

2009

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# Sand Fly Fever: What Have We Learned in One Hundred Years?

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**ABSTRACT** Sand fly fever has severely impacted military missions in southern Europe and the Middle East for hundreds of years. After a brief respite following the malaria eradication programs of World War II, it has returned as a significant disease among residents in and travelers to the Mediterranean rim. It is a more severe disease now, with potential vectors in the United States. Sand fly fever is discussed in terms of its viruses, vectors, disease, control, and potential domestic impact.

## INTRODUCTION

Sand fly diseases have elicited increased attention in domestic research and policy since Operations Desert Shield and Storm, and more recently against the backdrop of more sustained U.S. troop movements in the Middle East as a part of Operations Iraqi Freedom and Enduring Freedom. Activities generally have been focused on leishmaniasis,<sup>1</sup> including study on the possibility of importation of Old World disease into United States sand fly species.<sup>2</sup> Sand fly-borne disease also includes important viral pathogens.

Two thousand eight (2008) marks the 100th anniversary of the Austrian expedition sent to characterize Pappataciefieber—fever of the Pappataci (sand fly)—in the Balkans.<sup>3</sup> The history of the Balkans has been replete with foreign aid and invasion involving the French and Turks in the early 19th century, the Russians and Austrian-Hungarians in the late 19th century and early 20th century, and then later the Germans, Italians, and Allies.<sup>4</sup> As troops moved through this European underbelly, they suffered an entity well known to the locals. Known variably as sand fly fever, Pappataciefieber, dengue Mediterranean, evil dog (“Hundskrankheit”), *Phlebotomus* fever, and fever of the 3 days (Malta), its clinical characterization generally is credited to Pick in 1886.<sup>5</sup> However, an early manuscript on the *Phlebotomus* sand fly credits Pym in 1804.<sup>6</sup>

Recent research interest in sand fly fever has emerged because of cases of severe neurologic disease in European travelers.<sup>7</sup> However, Doerr and his colleagues understood much of what is known today about the pathogen and its disease:

- (1) Etiologic agent is a filterable virus.
- (2) Patients are infectious to the vector for 2 days.
- (3) The main vector is *Phlebotomus papatasi*.

- (4) Extrinsic incubation period is at least a week.
- (5) Incubation period is between 4 to 8 days.
- (6) First infection confers immunity (to the specific strain).
- (7) Blood from a patient infects another with a similar illness.
- (8) Hypothesis: transovarial transmission occurs in the vector.<sup>3,5,6</sup>

## The Pathogen and the Vector

The biological characteristics of both sand flies and the sand fly fever viruses result in predictable epidemiologic features. These afford opportunities for control and avoidance and so are explored here.

### Virology

Sand fly fever viruses are a heterogeneous group within the Bunyaviridae. They are enveloped, spherical viruses measuring 90–110 nm and containing three uneven negative-sense RNA strands.<sup>8</sup> These strands, named small (S), medium (M), and large (L), encode the nucleoproteins, glycoproteins, and viral RNA polymerase, respectively.<sup>9</sup> The S segment is ambisense and also encodes a nonstructural protein. Like most viruses, Bunyaviridae historically have been grouped by serotyping.<sup>5</sup> Although the viruses' G1 and G2 glycoproteins generally are responsible for the outcomes of serotyping results, the nucleocapsid is thought to be more important immunologically.<sup>8</sup>

As in most of virology, genotyping has become the standard methodology for describing the phylogeny of sand fly fever. Both the M and S segments have been used.<sup>10,11</sup> Genotyping has supported previous serotyping results. Analyses based upon both the M and S segments generally have retained the dominant groups—Sicilian, Naples, Toscana, and Punta Tora. Interestingly, although tested sand fly fever serotypes clustered closely within their own groups, groups were no more related to each other than they were to archetypal Bunyaviridae Rift Valley fever and Uukuniewi viruses.<sup>10,11</sup>

### Vector Biology

Sand flies are in the order Diptera, family Psychodidae. They have a 5- to 10-week life cycle undergoing complete metamorphosis—egg, four larval instars, pupa, and adult. The fourth instar may diapause over winter.<sup>5,12</sup> Sand fly larvae

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The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of NAVMED MPT&E, Missouri State University, Department of the Navy, Uniformed Services University, Department of Defense, nor the U.S. Government.

This manuscript was received for review in May 2008. The revised manuscript was accepted for publication in January 2009.

develop in warm, moist soil away from direct sunlight while feeding on detritus.<sup>5</sup> The larvae have a predilection for rubble and tree roots.<sup>12</sup> The adults typically are nocturnal or crepuscular (dawn and dusk) biters, some species biting in the early evening in cooler weather and then moving their activity later in hotter months.<sup>13</sup> In southern Europe and the Middle East, sand flies often reside among human populations, but in South America most species are primarily sylvatic.<sup>5</sup> Old World (Middle East and Mediterranean) vector species are primarily in the genus *Phlebotomus*, although New World (the Americas) vectors are all in *Lutzomyia*. Old World sand flies are well adapted to hot, dry habitats and are often associated with rodent burrows. In the New World, however, sand flies are more often associated with deciduous forests and established vegetation.<sup>14</sup>

Short-range fliers, sand flies rarely are found more than a few hundred meters from their larval habitat, though they have been observed traveling nearly 2.5 kilometers.<sup>12</sup> Their distribution is focal and uneven in a given surveillance area. Even a single building may have very specific and isolated sites of biting activity.<sup>15</sup> Adults are short lived, lasting less than 4 weeks in laboratory conditions.<sup>5,16</sup> Females take blood meals as part of their 6- to 8-day egg development cycles. Their blood intake per feeding is small, estimated to be between 0.3 and 0.5  $\mu\text{l}$ .<sup>16</sup>

For sand fly fever, vector competence—the ability of a vector physiologically to transmit a pathogen—is highly specific to virus strain and vector species. Most vector–pathogen studies have focused on Old World strains. Surprisingly, oral infection of the classical strains into their vectors is quite difficult. Although highly susceptible to thoracic injection of virus, experienced groups repeatedly demonstrated that in the laboratory oral infection of *P. papatasi* with sand fly fever Naples virus (SFNV) and *P. perniciosus* with sand fly fever Arbia virus (SFAV) are rare events.<sup>16,17</sup> In contrast, these same researchers observed successful oral infection of *P. perniciosus* with sand fly fever Toscana virus (TOSV).

At least two strains of TOSV circulate in some areas.<sup>18</sup> It is unclear how these multiple groups and strains developed. Unlike the cyclical antigenic shift and outbreak pattern observed in some viruses with multiple genomic segments such as influenza viruses, the lack of a vertebrate host and the slow rate of oral infection into the sand fly may lead to a slower evolution rate.

### Clinical Applications

#### Epidemiology

Southern Europe today is a focus of contemporary sand fly fever virus infection much as it was for the classically described disease of Pym and Pick. However, it has not been consistently so, and the dominant types have changed. An elegant age-cohort study in Greece, which remains endemic for sand fly fever, demonstrated that seroprevalences for sand fly fever Naples virus (SFNV) and sand fly fever Sicilian virus (SFSV) abated after the World War II era antimalaria efforts

in Europe.<sup>19</sup> Today, sand fly fever Toscana virus (TOSV) and, to a much less extent, sand fly fever Arbia virus (SFAV) dominate clinical concern.

Although TOSV has been studied for nearly 30 years, attention in the international press and clinical literature increased following severe infections in nonimmune Northern European tourists visiting the Mediterranean rim.<sup>20–24</sup> However, seroprevalence in endemic areas is high. Studies have demonstrated between 1 in 5 and 1 in 4 persons with significantly elevated IgG anti-TOSV antibody levels in regions of Spain, Cyprus, and Greece.<sup>7,25,26</sup> In contrast to these results, SFNV and SFSV had seroprevalences of 2% and 12%, respectively, in Spain.<sup>7,27</sup> Additionally, in these areas TOSV is akin to enterovirus in the United States as an important cause of aseptic meningitis, representing over 80% of such cases in Tuscany, Italy in the late 1990s.<sup>7,28</sup> Circulation of the viruses has been observed in France and Portugal, and they traditionally have occurred throughout the Middle East.<sup>5,15,29</sup> They appear to have a footing as far north as Germany as among healthcare workers and patients a seroprevalence of 1–2% was noted,<sup>7</sup> though this may be confounded by travel.

Strains in published phylogenetic analyses include clinical strains obtained in Central America and Amazonia.<sup>10,11</sup> These *Phleboviruses* continue to be identified.<sup>30</sup> However, the disease burden is thought to be low. Most of these New World species are sylvatic, and diagnostic confounders such as dengue are endemic. Both of these characteristics may contribute to less recognized disease.

Military operations have been severely impacted by sand fly fever. Attack rates up to 60% have been observed, and in World War II 6 to 10 man-days per case were lost in North Africa.<sup>3,15,25</sup> However, U.S. military physicians and entomologists were surprised by the virtual absence of sand fly fever in Operations Desert Shield and Desert Storm.<sup>31</sup> The timing of the operations during the winter and the location of troop placement were credited. In a subsequent vector study, *P. papatasi* was present in low numbers but SFNV and SFSV were not isolated.<sup>32</sup> Incidence of recognized sand fly fever in Operations Iraqi Freedom and Enduring Freedom has been low. Other sand fly-borne pathogens have been more problematic. Although visceral leishmaniasis also has been rare, cutaneous leishmaniasis incidence has been variable, and at times high.<sup>1,33,34</sup> Nearly 1,300 incident cases of cutaneous leishmaniasis were diagnosed in American military personnel deployed to Iraq and Afghanistan between 2001 and 2006.<sup>35</sup>

Animal reservoirs of sand fly fever viruses have not been found, though sporadic detection has occurred in Italian sheep, wood mice (*Apodemus sylvaticus*), and a single bat.<sup>36</sup> The presence of virus in wild-caught males (which do not take blood meals), as well as laboratory studies which demonstrate vertical passage of the viruses to progeny, implicate the sand flies as the essential reservoir.<sup>16,17</sup> When sand fly fever occurs, its epidemiology is dominated by the vector's biology, including the following observations:

- Cases are geographically clustered near typical vector habitats.
- In a nontropical area summer will be the most common season of infection.
- The secondary attack rate if observed by surveillance should be noise.
- The incubation period will be 4 to 8 days.

A variety of *Lutzomyia* sand flies populate the United States. Originally thought to be focused throughout the southern United States, foci as far north as New York have been identified.<sup>37–39</sup> Domestic *Lutzomyia* sand fly fever viruses have not been identified. *Culicoides* species are less important though recognized vectors of these viruses have been recognized in South America and elsewhere.<sup>5,10,25</sup> *Culicoides* midges can occur in enormous populations in the United States and so their potential as vectors cannot be discounted.

Sand fly fever viruses are on some biowarfare threat lists, but its Bunyaviridae cousins are of more interest, in particular Crimean-Congo hemorrhagic fever (CCHF) virus.<sup>5,25</sup> Some have speculated about the possibility of transfusion infections because of its high endemicity in some areas, and West Nile fever virus has done this despite a similarly short viremic period.<sup>40</sup> But, this has not been demonstrated.

*Clinical Manifestations*

In a manner similar to efforts in Havana against yellow fever in the same period, Doerr’s commission carefully demonstrated sand fly fever’s (likely SFNV or SFSV) characteristic 3-day temperature pattern by infecting volunteers with the serum of ill patients.<sup>3</sup> In infected patients, symptoms of meningeal irritation such as headache, photophobia, and retro-orbital pain

are common, as are anorexia, myalgia, and low back pain.<sup>25</sup> At least one European group notes observing in these patients leukopenia followed by a neutropenia, and a long convalescence complicated by depression.<sup>25</sup>

TOSV seems to have a broader clinical spectrum than SFSV and SFNV, including greater neuropathogenicity. Although most infections are subclinical or mild, Charrel and colleagues described the modern clinical experience of TOSV cases, which have presented for care (Table I).

Supportive care is selected on the basis of a presumptive diagnosis from clinical findings, probability of exposure, and the exclusion of other entities. In returning travelers with fever, malaria, typhoid fever, nontyphoidal enteric fever, bacterial meningitis, viral hemorrhagic fevers, rickettsioses, and amebiasis must first be considered as they each indicate specific interventions. Severe sand fly fever also may resemble dengue fever, West Nile virus infection, HSV encephalitis, and neuroborreliosis.

*Diagnosis and Treatment*

Rapid diagnostics are not available yet in the clinical setting. Serum samples collected at the time of presentation and later in convalescence can be assessed by agglutination assays for the presence of IgG and IgM antibodies against sand fly fever viruses. Significant cross-reactivity occurs across groups and strains, however, unless experienced research laboratories perform the tests.<sup>7,25</sup> Rapid, specific polymerase chain reaction-based assays including real-time PCR are in development and have shown both sensitivity and specificity in vitro.<sup>41,42</sup> These nucleic acid-based techniques remain research tools.

Interferon- $\alpha$  and ribavirin have been used against Bunyaviridae. New therapies are in development, including

**TABLE I.** Clinical Features of Toscana Virus and Look-Alikes

TOSV Clinical Feature: %	TOSV	Dengue Fever	Falciparum Malaria
<b>Typical</b>			
Abrupt, intense onset	70	Occurs	Occurs
Headache	100	69	50
Fever	(87)	93	81
Nausea, vomiting	(77)	76	12
Neck rigidity	(73)	Rare	Rare
Myalgias	18	50	23
CSF WBC 5–10 cells/mm <sup>3</sup> , normal glucose and protein	Most		
7-day duration of acute illness	Most	Variable	Variable
Favorable outcome	Most	Most	94, if treated early
<b>Observed in Severe Cases</b>			
Decreased consciousness	12	Rare	6
Tremors	3		
Paresis	2		
Nystagmus	5		
<b>Rare</b>			
Lymphadenopathy, hepatosplenomegaly	Occurs	Variable	Common (hepatosplenomegaly)
Erythematous rash	Occurs	53	1
Coma, death	Occurs	Rare	9

TOSV estimates from clinical features of sand fly fever Toscana virus (TOSV) described by Charrel and colleagues.<sup>7</sup> Parenthetical values are average values of ranges reported by the authors. Comparison frequencies of potential look-alikes are from returning adult European travelers.<sup>54,55</sup> Thrombocytopenia is a very common feature of both malaria and the dengue syndromes, though may not be present early in disease.

a pyrazine derivative.<sup>43</sup> The self-limited nature of most sand fly fever virus infections and a lack of clinical trials have left the role of such antiviral agents in their management an open question.

### Prevention and Outbreak Control

Personal protective measures against sand fly bites such as the use of permethrin-treated clothing, bed nets, and topical DEET against sand fly bites are efficacious.<sup>44</sup> A placebo-controlled trial performed in U.S. Army barracks outside Cairo in 1943 by Dr. Sabin and his group demonstrated both the focal nature of sand fly biting activity and a marked decrease in sand fly fever through the use of a topical repellent, dimethyl phthalate.<sup>15</sup> More recently, an entomological survey performed at Tallil Air Base in Iraq resulted in an aggressive leishmania control program before onset of human disease.<sup>34</sup> Although the program targeted vectors, it emphasized the use of personal protective measures and education. Vaccine development may be possible against TOSV as several animal models of disease recently have been elaborated.<sup>45,46</sup> Heterogeneity of sand fly fever viruses pose a challenge for broad applicability of a vaccine.

Although malaria control programs seem to have been successful in decreasing SFNV and SFSV in some areas, sand fly control differs in several aspects to *Anopheles* mosquito control. Guidelines make the following distinctions:

- Bed nets must be a fine mesh, 10 to 12 holes per linear centimeter and should be impregnated with insecticide or repellent.<sup>47</sup>
- Sleeping and evening gathering areas should be removed from sites with wood, brick, or rubble.
- Following a survey for sand flies, low lying bushes should be sprayed within 115 meters of such areas.
- A 300-meter rodent-free zone around these areas should be established.<sup>5,12</sup>

Area sprays are a sensitive political and environmental issue. However, in a recent trial of a pyrethroid spray system in the middle of a village highly endemic for cutaneous leishmaniasis, biting activity from both *P. papatasi* and the culicine mosquito *Ochlerotatus caspius* were reduced by more than 90% in a 6.5-meter diameter area.<sup>48</sup> Habitat control, personal protective measures, screened structures, and indoor residual sprays are the preferred control modalities. Indoor residual spraying (IRS) remains recommended against a variety of disease vectors including sand flies. The World Health Organization recently reversed its position on DDT use in IRS against malaria transmission, now supporting the practice.<sup>49,50</sup>

In general, indoor residual spraying and other repellent applications of DDT and pyrethroids are effective at reducing sand fly exposure in endemic areas.<sup>44,47,51–53</sup> In one study, however, *Lutzomyia youngi* and *L. columbiana* (not statistically significant for *L. columbiana*) had increased activity when 1% deltamethrin was used, a formulation successful in other

studies with different sand fly vectors.<sup>51</sup> So, some lessons of sand fly control may not be universal across species.

### Final Thoughts

Sand fly fever again is an important disease 100 years following its systematic description. Newer varieties, in particular sand fly fever Toscana virus (TOSV), dominate clinical concern. The underlying viral pathogens have evolved. Sand flies probably serve as the reservoir as well as the vector. Sand fly fever in South America is poorly described, likely sylvatic, and sporadic. Disease typically is self-limited, but neuropathogenicity with TOSV results in more serious disease than previously described by other sand fly fever virus serotypes. Diagnosis is indirect though direct PCR assays are available at research laboratories, and commercial tests are in development. Control relies upon personal protective measures and knowledge of the vector habitat.

In the United States, despite wide distribution of *Lutzomyia* sand fly species, introduction of a domestic sand fly fever reservoir has not yet occurred. It is a disease of travelers. Highly specific sand fly fever virus type and vector species tropism, as well as the slow rate of sand fly infection by blood meal, make domestic capture from a returning traveler or service member a difficult obstacle. This is particularly so as healthy patients are viremic for only 2 days.

### Key Points

- Sand fly fever is highly endemic in the Mediterranean rim, but is widely distributed.
- It is transmitted predominantly by sand flies, which have unique habitats and behaviors that can be avoided.
- Modern disease can be severe and should be considered in recently returning travelers with fever.

### Review Questions and Answers (Answers in Italics)

1. Which statement best characterizes the sand fly fever virus?
  - a. There is one virus which causes all disease.
  - b. Sicilian and Naples viruses are the most common and dangerous.
  - c. Toscana virus is widely distributed in South America.
  - d. *Its viruses are heterogeneous and comprise several groups separated by geographic area.*
  - e. It is transmitted only by sand flies of the genus *Phlebotomus*.
2. Which statement is most true regarding clinical disease caused by sand fly fever Toscana virus (TOSV)?
  - a. It is an uncommon cause of meningitis.
  - b. *Lymphadenopathy may be present, as well as an erythematous rash.*
  - c. It cannot be confused with West Nile Fever virus because weakness is not seen in these patients.
  - d. When lumbar puncture is performed, low cerebrospinal fluid glucose and elevated protein are common findings.
  - e. Death is common.

3. What might you tell a traveler regarding avoidance of this disease while visiting Cyprus or Spain?
  - a. Take ribavirin prophylaxis.
  - b. *Particularly if traveling in summer, wear light, long-sleeved clothes and pants and consider DEET use if outside in unscreened areas between evening and morning.*
  - c. Bed nets are not helpful.
  - d. Dry, rubble-filled ruins are safer from this disease than coastline.
  - e. Red wine prevents sand fly fever.

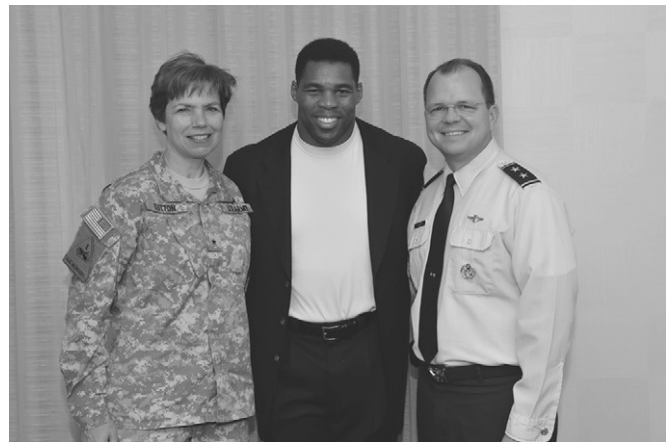
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BG Loree Sutton, Director of Defense Centers of Excellence & Former NFL Player Herschel Walker shown following a special Brain Injury Seminar



BG Loree Sutton, Herschel Walker, and Maj Gen Bruce Green, Air Force Deputy Surgeon General