in coinfected patients is the increased up-regulation of inhibitory chemokine, which can alter disease progression by slowing the rate of decrease of CD4+ cell counts.

Up-regulation of HTLV-1 expression in patients with HIV-1 and HTLV-1/2 coinfection may be a risk factor for HAM/TSP. It has been reported that both HIV/HTLV-1 coinfection and HIV/HTLV-2 coinfection are associated with higher levels of HTLV-1/2 tax/rex messenger RNA (Figure) and viral antigen expression in peripheral blood mononuclear cells (PBMCs) compared with samples obtained from either HTLV-1 or HTLV-2 monoinfected persons.

Case-controlled comparison studies...
have illustrated that HIV/HTLV coinfection does not appear to be associated with a change in the HIV RNA level. Higher levels of HTLV-1 and HTLV-2 proviral burden in PBMCs are associated with higher CD4+ T-cell counts. The vacular myelopathy associated with HIV infection of the spinal cord typically presents in patients with advanced immunodeficiency and often in conjunction with low CD4+ T-cell counts, dementia, and opportunistic infections.

In the 2 cases presented here, the patients had high CD4+ cell counts despite the duration of illness and the fact that they have not been receiving ART. A negative test result for chemokine receptor 5 mutation was a reason why the HIV infection status of the patient described in case 1 was deemed chronic nonprogressive.

Little information is available concerning the benefit of ART for treatment of HAM/TSP. Efforts to treat HAM/TSP and HTLV-1-associated autoimmune diseases using various antiretroviral compounds have been disappointing.

The treatment of HAM/TSP with corticosteroids, cyclophosphamide, and interferon alfa benefit some patients, particularly when given early in the clinical course or when given to patients with rapidly progressing forms of the disease. Treatment with danazol, an androgenic steroid, has reversed urinary and fecal incontinence in some cases but not the spastic limb disease or the underlying neurological deficit. Corticosteroids and immunosuppressive agents, such as azathioprine, may ameliorate disease progression but are unsuitable for long-term use because of adverse effects. Immunotherapy with interferon alfa and interferon beta has had minimal to moderate results, depending on the degree of inflammation and tissue destruction involved. Given these data, early treatment of patients with HIV/HTLV-1 coinfection who present with HAM/TSP is not recommended.

**Conclusion**

Whether coinfection with HTLV-1/2 and HIV-1 results in a slower progression to AIDS is controversial. Our cases suggest that a protective element may exist. It is noteworthy that coinfected persons have increased CD4+ cell counts but are still at risk for opportunistic infections. Infection with these other retroviruses should routinely be considered in patients with a long history of HIV-positive status and high CD4+ cell counts who are not receiving ART and whose HIV infection is considered to be chronic nonprogressive. This is especially true if the patient has ties to countries in which HTLV-1 is endemic. Appropriate serological tests should be done if the patient has any combination of neurological signs and symptoms.

Research is needed to understand the mechanisms that underlie chronic nonprogression of HIV infection in these patients with dual diagnoses. Future studies should place emphasis on the microbial differences between uncomplicated HIV infection and HTLV-1/2 infection and HIV/HTLV-1/2 coinfection in a longitudinal manner. Furthermore, the role of HAM/TSP should be explored long term to allow for a better understanding of the noticeable differences in progression among these various disease entities.

**REFERENCES**

Meeting the Challenge of New Infectious Scourges: MRSA, C difficile BI/NAP1, and New Strains of STD Pathogens

Thomas Fekete, MD

Within the past decade, the incidence of methicillin-resistant Staphylococcus aureus (MRSA) has increased significantly, spreading from the hospital to the community setting. Patients with skin infections whose condition is stable should be treated with antibiotic therapy as well as with incision and drainage, whereas patients with severe disease require hospitalization and intravenous therapy. In addition to community-acquired MRSA, a new strain of Clostridium difficile, BI/NAP1, has led to clinical challenges in infectious diseases medicine. The strain has been associated with recurrent infection; more severe disease that mandates urgent colectomy; and dramatically higher mortality in vulnerable populations, such as older adults. Oral vancomycin, rather than metronidazole, may be slightly more effective in patients with severe disease. Also, new strains of Chlamydia and Treponema are posing potential complications to the treatment of sexually transmitted diseases such that clinicians need to be judicious in selecting antibiotic therapy in accordance with factors related to geography and patient population. [Infect Med. 2008;25:421-424]

Key words: Methicillin-resistant Staphylococcus aureus (MRSA) ■ Clostridium difficile BI/NAP1 ■ Syphilis

Whereas infectious diseases overall remain major threats to health in the developing world, infection control in wealthier, more technologically advanced countries generally has been handled with ease, thanks to a broad armamentarium of antibiotic agents. The complacency that has set in, however, has been shaken in recent years by the emergence of new, often antibiotic-resistant strains of bacteria. Among these threats are methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile BI/NAP1.

MRSA

Beginning in 2001, the prevalence of skin and soft tissue infections caused by MRSA greatly increased. Unlike previous MRSA infections, these infections were more severe and recurrent and affected persons who were not previously ill and who had not recently been in a hospital or nursing home (eg, active and healthy children, soldiers, athletes).

A thorough analysis of the MRSA strains showed that community-acquired MRSA (CA-MRSA) strains are closely related to one another and are unlike the traditional MRSA isolates found in hospitalized patients (Figure 1). The most common CA-MRSA strain, USA-300, contains a significant number of toxin genes as well as an adherence property previously associated with other species of Staphylococcus (including the common skin bacterium Staphylococcus epidermidis). This adherence property might account for the ease of transmission from person to person; meanwhile, the presence of the toxins may explain the severity of ill-
ness caused by CA-MRSA, including systemic illness that can lead to pneumonia or death.

Epidemiological analysis showed that the acquisition of CA-MRSA is related to both exposure opportunities and diminution of host protection. Exposure to the organism was found among close, frequent contacts living in various environments, such as dormitories, prisons, and military barracks. Transmission may have been abetted by poor hygiene (e.g., the sharing of towels and personal grooming supplies that are colonized with these adherent strains).

Reduced host defenses are a more complex risk factor. However, there is a striking association between previous antibiotic therapy and new infections with MRSA. In an outbreak of CA-MRSA skin infections among professional football players, the mean number of antibiotic prescriptions was 2.6 per year. In military recruits who were colonized on entry into boot camp, any antibiotic use during the previous 6 months was a risk factor for nasal colonization with CA-MRSA ($P = .03$). Nasal colonization resolved within weeks; however, subsequent infections developed in 38% of those with nasal colonization, compared with 3% of those without colonization.

The difference between classic *S. aureus* infection and MRSA infection can be subtle. MRSA strains have a propensity to lead to deeper soft tissue infections and pneumonia. When confined to the skin, MRSA infections can be difficult to distinguish from classic *S aureus* infections (Figure 2). Unless there is strong evidence to the contrary, MRSA should be considered in cases in which antibiotic treatment is needed. When coverage for MRSA is not possible, close follow-up should be arranged so that treatment can be changed if the patient’s condition worsens.

In the past, the classic clinical picture of a staphylococcal infection was an acutely ill patient with a localized skin lesion, such as an abscess, or a more diffuse skin infection, such as cellulitis. This infection would respond to oral antibiotics and drainage of any pus collections. In fact, incision and drainage was thought to constitute adequate management of an *S. aureus* skin abscess. Incision and drainage is still an important component of treatment, although close follow-up is needed to assess the response to drainage and to look for recurrence. Patients who have lesions that are identified early and treated medically or who have small lesions that are treated expectantly can often avoid incision and drainage.

In addition to incision and drainage, oral antibiotic therapy is recommended for stable patients. Hospitalization with intravenous antibiotic therapy is recommended for patients whose condition is unstable or who are unlikely to adhere to an oral regimen. For oral therapy, the usual choices include trimethoprim/sulfamethoxazole, clindamycin, doxycycline or minocycline (sometimes with rifampin), and linezolid.

C *difficile*

Antibiotic-associated diarrhea and colitis have long been major concerns for clinicians who care for hospitalized patients (Figure 3). Studies from the mid-1980s onward have shown that the most severe kinds of hospital-acquired colitis are related to *C. difficile* colonization (Figure 4). The presence
of this bacterium is almost uniformly associated with previous antibiotic therapy, without which the risk of *C. difficile* colitis is very low. Antibiotics that suppress the normal anaerobic flora in the gut—without also suppressing *C. difficile*—predispose patients to *C. difficile*-associated diarrhea (CDAD). Such antibiotics include clindamycin and various penicillins and cephalosporins.

In 2000, the incidence of CDAD surged. This increase was worrisome because it was accompanied by higher than usual mortality, and cases occurred in patients who had taken antibiotics not typically associated with CDAD or who had not received antibiotics. These new cases were also difficult to treat effectively without recurrence. Furthermore, the severity of the disease was associated with a greater need for urgent colectomy and with dramatically higher mortality in vulnerable populations, such as older adults.

A new strain of *C. difficile*, BI/NAP1, was detected by in vitro testing. Most isolates of this strain are highly fluoroquinolone-resistant, which may account for the high risk of CDAD in patients who receive this class of drug. Tests showed extremely high levels of the usual *C. difficile* toxins as a result of derepression of the toxin gene as well as a binary toxin gene complex that had previously rarely been found in *C. difficile*. The role of the binary toxin has not been completely illuminated. The isolates of this BI/NAP1 strain have been found predominantly in Canada and the United States (in the northeast and southeast quadrants and on the West Coast). The precise origin of the BI/NAP1 strain is unknown. The clinical manifestations of patients infected with this new strain overlap with the classic symptoms (fever, diarrhea, abdominal pain) and laboratory test results (increased white blood cell count, positive results on *C. difficile* toxin assays) of patients with *C. difficile* infection.

Treatment of infection with the BI/NAP1 strain is the same as that of classic *C. difficile* infection, but clearly there is a need for vigilance and an early change of therapy (possibly including surgery) for slow responders. Although oral metronidazole alone has been the mainstay of treatment for *C. difficile* infection, oral vancomycin may be slightly more effective for patients with severe disease. The treatment of patients who cannot tolerate oral medications is difficult; for these patients, vancomycin enemas have been suggested.

Recommended preventive strategies include:

- Limiting antibiotic use (especially
clindamycin, cephalosporins, and fluoroquinolones).
- Patient isolation.
- Zealous hand hygiene, preferably hand washing, because alcohol-based hand hygiene products are less effective against spore-forming organisms, such as clostridia.
- Environmental cleaning.

New strains of STD pathogens

Meningococcal resistance to penicillin is still very rare, and pneumococcal resistance to penicillin is not yet a critical clinical problem for patients with respiratory tract infections. However, unexpected resistance can result from unusual selection pressures.

A Dutch study reported an outbreak of lymphogranuloma venereum, a chlamydial sexually transmitted disease (STD), that occurred mostly in HIV-1-infected men who had sex with men.\(^5\) Eventually, other cases were found outside the initial Rotterdam cohort, and some have appeared in the United States. Azithromycin is preferred to treat lymphogranuloma venereum and sometimes even syphilis; however, this drug has had substantial exposure among men with advanced HIV-1 infection because it is a preventive agent for Mycobacterium avium complex (MAC) infection.

A strain of Treponema pallidum that is resistant to macrolides (including azithromycin) has been identified, and the resistance phenotype is thought to be the result of a specific, new mutation in the 23S ribosomal RNA gene.\(^8\) Researchers theorize that this ribosomal mutation is more prevalent in populations that are heavily exposed to macrolides (for management of pneumonia, MAC infection prophylaxis, and chlamydial genital infection) and that are at high risk for syphilis. Variants of this azithromycin-resistant strain have been found on the West Coast of the United States, in Maryland, and in Ireland. Azithromycin should be used to treat syphilis only in areas in which it is likely to be effective (based on regional resistance data) and in patients who can be monitored for possible failure.

Conclusion

When it comes to infections, nature does not pull her punches but instead responds to our successes in treatment with new and surprising challenges. A reflexive approach that involves aggressive use of empirical antibiotics for persons with viral or trivial bacterial infection seems harmless in the short run, but it has likely contributed strongly to our current predicament with highly resistant bacteria.

Luckily, the formula for success in treating bacterial infections already exists if we are willing to stick with it. We must educate patients to not expect to receive antibiotics for every cough or rash. We must remind one another to use bacterial cultures wisely so that we can learn about the flora in our communities and be apprised of changes, which are ongoing. We should strive to reduce the transfer of resistant bacteria in the community and in hospital settings in efforts to interrupt the chain of transmission. Finally, we need to lobby both industry and government to prioritize the development of new antibiotics to handle the current troublemakers as well as the inevitable emergence and spread of resistant bacteria that will bedevil doctors and patients in years to come.

EMERGING DRUG-RESISTANT INFECTIONS continued

Therapeutic agents mentioned in this article

- Azithromycin
- Ciprofloxacin
- Clindamycin
- Doxycycline
- Linezolid
- Metronidazole
- Minocycline
- Penicillin
- Rifampin
- Trimethoprim/sulfamethoxazole
- Vancomycin

REFERENCES

**What Is New With Ehrlichiosis?**

Jerome Goddard, PhD

*Ehrlichia* species, which are transmitted by ticks, may cause human monocytotrophic ehrlichiosis and human granulocytic anaplasmosis. Symptoms of infection include fever, headache, myalgia, progressive leukopenia, thrombocytopenia, and anemia. Diagnosis is based on clinical findings, although serological tests can identify the specific infectious ehrlichial organism. Tick repellents, particularly permethrin, can help prevent tick bites and lower the risk of infection by tick-borne pathogens. Tetracycline antibiotics are therapeutic for treatment of ehrlichial infections. [Infect Med. 2008;25:425-429]

**Key words:** *Ehrlichia chaffeensis* ■ *Anaplasma phagocytophilum* ■ *Ehrlichia ewingii* ■ Human monocytotrophic ehrlichiosis ■ Human granulocytic anaplasmosis ■ Lone Star tick ■ *Amblyomma americanum*

*Ehrlichia* species are bacteria of the family Anaplasmataceae. They are small, gram-negative, pleomorphic organisms that primarily infect circulating leukocytes. The 3 main ehrlichial species that currently cause infection in humans in the United States are *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum* (formerly *Ehrlichia phagocytophilum*), and *Ehrlichia ewingii*.

*E. chaffeensis*, the causative agent of human monocytotropic ehrlichiosis (HME), is endemic to the southeastern and southern central United States. The pathogen infects mononuclear phagocytes in blood and tissue. Strains of *E. chaffeensis*, such as the Arkansas strain and strain 91HE17, differ pathogenically.2

Since it was first recognized in 1986, HME has become an important public health issue in the southeastern and southern central United States. The average reported annual incidence is approximately 0.7 cases per million population.3 In 2007, 743 cases were reported.5

HME may cause morbidity and can result in severe illness if left untreated or if treatment is delayed. Death also is possible; the case fatality rate is approximately 2.7%.5-10 The history of a patient with HME typically includes a tick bite 2 to 3 weeks before presentation. An associated rash is uncommon, occurring in approximately 1% of patients, whereas a rash develops in approximately 80% of patients with Rocky Mountain spotted fever.11 On average, patients are men (75%) who reside in rural areas and are about 44 years of age.10

*A. phagocytophilum* infects granulocytes and causes human granulocytic anaplasmosis (HGA). It is endemic to New England and the north central and Pacific states. The average reported annual incidence of HGA is 1.6 cases per million population.3 A total of 672 cases were reported in 2007.4

Symptoms of HGA include headache, myalgia, rigors, and malaise. GI, respiratory, and CNS abnormalities occur in a minority of patients.12 Rash is rare. Opportunistic infections caused by *Ehrlichia*-associated immunosuppression may develop in the setting of HGA infection. These infections include disseminated candidiasis, herpetic esophagitis, cryptococcal pneumonitis, and invasive pulmonary aspergillosis.12,13

*E. ewingii* is primarily a dog and deer pathogen, although it occasionally causes human illness in immunocompromised patients.14 *E. ewingii* infection causes disease similar to HME but is milder and is associated with fewer complications; it has not been associated with deaths.12 The organism is endemic to the south central and south atlantic states.

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Clinical and Laboratory Findings

Clinical and laboratory manifestations of HME and HGA are similar. The patient usually presents with fever, headache, myalgia, progressive leukopenia (often with a left shift), thrombocytopenia, and anemia. In addition, there may be moderate elevations in hepatic transaminase levels. Sometimes cough, gastroenteritis, or meningitis is present. Presence or absence of a rash may help diagnosis because rash is observed only occasionally in HME and rarely in HGA or E ewingii infection.

Illness caused by E chaffeensis may be more serious than that caused by A phagocytophilum. Fatality rates are 2% to 3% for HME and less than 1% for HGA. As mentioned, ehrlichial organisms may alter the patient’s immune system, allowing opportunistic infections such as fungal pneumonia and candidiasis to occur.15

Diagnosis of ehrlichiosis mainly depends on clinical findings, although serological tests may be used to detect antibodies against the respective ehrlichial organism. A 4-fold increase in antibody titer to E chaffeensis antigen (minimum, 64) or a single serum antibody titer of 256 or higher for a patient with a clinically compatible history serologically confirms that E chaffeensis is the causative pathogen. Although not widely available, polymerase chain reaction (PCR) amplification of DNA from blood or cerebrospinal fluid using primers derived from E chaffeensis species–specific nucleotide sequences of the 16S ribosomal RNA gene13 has been used to diagnose a substantial number of cases.

HGA may be diagnosed during the acute stage of illness by visualization of Ehrlichia–laden morulae in peripheral blood neutrophils, but PCR detection of Ehrlichia DNA has greater sensitivity.13 Visualization of morulae (Figure 1), however, is extremely difficult, more so for HME than for HGA. False positives may occur because of toxic granulations, Döhle bodies, or superimposed platelets or contaminant particles that may be mistaken for organisms.

Diagnostic confirmation of HGA requires a serological reaction or a 4-fold increase in antibody titer to A phagocytophilum antigen (minimum, 80). Cross-reactivity of antibodies with E chaffeensis are diagnostically misleading, but anti–A phagocytophilum titers are consistently higher than anti–E chaffeensis titers in patients who have HGA. Because E ewingii has not yet been cultured and a specific serological test is not available, diagnosis is primarily based on molecular detection of organisms (by PCR) or on evidence of morulae in neutrophils.

Ecology of Ehrlichiosis

Ehrlichiosis is transmitted to humans by the bite of an infected tick. HME cases primarily occur within the geographic area inhabited by the Lone Star tick (LST) Amblyomma americanum (Figure 2) and the white-tailed (WT) deer. The geographic range of the LST is central Texas east to the Atlantic Coast and north to the environs of Iowa and New England.16 Although WT deer appear to be the primary reservoir and host for the ticks, other animals may become infected with E chaffeensis.17,18 In addition, domestic dogs and red foxes have been experimentally infected with E chaffeensis.19 In fact, dogs have become a suitable model for several studies of E chaffeensis.20-22 Even though the LST is the primary vector, detection of E chaffeensis in other ticks such as the American dog tick Dermacentor variabilis in Arkansas and the occurrence of HME cases in the geographic range of D variabilis suggest that ticks besides the...
LSTs may be vectors of *E. chaffeensis*. LSTs heavily populate the southern United States (Figure 3), and bites commonly occur in persons living in rural areas of that region. The incidence of HME in relation to the high incidence of LST bites suggests that the rate of infection with *E. chaffeensis* may be relatively low. In one case report, serological evidence of ehrlichial infection was demonstrated in 7 of a few hundred soldiers who had exposure to areas of extremely high LST populations. Two of the 7 soldiers became clinically ill (Mississippi Department of Health notes and records, unpublished data, 1989). Some of the soldiers who were interviewed during the study detailed how they often crawled on their stomachs through brush and grassy areas, resulting in the accumulation of hundreds of ticks on their bodies. Using a drag cloth, 31,056 ticks were collected over a 2-day period from the area in which the soldiers trained; 99.7% of the ticks were of the Lone Star species.

Only a paucity of information about the ecology of HGA is available at this time. It mostly has been diagnosed in patients from the upper Midwest and northeastern United States, although cases have occurred in southern states and California. The primary tick vector is Ixodes scapularis (some may still remember it as *Ixodes dammini*). It is the same species that transmits *Borrelia burgdorferi*, which causes Lyme disease; thus, a tick bite from this species carries with it the possibility of coinfection with Lyme disease and even babesiosis. Possible animal reservoirs of *A. phagocytophilum* include deer, elk, and wild rodents.

As for the ecology of *E. ewingii*, transmission by the LST was demonstrated experimentally in 1990. Evidence of this *Ehrlichia* species in LSTs has been shown repeatedly. *E. ewingii* can be transmitted to deer from infected LSTs, and its transmission to goats has been shown to cause clinical illness.

**PREVENTION AND TREATMENT OF EHRlichiosis**

Prevention of ehrlichiosis is essentially the same as that of Rocky Mountain spotted fever and other tick-borne rickettsial diseases (TBRDs). Personal protection techniques against ticks should be used when working or playing in the outdoors during warmer months. Tucking pant legs inside socks or rubber boots will go a long way toward keeping ticks away. In addition, insect repellents may help deter biting ticks, but not all are equally effective.

**DEET products**

Insect repellents containing the active ingredient N,N-diethyl-meta-toluamide (DEET) have been widely available for at least 40 years and have some repellency against ticks. One study demonstrated that DEET-treated military uniforms provided between 10% and 87.5% protection against ticks, depending on the species and life stage of the tick. The average rate of protection against all species of ticks was 59.8%. Obviously, protection levels in the 50% range are less than desirable, considering the fact that only 1 infected tick is required to transmit a tick-borne disease.

In a US Army repellent rating system, DEET is assigned a 2X rating, whereas permethrin products are given a 3X rating. DEET products are simply not as effective as permethrin products in protecting a person from ticks. However, the advantage of DEET is that it can be applied to human skin in places likely to make contact with ticks: ankles, legs, and arms.

**Permethrin products**

The most effective tick repellents contain permethrin, a synthetic pyrethroid pesticide with very low mammalian toxicity. It is for clothing use only, not to be applied directly to human skin. In one study, a pressurized spray of 0.5% permethrin was compared with 20% and 30% DEET products on military uniforms worn...
in a highly tick-infested area. A 1-minute application of permethrin provided 100% protection, compared with 86% and 92% protection with the 2 DEET products, respectively. In addition, permethrin has been shown to remain in clothing, providing 100% protection against ticks after several washings.

Permethrin is applied to clothing by slowly sweeping the aerosol spray over the garment until it is slightly wet (Figure 4). Label instructions should be followed. Some persons hang garments on a clothesline, spray them, and wear them after they dry. When ticks subsequently crawl on the treated clothing, they are either killed or repelled.

Permethrin is extremely effective against New World ticks, but there is some evidence that not all tick species are equally repelled by permethrin products. One Old World species, the camel tick *Hyalomma dromedarii*, exhibits a high tolerance to permethrin and an increased biting response when exposed to the substance.

**THERAPEUTIC INTERVENTION**

Dumler and Bakken point out that treatment of HME and HGA should solely consist of a tetracycline such as doxycycline (rifampin may be an alternative for patients who are allergic to tetracycline). The dosage of oral or intravenous doxycycline is 100 mg twice daily for adults and 2 mg/lb of body weight per day in 2 divided doses for children who weigh less than 100 lb (45.4 kg).

*E. ewingii* infection also has been treated successfully using the same tetracycline dosage that is used in the treatment of HME. Tetracyclines typically are contraindicated for use during pregnancy but might be warranted in life-threatening situations where clinical suspicion of TBRDs is high. Fever typically subsides within 24 to 48 hours after initiation of treatment when the patient receives doxycycline or another tetracycline during the first 4 to 5 days of illness. Failure to respond to early treatment might be an indication that the patient does not have a TBRD but another disease entity.

**REFERENCES**

2. Dumler JS, Chen SM, Asanovich K, et al. Isola-
4. Centers for Disease Control and Prevention. Provisional cases of infrequently reported notifiable diseases (< 1,000 cases reported during the preceding year)—United States, week ending March 14. MMWR. 2008;57:266.
West Nile virus (WNV) is a mosquito-borne virus that first appeared in North America in New York City in 1999. Since then, the virus has spread across the United States, causing disease in virtually every state. Arizona experienced its first cases—15 total—in 2003. In 2004, the number of proven cases increased to 391 (Craig Levy, personal communication, from the Arizona Department of Health Services, Vector-Borne and Zoonotic Diseases Program, October 4, 2005). The more than 25-fold increase in cases in 2004 was unexpected, given the hot and dry climate of Phoenix where the majority of cases occurred. We report on 34 cases that were treated in 3 community hospitals. About 68% (265 of 391) of cases of WNV infection seen in Arizona in 2004 were clustered around these 3 hospitals in metropolitan Phoenix (Figure 1).

Clinical observations
All 34 patients were initially seen in the emergency department, and all but 1 were admitted to the hospital after evaluation. After admittance, the patients were evaluated by a hospitalist. The hospitalist, in turn, made a request for an infectious disease consultation. All cases of WNV infection were confirmed serologically. A test for WNV-specific IgG and IgM in serum and a WNV IgM antibody-capture enzyme immunoassay (EIA) of cerebrospinal fluid (CSF) were performed. Antibody-capture EIA was also used to detect St Louis encephalitis virus–specific IgM antibodies in CSF. Testing for herpes simplex virus (HSV) antigen by polymerase chain reaction was performed on CSF for all cases of neu-
Invasive disease. All test results for St Louis encephalitis and HSV infection were negative.

The charts of 34 patients with confirmed WNV infection were reviewed and a consensus clinical diagnosis was made. There were 13 cases (38%) of meningitis and 12 cases (35%) of encephalitis. The distinction between meningitis and encephalitis was made on the basis of the absence or presence of mental confusion.

Typically, those patients with neuroinvasive disease classified as meningitis had fever, headache, and little or no neck stiffness. Those patients with neuroinvasive disease classified as encephalitis had fever and altered mental status. We observed that headache was less of a concern in patients with encephalitis, but patients tended to have more weakness. In addition to meningitis and encephalitis, 5 patients (15%) had unexplained fever, 3 (9%) had transverse myelitis, and 1 (3%) had carditis.

A lumbar puncture was performed in 27 of 28 patients (96%) with neuroinvasive disease. A summary of the CSF findings is given in Table 1. CSF specimens in the majority of patients (74%) demonstrated lymphocytic pleocytosis. Seven of 27 patients (26%) had CSF white blood cell pleocytosis with greater than 50% predominance of polymorphonuclear leukocytes. This initially raised suspicion of a bacterial infection; however, subsequent tests confirmed WNV infection.

The CSF protein level was above the normal range in 26 of 27 patients (96%), and CSF glucose levels below the normal range were not detected in any of these patients. The results of routine laboratory studies, such as complete blood cell count and complete metabolic panel, were similar to laboratory results reported in the literature and were not definitive for WNV infection.

Patients with suspected meningitis were administered ceftriaxone in the emergency department, admitted, and seen by a hospitalist after which they were referred to an infectious disease specialist who added acyclovir to the therapeutic regimen. Therapy was continued until clinical improvement was seen.

Because serological tests were not
performed in-house but by commercial laboratories or the Arizona Department of Health, the time between a presumptive clinical diagnosis and a confirmation of a WNV infection varied. The lag time ranged from 1 to 16 days (mean, 5.7 days; median, 5.0 days). Prolonged time to acquisition of serological test results delayed treatment and prevented the timely discontinuation of ceftriaxone and acyclovir.

Six patients (18%) were treated with ribavirin and interferon alfa 2b. Five of the 6 patients (aged 60 to 73 years) were among those patients who had encephalitis and respiratory failure. One patient (aged 58 years) had transverse myelitis.

Interferon alfa 2b at a dosage of 3 million units daily was administered subcutaneously along with ribavirin, 400 mg twice daily (ie, every 12 hours) delivered through a nasogastric tube. The therapeutic regimen continued for 2 weeks or until improvement was seen. The criteria for improvement was successful weaning from mechanical ventilation or being stable enough to be discharged from the hospital. The patient with transverse myelitis received a week of therapy, but the treatment was stopped because of lack of response. (This patient’s neurological deficit was well established at the time of interferon therapy and reversibility seemed unlikely.)

Approximately 12 months following the 2004 WNV outbreak, an attempt was made to contact the 34 patients by telephone. We were able to obtain follow-up information on 22 patients (65%), although we did acquire information on mortality in relation to the whole group. The results are summarized in Table 2. Fatigue, forgetfulness, muscle weakness, and anxiety were the main residual problems that persisted at 1-year follow-up. Four deaths (12%) attributable to WNV occurred, and at least 8 patients (36%) required inpatient rehabilitation at a skilled nursing facility or outpatient visits for physical therapy.

**Case reports**

The signs and symptoms seen in the 34 patients were similar to those typically reported for WNV infections. Two patients with atypical presentations stood out in our patient population. The first case was that of a 49-year-old woman who presented with fever and arthralgia. She did not experience headache or other neurological symptoms. She had scattered, tender skin lesions suggestive of septic emboli and a lesion on her thumb that was consistent with an Osler node (Figure 2). Her physical examination demonstrated a symmetrical, polyarticular arthritis. She did not have a cardiac murmur, but a presumptive diagnosis of endocarditis was made during the initial examination. She had an extensive workup while in the hospital that included blood cultures and

![Table 1 – CSF findings in 27 patients with neuroinvasive WNV infection](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient range</th>
<th>Results (%)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count (/µL)</td>
<td>0 - 847</td>
<td>0 - 5</td>
<td></td>
</tr>
<tr>
<td>PMN cells</td>
<td>&gt; 50%</td>
<td>7 (26)</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&gt; 50%</td>
<td>20 (74)</td>
<td></td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>18 - 195</td>
<td>26 (96), above normal</td>
<td>15 - 50</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>47 - 122</td>
<td>0 (0), below normal</td>
<td>40 - 80</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; WNV, West Nile virus; WBC, white blood cell; PMN, polymorphonuclear.

![Figure 2 – Pictured is an Osler node on the thumb of a 49-year-old woman with West Nile virus infection.](image)
a transesophageal echocardiogram, the results of which were negative.

The patient received empirical antibiotic therapy, became afebrile, and was discharged when symptoms improved. Sera taken during the acute and convalescent phases of the infection showed increases in WNV IgM antibody titers.

The second case involved a 44-year-old woman who presented with fever, chest pain, and abnormal findings on an ECG. She had no neurological manifestations. A cardiac catheterization was performed. It showed normal coronary arteries but severe left ventricular dysfunction. A global hypokinesis of the heart was present with an ejection fraction of 15%. After discharge, cardiac function improved, approaching baseline measurements. The patient had a history of recent mosquito bites, prompting WNV serological testing, the results of which were IgM antibody–positive, consistent with a diagnosis of acute WNV infection.

**DISCUSSION**

At the community level, the ability to diagnose a new or unusual disease can be difficult. In our experience, it was the initiative of the infectious disease specialist that drove the diagnosis of WNV during an epidemic that occurred in Phoenix. Although mosquitoes are present in Phoenix, the epidemic of WNV infection was somewhat surprising. Irrigation systems, swimming pools, and standing water are capable of sustaining mosquito habitats even in environments that are not particularly conducive to mosquito infestation. In our opinion, flood irrigation systems common to central Phoenix but not to outlying areas were a major factor in the high incidence of cases of WNV infection in 3 hospitals. As long as the nonimmune bird and human population densities are high enough, a WNV epidemic is possible in such areas.

We believe that some of the challenges we experienced clinically were a reflection of the disparity between public health/research communities and those directly involved in patient care. The first 15 cases of WNV infection in Arizona, which occurred in 2003, were a harbinger of things to come. As evidenced by outbreaks of WNV infection in other states, incidence of the infection the year after the initial outbreak in Phoenix should have been expected to be—and was—worse. As clinicians engaged in managing the unique epidemic in Phoenix, we did not feel adequately prepared. It is estimated that there are 150 cases of WNV infections for every hospitalized case of neuroinvasive disease, suggesting that about 50,000 cases of WNV infection have occurred in Phoenix.

One of the major challenges during the epidemic was the delay in getting serological test results. None of the 3 hospitals in our study was equipped to perform in-house WNV serological tests; outside sources had to be used for this task. Because the delay in the receipt of serological test results (mean turnaround time for serological and CSF test results was 6 days), many days passed in which clinicians dealt with a critically ill patient without a definitive diagnosis. Fortunately, because patients with similar presentations and clinical findings were being admitted every few days, the staff became more confident about making clinical diagnoses before confirmation by serological test results.

The IgM antibody-capture EIA for WNV is a relatively simple, sensitive test, and it should be readily available for use in anticipation of epidemics. Almost 5 years had passed since the first cases of WNV infection had been described in the United States, yet there was little preparedness in Phoenix. A more efficient system of diagnosis should have been available to community-based physicians throughout the country. Furthermore, more robust guidelines for treating critically ill patients should

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**Therapeutic agents mentioned in this article**

- Acyclovir
- Ceftriaxone
- Interferon alfa 2b
- Ribavirin

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**Table 2 – One-year follow-up of patients with WNV infection**

<table>
<thead>
<tr>
<th>Findings</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients contacted</td>
<td>22/34 (65)</td>
</tr>
<tr>
<td>Most common concerns</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>12/22 (55)</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>11/22 (50)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>8/22 (36)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8/22 (36)</td>
</tr>
<tr>
<td>Required supervised rehabilitation</td>
<td>8/22 (36)</td>
</tr>
<tr>
<td>Deaths attributable to WNV infection</td>
<td>4/34 (12)</td>
</tr>
</tbody>
</table>

WNV, West Nile virus.
have been developed within the 5 years between the first reports of WNV infection and the epidemic in Phoenix.

We treated 6 of the most ill patients with interferon alfa 2b and ribavirin in hopes of improving their prognosis. The recommended treatment of WNV infection is supportive care. However, when we were faced with critically ill patients who were receiving mechanical ventilation and were too weak to lift their arms and legs, empirical therapies that appeared to be beneficial seemed reasonable.

We chose to use ribavirin and interferon alfa 2b therapy because in our experience, it had been effective in patients with hepatitis C virus infection. We reasoned that because hepatitis C virus was an RNA virus belonging to the same Flavivirus genus as WNV, antivirals effective against hepatitis C virus might also be effective against WNV. We were not able to conduct a case-control study because the number of critically ill patients who received ribavirin and interferon alfa 2b therapy in our cohort was small. Our clinical impression was that interferon alfa 2b and ribavirin helped the 5 severely ill patients with encephalitis but had no effect on a patient with transverse myelitis. Additional studies are needed to confirm the usefulness of interferon alfa 2b and ribavirin and whether these agents are more effective than ceftriaxone and acyclovir in the treatment of WNV infection.

Hyperimmune globulin therapy was theoretically available to our patients but was deemed to be an unsatisfactory option because it involved moving critically ill patients to another facility for treatment. We also were of the opinion that giving immunoglobulin to immunocompetent patients who already had WNV antibodies would be of little benefit.

Data from 1-year follow-up suggests that those patients who were hospitalized for severe WNV infection will continue to have residual effects. Four of these patients (12%) died as a consequence of the infection; thus, morbidity and mortality seems to be high. We also observed that aspiration pneumonia contributed to residual problems in patients after hospital discharge.

**REFERENCES**

