PUBLIC AND ANIMAL HEALTH IMPORTANCE OF CRIMEAN-CONGO HAEMORRHAGIC FEVER AND OTHER TICK-TRANSMITTED DISEASES OF ANIMALS IN THE MIDDLE EAST

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Original: English

Summary: Crimean-Congo haemorrhagic fever (CCHF) was first observed in the Crimea in 1944 and 1945. The agent was detected in the larvae and in adult ticks, as well as in the blood of patients during the fever. This agent, presumably a virus, was not maintained in the laboratory and was lost. Congo virus was first isolated in Africa from the blood of a febrile patient in Zaire in 1956. Simpson showed that these viruses were similar to the one isolated in 1956. Casals then showed that the viruses isolated in cases of Crimean haemorrhagic fever and the Congo virus were serologically indistinguishable and demonstrated that other virus strains from Central Asia, the former USSR and Bulgaria were similar.

Recent changes in both demographics and living preferences have influenced the number of both animal and human tick-transmitted diseases. Increased human populations in rural areas has resulted in both reducing the number of some hosts that ticks might normally feed upon or conversely, increased the number of a particular host that ticks feed on. There are at least 840 tick species in two major families, namely the Ixodidae or 'hard' ticks and the Argasidae or 'soft' ticks. Ticks are the most important ectoparasites of livestock in tropical and sub-tropical areas, and are responsible for severe economic losses both through the direct effects of blood sucking and indirectly as vectors of pathogens and toxins. The major losses, however, caused by ticks are due to their ability to transmit protozoan, rickettsial and viral diseases of livestock, which are of great economic importance world-wide.

1. INTRODUCTION

Russian scientists first observed Congo-Crimean haemorrhagic fever in the Crimea (6) in 1944 and 1945. At that time it was established by studies in human volunteers that the aetiological agent was filtrable and that the disease in man was associated with the bite of the tick Hyalomma marginatum. The agent was detected in the larvae and in adult ticks, as well as in the blood of patients during the fever. This agent, presumably a virus, was not maintained in the laboratory and was lost.

Congo virus was first isolated in Africa from the blood of a febrile patient in Zaire in 1956. In 1967, Simpson et al. described 12 cases of a feverish illness of which 5 were laboratory infections; the virus was isolated by the inoculation of blood into new-born mice. Simpson showed that these viruses were similar to the one isolated in 1956. Casals then showed that the viruses isolated in cases of Crimean haemorrhagic fever and the Congo virus were serologically indistinguishable and demonstrated that other virus strains from Central Asia, the former USSR and Bulgaria were similar.

The virus has been classified as a Nairovirus in the genus Bunyavirus in the family Bunyaviridae. It contains RNA and is inactivated by lipid solvents and detergents. Laboratory studies have shown that Congo virus is related to Hazara virus isolated from ticks in Pakistan, and to Nairobi sheep disease virus; together they form the Nairovirus group.

In Africa, the virus has been isolated from a variety of animals, including cattle, sheep, goats, hares and hedgehogs, and from a number of ticks that parasitise them, including Hyalomma sp., Amblyomma variegatum, Boophilus decoloratus and Rhipicephalus sp.

The synonym or cross reference of CCHF is Central Asian haemorrhagic fever.
2. CHARACTERISTICS OF THE CAUSATIVE VIRUS

The virus that causes CCHF, is a Nairovirus, a group of related viruses forming one of the five genera in the Bunyaviridae family of viruses. All of the 32 members of the Nairovirus genus are transmitted by argasid or ixodid ticks. Nairovirus, Bunyaviridae, spherical, enveloped virion 85-100 nm in diameter, genome contains 3 segments of single-stranded, negative-sense RNA.

Drug susceptibility: the virus is sensitive to ribavirin

Susceptibility to disinfectants: susceptible to 1% hypochlorite, 2% glutaraldehyde

Physical inactivation: the virus is sensitive to heating at 56°C for 30 min

Survival outside host: virus stable in blood up to 10 days at 40°C

3. PATHOGENICITY AND SYMPTOMS

Sudden onset of fever, malaise, weakness, irritability, headache, severe pain in the limbs and loins and marked anorexia; vomiting, abdominal pains and diarrhoea may occur; haemorrhagic exanthem of soft palate, uvula and pharynx and a petechial rash are generally associated with the disease; bleeding from the gums, nose, lungs, uterus, intestine can occur, in some cases associated with liver damage and death due to loss of blood (4).

The mortality rate from CCHF is approximately 30%, with death occurring in the second week of illness. In those patients who recover, improvement generally begins on the ninth or tenth day after onset of illness.

4. EPIDEMIOLOGY

The geographical distribution of the virus, like that of its tick vector, is widespread. Evidence of CCHF virus has been found in the Eastern Hemisphere, Southern Europe, Near East. (3).

5. HOST RANGE

Humans, birds, ticks (Hyalomma spp. in Eurasia and South Africa), domestic animals, rodents and mosquitoes.

Tick remains infected through its developmental stages, and the mature tick may transmit the infection to large vertebrates.

Domestic ruminant animals, such as cattle, sheep and goats, are viraemic (virus circulating in the bloodstream) for around one week after becoming infected.

Humans who become infected with CCHF acquire the virus from direct contact with blood or other infected tissues from livestock during this time, or they may become infected from a tick bite.

6. MODE OF TRANSMISSION

By the bite of an infective adult tick (Hyalomma spp.); nosocomial outbreaks have occurred due to exposure to blood and secretions; infections also associated with slaughtering infected animals.

Many birds are resistant to infection, but ostriches are susceptible and may show a high prevalence of infection in endemic areas.

Animals become infected with CCHF from the bite of infected ticks.

A number of tick genera are capable of becoming infected, but the most efficient and common vectors appear to be members of the Hyalomma genus.
Trans-ovarian transmission occurs from infected female ticks to offspring via eggs.

Venereal transmissions have been demonstrated amongst some vector species, indicating one mechanism, which may contribute to maintaining the circulation of the virus in nature. However, the most important source for acquisition of the virus by ticks is believed to be infected small vertebrates on which immature Hyalomma ticks feed.

Incubation Period: Usually 1 to 3 days (Range 1 to 12 days)

Communicability: Highly infectious, especially through the nosocomial route. Infective ticks remain so for life.

Reservoir: Hares, birds, ticks, rodents, domestic animals

Vectors: Ticks (Hyalomma spp.).

Humans are not bitten by the immatures ("seed" or "pepper" ticks) of Hyalommas (14).

Other ticks can transmit, but there seems to be a particular link with Hyalommas, and this has certain epidemiological consequences, relating for instance to the host preferences of the immature and adult ticks (that differ from ticks of other genera).

Surveillance: Monitoring for symptoms; confirmation by serological analysis and virus isolation from blood sample.

7. DIAGNOSIS

Antibody detection and PCR were very efficient in rapid laboratory confirmation.

Diagnosis is suggested on clinical grounds when the patient has a history of tick bites or of exposure to ticks in the environment, and after an incubation period of 2-7 days develops an illness of sudden onset of muscle pains, headache, fever and a rapidly evolving severe illness with the development of a haemorrhage state with bleeding from the mucous membranes and petechiae in the skin, associated with thrombocytopenia and leucopenia.

The diagnosis may be confirmed in the laboratory by intracerebral inoculation of baby mice with blood of a patient; the mice sicken about 1 week after inoculation.

The virus is identified by using known specific Congo virus antiserum in an immunofluorescent test.

The development of antibodies in patients' serum as the illness progresses may be demonstrated in immunofluorescent tests using chamber slides with tissue culture cells infected with Congo virus.

8. FIRST AID AND TREATMENT

Treatment of CCHF is mainly supportive.

The role of prophylactic plasma, ribavirin and interferon in reducing the severity of illness could not be evaluated in this situation.

Although its efficacy is not firmly established, some reports suggest a beneficial role for plasma therapy, especially when administered early in the course of illness.

Antiviral drugs, such as ribavirin, are of potential use in the treatment of CCHF, but they have yet to undergo clinical trials.

9. PREVENTION AND CONTROL

Although an inactivated, mouse brain-derived vaccine against CCHF has been developed and used on a small scale in Eastern Europe, there is no safe and effective vaccine widely available for human use (18).

The tick vectors are numerous and widespread and tick control with acaricides is only a realistic option for well-managed livestock production facilities.
Persons living in endemic areas should use personal protective, such as avoidance of areas where tick vectors are abundant and when they are active (spring to autumn).

Persons who work with livestock or other animals in the endemic areas can take practical measures to protect themselves, including the use of repellents on the skin (e.g. DEET) and clothing (e.g. permethrin) and wearing protective clothing to prevent skin contact with infected tissues or blood.

Using barrier-nursing techniques is imperative with suspected or confirmed CCHF.

Sharps (needles and other penetrating surgical instruments) and body wastes should be safely disposed.

Healthcare workers are at risk of acquiring infection from sharps’ injuries during surgical procedures and, in the past, infection has been transmitted to surgeons operating on patients to determine the cause of the abdominal symptoms in the early stages of (at that moment undiagnosed) infection.

Healthcare workers who have had contact with tissues or blood from patients with suspected or confirmed CCHF should be followed up with daily temperature and symptom monitoring for at least 14 days after the putative exposure.

Keeping the birds free of ticks for 14 days before slaughter could prevent the occurrence of infection from ostriches at abattoirs.

The most widespread form of control is the use of anti-tick solutions into which animals are literally dipped – a practice that causes extreme trauma and must be repeated regularly to be effective.

Prophylaxis: Convalescent plasma with high neutralising antibody titre shown to be beneficial

10. PUBLIC HEALTH IMPORTANCE

Humans, birds, ticks (Hyalomma spp. in Eurasia and South Africa), domestic animals, rodents and mosquitoes. Only humans and new-born mice readily succumb to disease; other animals, including non-human primates, are either refractory or undergo mild infection, sometimes with transient viraemia - including sheep and cattle.

Sheep and cattle are viraemic for up to about a week, and often exposure to ticks and virus infection occurs at an early age.

Farmers may castrate, dehorn, attach ear tags or immunise the young animals, and thus expose themselves through getting infected blood onto broken skin.

Animals sometimes meet tick infestation for the first time late in life and then succumb to tick-borne diseases of livestock (such as babesiosis or anaplasmosis) at the same time as they happen to have first met the CCHF virus, and are thus viraemic at a time when they are treated, autopsied, or even butchered by farmers, veterinarians or farm workers respectively. This constitutes another type of incident leading to common source outbreaks.

CCHF, as well as other viral haemorrhagic fevers, such as Ebola virus disease, Marburg virus disease and Lassa fever, have the potential to spread in a hospital setting (15). Therefore, simple isolation procedures, such as barrier nursing on open wards, can effectively halt transmission of these viruses. It is thus imperative that diagnosis of a viral haemorrhagic fever be considered in any patient with an unknown febrile disease.

Despite the apparent lack of evidence of disease in urban consumers of meat, it remains unacceptable that CCHF infected animals should reach abattoirs to pose a potential threat to workers and the public.

Tick infested animals pose an additional threat to abattoir workers, as partially engorged ticks tend to detach from their hosts after slaughter, or from the hides and skins of the hosts, and may then attach to any humans in the vicinity.

Primary hazards: Droplet exposure of the mucous membrane to infective blood; aerosols; accidental parenteral inoculation. Ticks that detach from hides and skins at slaughterhouses, after their engorgement has been so rudely interrupted, will sometimes attach to whatever is available, and this constitutes another hazard for abattoir workers.

Special hazards: Exposure to aerosols when working with infected animals.
11. OTHER TICK-TRANSMITTED DISEASES

Recent changes in both demographics and living preferences have influenced the number of both animal and human tick transmitted diseases. The increase in human populations in rural areas has resulted in both reducing the number of some hosts that ticks might normally feed upon or conversely, increased the number of a particular host that ticks feed on. Often, when parasitic organisms are transmitted to new or different hosts, diseases may be either non apparent or more pronounced. There are at least 840 tick species in two major families, namely the *Ixodidae* or 'hard' ticks and the *Argasidae* or 'soft' ticks (7).

Identification of ticks:
- Ticks can be identified microscopically to the generic level by examining the mouthparts that consist of a spined hypostome surrounded by a pair of palps. The area where the mouthparts are attached to the cephalothorax (the base of the mouthparts) is called the basis capituli.
- The *Ixodidae* or hard ticks are characterised by having a visible scutum or shield that covers all or part of the dorsal surface and mouthparts that originate on the anterior margin. *Argasidae* or soft ticks are characterised by lacking a scutum and having mouthparts that originate on the ventral surface.
- Male and female hard ticks can be separated by the presence of a complete scutum covering the entire dorsal surface of the male (below, bottom row) and a partial scutum on the female (below, top row).

Life cycle:
- Four stages are included (egg-larvae-nymph-adult). In the majority of species, the ticks drop off the host animal between stages (exceptions are one-host ticks that remain on the same animal through all stages).
- Larvae (seed ticks) hatch from the eggs and attach to vegetation to come into contact with passing animals. Larvae possess three pairs of legs. Attraction to the host is due to heat and carbon dioxide concentrations. Once on the new host, they attach and feed on blood. Nymphs and adults employ the same method of host seeking.
- Mating of adults takes place on the host while attached and feeding. Egg laying by the female tick occurs after detachment. Both nymphal and adult ticks possess four pairs of legs.

Methods of transmitting diseases:
- Ticks can transmit pathologic agents to a host by several means. They can transmit organisms from one host to another by simple mechanical transfer. This usually occurs when ticks move from one host to another and their mouthparts are contaminated with blood-containing organisms.
- Ticks can also transmit organisms biologically. This means that the infectious organism goes through some sort of development or maturation within the tick. After this occurs, the organisms can be transferred either transstadially (between stages) or transovarially (from female to offspring via the egg).
- Transstadiial transmission usually occurs in three-host ticks when one immature stage acquires the infectious agent while feeding and then maintains the infection through the next molt and transfers it to a new host the next time that it feeds.
- Transovarial transmission occurs when the female tick acquires the infection while feeding and transfers the agent to the developing ova. In this case, the newly hatched larvae are infected without having to take a blood meal. This is most common in one-host ticks.
- Some ticks employ all of the above methods of transmission while others utilise only one.

According to their blood feeding activities, ticks are of medical importance, because they can transmit many pathogenic organisms. Ticks transmit many diseases of importance to both human and veterinary medicine.
### 12. MAJOR TICK-BORNE DISEASES

<table>
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<tr>
<th>Disease</th>
<th>Causative agent</th>
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<th>Host</th>
<th>Geographical distribution</th>
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<tbody>
<tr>
<td>Tularaemia (9)</td>
<td>Francisella tularensis</td>
<td><em>A. americanum</em></td>
<td>Logomorphs (rabbits &amp; hares), rodents and beavers</td>
<td>Northern North America and Northern Eurasia (world-wide)</td>
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<tr>
<td></td>
<td></td>
<td><em>D. andersoni</em></td>
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<td></td>
<td></td>
<td><em>D. variabilis</em></td>
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<tr>
<td>Theileria (10)</td>
<td>T. Parva T. annulata</td>
<td>Ixodae</td>
<td>Wild and domestic bovidae</td>
<td>Large part of the old world</td>
</tr>
<tr>
<td>Heartwater (Cowdriosis)(11)</td>
<td></td>
<td>Cowdria ruminatum</td>
<td></td>
<td>Sub-Saharan Africa &amp; Madagascar, Caribbean and American mainland</td>
</tr>
<tr>
<td>Nairobi Sheep Disease (12)</td>
<td>Nairobi virus of the family Bunya viridae</td>
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<td>Sheep and Goats</td>
<td>East Africa, Somalia and Rwanda</td>
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<tr>
<td>Bovine Anaplasmosis (13)</td>
<td><em>A. marginale</em></td>
<td>14 tick species</td>
<td>Bovine</td>
<td>Australia, South America, South-East Asia, Middle East</td>
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<td></td>
<td><em>A. centrale</em> (Genus Anaplasma, family Anaplasmataceae, order Ricketsiales)</td>
<td>Male vectors are common in transmitting</td>
<td></td>
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</tr>
<tr>
<td>Babesiosis (Piroplasmosis) (5)</td>
<td>Babesia Sp.</td>
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<td>Wide variety of vertebrate hosts other than human</td>
<td>World-wide</td>
</tr>
<tr>
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<td>Rickettsia rickettsii</td>
<td><em>Dermacentor variabilis</em></td>
<td>Vertebrate hosts</td>
<td>Western hemisphere, although other distinct strains are world-wide</td>
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<td></td>
<td></td>
<td><em>D. andersoni</em></td>
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<td><em>I. pacificus</em></td>
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<tr>
<td>Lyme Disease</td>
<td>Borrelia burgdorferi</td>
<td><em>Ixodes scapularis</em> (= <em>I. dammini</em>)</td>
<td>Vertebrate Hosts</td>
<td>North America</td>
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<td></td>
<td><em>I. pacificus</em></td>
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<tr>
<td>Ehrlichiosis</td>
<td>Ehrlichia chaffeensis E. equi</td>
<td><em>D. variabilis</em></td>
<td>Human and wide variety of animals</td>
<td>World-wide</td>
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<td></td>
<td></td>
<td>Amblyomma americanum</td>
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<td><em>I. scapularis</em></td>
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<tr>
<td>Tick paralysis</td>
<td>Toxins</td>
<td><em>D. andersoni</em></td>
<td>Human and animals</td>
<td>Numerous species of ticks world-wide</td>
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<td></td>
<td></td>
<td><em>D. variabilis</em></td>
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<tr>
<td>Tick-Born Encephalitis (1)</td>
<td>Arbovirus</td>
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<td>Human</td>
<td>Eastern and Central Europe</td>
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<td></td>
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<td><em>I. ricinus</em></td>
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### 13. PUBLIC AND ANIMAL HEALTH IMPORTANCE

**Economic importance**

- Ticks are the most important ectoparasites of livestock in tropical and sub-tropical areas, and are responsible for severe economic losses both through the direct effects of blood sucking and indirectly as vectors of pathogens and toxins. Feeding by large numbers of ticks causes reduction in live weight gain and anaemia among domestic animals, while tick bites also reduce the quality of hides (2).

- The major losses, however, caused by ticks are due to their ability to transmit protozoan, rickettsial and viral diseases of livestock, which are of great economic importance world-wide. Losses to the livestock industry, in particular the production of cattle and small ruminants in tropical and sub-tropical areas, have been estimated to be in the range of several billions (109) of US dollars annually. In many developing countries, tick-borne protozoan diseases (e.g. theilerioses and babesioses) and rickettsial diseases (e.g. anaplasmoses and cowdriosis and tick-associated dermatophilosis) are major health and management problems of livestock in many developing countries.
Medical importance

- Changes in both hunting and trapping laws and social changes related to many wild animals’ products have also influenced the numbers and diversity of many animal species. Consequently, these changes have placed both humans and their pets in more direct contact with wild animals and the ticks that feed on them.

- All ticks are obligate ectoparasites of vertebrates. The family Ixodidae comprises approximately 80% of all tick species and the economically most important ixodid ticks on livestock in tropical regions belong to the genera of Hyalomma, Boophilus, Rhipicephalus and Amblyomma.

- *Hyalomma* species are abundant in semi-arid zones, where they transmit *Theileria annulata*, the causative protozoan pathogen of tropical theileriosis. The distribution of this disease reaches China to the east, and Spain and Mauritania to the west.

- *Boophilus* species are one-host ticks that occur in all tropical and sub-tropical regions of the world, where they feed preferably on cattle. They are the main vectors of the *Babesia* species, *B. bovis* and *B. bigemina*, causing babesiosis in cattle. Boophilus ticks, together with many other tick species, transmit *Anaplasma marginale*, the rickettsia that causes anaplasmosis of cattle on all continents.

- Most *Rhipicephalus* species are found on mammals on the African continent. *R. appendiculatus* is the most important rhipicephalid tick in eastern and southern Africa, where it occurs on a wide variety of domestic and wild ruminants. It is the vector of *Theileria parva*, the causative agent of East Coast fever and related disorders.

- *Amblyomma* ticks are 3-host ticks that are widespread in tropical and subtropical zones, where they parasitise a wide variety of mammalian hosts, but also reptiles and amphibians. Immatures of some species infest birds, which can play an important role in dispersing the ticks. *A. variegatum* is the most important species on the African continent. *A. hebraeum* is another important pest of livestock that inhabits the south-eastern part of the African continent. In addition to its widespread distribution in Africa, *A. variegatum* has been introduced into the Caribbean region.

- *Amblyomma* ticks are vectors of cowdriosis (or *heartwater disease* of cattle and small ruminants), one of the most important tick-borne diseases in Africa. Furthermore, severe forms of cutaneous dermatophilosis (due to the bacterium *Dermatophilus congolensis*) are associated with the presence of this tick (although it is not a vector).

- Although pet animals such as dogs and cats can become infected with many of the same tick-transmitted organisms as humans and are often heavily infested with ticks, rarely do these animals play a role in either increasing the likelihood of human infections nor are they the source of infected ticks that might feed on humans.

- Viruses of the Tick-Borne Encephalitis complex occur across Europe to North-East Asia and are the cause of significant losses in small ruminant production. Thogoto virus, which can be transmitted by Ixodid ticks, has been associated with abortion storms in sheep; it may contribute to the large proportion of abortions that are due to unknown causes. Nairobi sheep disease is the most pathogenic virus disease known for sheep and goats in East Africa. *Ganjam virus* in India may ultimately be shown to be a significant cause of disease in small ruminants. Some unidentified Orbiviruses have been found both in ticks and sick sheep, and are thought to be a cause of some losses in African sheep and goats. Small ruminant populations in both Africa and Asia are vertebrate host for *Congo-Crimean haemorrhagic fever*.

- Tick-borne encephalitis (TBE) is a classical obligatorily transmissible viral infection with natural focality, which is widespread mainly in Eurasian forests of the temperate zone. Its main long-term reservoirs and vectors in natural foci are *Ixodes persulcatus* and *I. ricinus* ticks. Boundaries of the virus range and the location of natural foci within it are closely associated with the distribution pattern of these ticks (8).

- The epidemiological concept of tick-transmitted diseases has increased in importance with the recognition of the emerging infectious diseases, *Lyme borreliosis*, human monocytotropic and granulocytotropic ehrlichioses, and three different babesioses. Effective public health control of these diseases would depend upon critical knowledge of the vector biology of the ticks that transmit them. Rocky Mountain spotted fever and the human ehrlichioses are life-threatening yet treatable diseases. A major problem remains establishment of the diagnosis when treatment decisions are being made. Clinical manifestations, other than erythema migrans for *Lyme borreliosis*, do not provide strong diagnostic clues. Ehrlichiae or babesiae are often not detected in peripheral blood smears. Frequently, there are no antibodies to these diverse agents at the time of presentation, and isolation does not yield sensitive and timely results. Polymerase chain reaction, still a research tool, promises the greatest sensitivity, specificity and timeliness. Prevention by vaccines is not yet a reality, although OspA-based vaccines offer hope for the prevention of Lyme disease (17).
- Tick control has become less reliable, because acaricides are expensive, resistance has developed to many of them, regulations regarding cattle movement and quarantine are not strictly enforced, and management and maintenance of dips and spray races are often poor. More reliable systems are desirable, and vaccination should provide better control of theileriosis.

- Anaplasma spp. are transmitted either mechanically or biologically by arthropod vectors. A review based on a careful study of reported transmission experiments lists 14 tick species as capable of transmitting *A. marginale* experimentally. These are *Argas persicus*, *Ornithodoros lahorensis*, *Boophilus annulatus*, *B. decoloratus*, *B. microplus*, *Dermacentor albipictus*, *D. andersoni*, *D. occidentalis*, *D. variabilis*, *Hyalomma excavatum*, *Ixodes ricinus*, *Rhipicephalus bursa*, *R. sanguineus* and *R. sinus*. The researchers concluded that some reports, including those incriminating *R. bursa*, *H. excavatum* and *O. lahorensis*, were not entirely convincing, and that the ticks identified as *A. persicus* were probably either *A. sanchezi* or *A. radiatus*. In addition, *Rhipicephalus e. evertsi* and *Hyalomma m. rufipes* have been incriminated as experimental vectors in South Africa. While a few cases of successful transovarial transmission have been described, it seems that stadial or trans-stadial transmission is the usual method, even in the one-host *Boophilus* species. Male ticks may be particularly important as vectors. Experimental demonstration of vector competence does not necessarily imply a role in transmission in the field. However, *Boophilus* species are clearly important vectors of anaplasmosis in countries such as Australia and countries in Africa, and there is fairly good evidence that some species of *Dermacentor* are efficient vectors in the United States of America.

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