EPIDEMIOLOGY OF RICKETTSIAL DISEASES

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Rickettsial diseases have a diversity of epidemiologic characteristics reflective of the variety of
ecologic situations in which the obligate intracellular bacteria are transmitted to humans. For the
spotted fever group (SFG) rickettsiae, Rickettsia typhi, R. tsutsugamushi, Coxiella burnetii, and the
human ehrlichial agent, humans are a dead-end host who plays no role in the maintenance of
the organism in nature. All rickettsioses exist as zoonoses. Moreover, all rickettsiae are found in
infected arthropods, which generally serve as the natural hosts and can transmit the infection to the
next generation of ticks, mites, chiggers, or fleas. From our anthropocentric viewpoint, Q fever
aerosol infection from parturient animals and Brill-Zinsser disease ignited epidemics of louse-borne
epidemic typhus are exceptions. However, silent cycles of C. burnetii in ticks and R. prowazekii in the
flying squirrel flea may have maintained these agents in transovarial or enzootic cycles for eons
before humans and their domestic animals arrived on the scene. Thus, the epidemiology of
rickettsial diseases must be recognized as an unfortunate aberration of the rickettsial economy.

Several excellent reviews of rickettsial ecology contain a wealth of useful information (2, 8, 55,
70, 84).

Human Ehrlichiosis

The first case of a human infection with an
organism closely related to Ehrlichia canis was
documented in 1986 (49). A 51-year-old man became ill
12-14 days after tick bites in rural Arkansas. His hospital
course was characterized by fever, hypotension,
confusion, acute renal failure requiring hemodialysis,
coagulopathy, upper gastrointestinal and cutaneous
hemorrhages, pancytopenia, and hepatocellular injury.
The diagnosis of ehrlichial infection was established by
observation of morula inclusions comprising clusters of
0.2 - 0.8 μm gram negative bacteria within cytoplasmic
vacuoles in lymphocytes, monocytes, and
polymorphonuclear leukocytes and by IFA antibodies
reactive with E. canis with titers falling from 640 to 40
in late convalescence.

Search among sera from patients initially suspected
to have Rocky Mountain spotted fever (RMSF)
revealed cases of human ehrlichiosis in several
southeastern and south central states (33, 39, 79). In
some areas endemic for RMSF, the incidence of human
ehrlichiosis and RMSF were approximately equal. One
asymptomatic patient seroconverted after being treated
prophylactically with tetracycline after tick bite.

Currently, more than 160 cases have been reported
from 19 states (15, 16, 20). There is a substantial male
predominance (74%). Although patients' ages have
ranged from 2-82 years, nearly half of patients are 50
years or older. The seasonality of onset with 50% of
cases in May and June and history of tick exposure in
more than 80% of patients support the hypothesis of a tick vector. Most cases have been rural.

Cases have been defined principally by demonstration of a significant antibody response to *E. canis*, particularly among patients with illness resembling RMSF (39, 79). Thus, the clinical case description may be biased in the proportions of patients reporting fever, headache, myalgia, anorexia, nausea, vomiting, and thrombocytopenia. However, patients with human ehrlichiosis are less likely to manifest rash and more likely to have leukopenia than patients with RMSF. Fatal cases have been reported.

Evaluation of sera from a group of Army reservists exposed to ticks in New Jersey revealed a milder illness (62). Among 9 subjects diagnosed serologically, all recalled tick bites, none were hospitalized, and 2 remained asymptomatic without any treatment. All 3 with white blood cell counts performed had leukopenia (< 3600/μl). Prospective study of febrile patients admitted to a local hospital in southeastern Georgia during the tick seasons of 1987 and 1988 evaluated 75 patients among whom 8 had ehrlichiosis (32). Frequently observed were onset in May and June (75%), history of tick bite (63%), anorexia (88%), rigors (75%), weight loss (75%), headache (63%), nausea (50%), myalgia (50%), thrombocytopenia (75%), and mildly elevated AST (100%) and ALT (75%). Less often patients had arthralgia (38%), vomiting (38%), cough (25%), diarrhea (25%), abdominal pain (25%), and leukopenia (38%). Seven patients treated with tetracycline defervesced in an average of 3 days; one patient treated with penicillin was febrile for 19 days. The incidence (5.3/100,000) was much greater than RMSF in that area.

The laboratory test upon which the diagnosis of human ehrlichiosis relies is demonstration of antibody reactive with cell culture-propagated *E. canis* by indirect immunofluorescence (18). Because sera from healthy persons seldom have antibodies reactive at a titer of 80, the diagnostic criteria are a four-fold rise or fall in titer and a peak titer of > 80. A GMT peak of 1280 occurs 6 weeks after onset; at 17-31 weeks after onset the GMT again falls to < 80. Thus, the assay appears adequate for diagnosis but not for seroprevalence studies. The specificity is less than perfect; 5% of subjects with diagnostic titers were considered not to have ehrlichiosis. Curiously, 36.5% of subjects with diagnostic titers for ehrlichiosis also have concurrent significant titers for *C. burnetii, R. rickettsii*, or *R. typhi*. No clinical, microbiologic, or immunologic explanation is apparent at present. Epidemiologic investigations will advance when we can isolate the etiologic ehrlichia, develop additional confirmatory laboratory diagnostic methods, and determine the vector tick and animal reservoir.

Spotted fever group rickettsioses

Oriental spotted fever

A human disease caused by a newly recognized species of SFG rickettsia, *R. japonica*, has been identified on 3 of the 4 major islands of Japan (Shikoku, Kyushu, and Honshu) as well as the smaller Awaji Island (34, 42, 60, 86-88, 96). The prototype strain of *R. japonica* was isolated from a 62-year-old male woodcutter who in October 1985 suffered a febrile disease with eschar and rash after a tick bite (87). Four additional strains isolated by Uchida from the blood of patients along the southeast coast of Shikoku Island were shown to be distinct from other pathogenic SFG rickettsiae by micro-immunofluorescence, species-specific monoclonal antibodies, and the electrophoretic mobility and antigenic reactivity of the surface-exposed proteins (86, 87). Similarly SFG rickettsiae isolated from this area and an island belonging to Hyogo Prefecture by Okada, Tange, and Kobayashi appear to have the same characteristics as *R. japonica* (60).

Twenty-three patients from the Muroto area of Shikoku Island diagnosed between 1983 and 1986 had an incubation period of 4-7 days, onset between April and October, and illness similar to boutonneuse fever with febrile exanthem (100%) and eschar (48%) (34). Four patients on Kyushu and Honshu islands had fever, rash, eschar, and seroconversion to SFG rickettsial antigens by IFA (42,96). This interesting newly recognized disease must be investigated to determine its geographic distribution both within and outside of Japan and to identify its reservoir and vector hosts.

Rocky Mountain spotted fever

Rocky Mountain spotted fever occurs in the U.S., Canada, Mexico, parts of Central America including Costa Rica and Panama, and parts of South America including Colombia and Brazil. A well documented series of cases representative of the RMSF in the U.S. showed that the disease occurs most often in young patients, particularly the 5-9-year-old age group, males (55%), and whites (85%) (40). The onset of 92% of cases was between April and August overall (45); however, in Oklahoma, Texas, and Arkansas 11% of cases occurred during October-March with 17% of the Texas cases in these months (81). Fatalities have been associated primarily with delay or failure to give antirickettsial treatment, absent or delayed rash, absence of history of tick exposure, older age, black race, glucose-6-phosphate dehydrogenase deficiency, and wintertime onset (5, 14, 16, 17, 29-31, 40, 90).

Active surveillance for RMSF during 1979-81 in two high incidence counties in North Carolina confirmed 98 cases with 3 deaths, an incidence of 14.6/100,000 as compared with rates of 0.2-0.3/100,000 for the U.S. overall (94). Among cases reported solely on a clinical basis, 60% were not actually RMSF. Conversely, some actual cases were not reported. Males accounted for 63% of cases. High incidence was observed not only in 5-9 year old children but also in men more than 60-years-old. Children 0-14-years-old were taken to physicians sooner (1.37 days) than person 15-years and older (2.47 days). Ticks were quite