UPDATE

Human granulocytic ehrlichiosis in Europe

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Ehrlichiosis comprises a group of emerging tick-borne infectious diseases caused by obligate intracellular Gram-negative bacteria that infect leukocytes. Infections caused by members of the genus *Ehrlichia* have been described in animals and humans, but to date there are no convincing reports of the presence of other types of human ehrlichiosis different from human granulocytic ehrlichiosis (HGE) in Europe. The European vector is the same as that of Lyme borreliosis, the hard tick *Ixodes ricinus*, and HGE has a similar epidemiology to that of *Borrelia burgdorferi* infection. Across Europe, *I. ricinus* is infected to a variable extent (0.4–66.7%) with the causative agent *Ehrlichia* (*Anaplasma*) *phagocytophila* genogroup, and since its first description in Slovenia in 1997, details of 15 patients have been published. Diagnosis requires careful consideration of all circumstances and symptoms (history of tick bite and the presence of a flu-like syndrome with variable degrees of anemia, thrombocytopenia, and leukopenia, and elevated liver enzymes). Some differences can be seen between US and European HGE patients. European HGE cases have a less severe course, and the presence of morulae is uncommon. In Europe, verification of HGE has been based on PCR and immunofluorescence antibody tests, because no isolation from humans has been reported.

Keywords Ehrlichiosis, ehrlichia, human granulocytic ehrlichiosis

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Tick-borne diseases (TBDs) represent a public-health problem of growing importance. The emergence and recognition of an increasing number of new TBDs in recent years highlights the significance of this zoonosis [1,2].

Ehrlichiosis comprises a group of emerging infectious TBDs caused by obligate intracellular Gram-negative bacteria that infect leukocytes. Some of these have been demonstrated to be human pathogens [3,4]. The species mainly implicated in human diseases are shown in Table 1.

The causative agent of human granulocytic ehrlichiosis (HGE) still has no name but is closely related to *Anaplasma phagocytophila* (formerly *Ehrlichia phagocytophila*) and *Ehrlichia equi* (*E. phagocytophila* genogroup) [3]. To date, there are no convincing reports of the presence of human ehrlichiosis different from HGE in Europe [1,5–7]. Its vector in Europe is the tick *Ixodes ricinus* [1,4,5,8–20]. In this update, we review HGE in Europe, and we will make reference to US series when there are differences. Obviously, the increase in travel between continents increases the risk of other types of human ehrlichiosis.

The first description of HGE was communicated in the USA in 1994 [3,21], and since then about 600 cases have been reported [22]. In Europe, we have had knowledge of animal infections with ehrlichias of the *E. phagocytophila* genogroup have been acknowledged since before the middle of the last century [5], and the first (serologic) evidence of the presence of an HGE agent in humans was described in Switzerland in 1995 [23]. The first confirmed case of this infection was described in Slovenia in 1997 [24]. Since then, HGE infection has been described in Slovenia [6,7,24], The Netherlands [25], Spain [26], Sweden [27–29], Norway [29], Croatia [30], and Poland [31]. Tables 2 and 3 show the epidemiological, clinical and microbiological characteristics of the accessible reported European cases.

EPIDEMIOLOGY

The natural history of HGE is still being defined, but it is possible that the HGE agent is maintained

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Table 1 Main ehrlichiosis agents implicated in human pathology

***Ehrlichia* spp.**	**Target cell**
E. canis genogroup	
E. canis	Monocytes
E. chaffeensis	Monocytes
E. ewingii	Granulocytes
E. phagocytophila genogroup	
Human granulocytic ehrlichiosis agent	Granulocytes
E. sennetsu genogroup	
E. sennetsu	Monocytes

in nature in a tick–ruminant–rodent cycle. Humans are involved only as accidental 'dead-end' hosts. Most patients report exposure to ticks or tick bite between 7 and 30 days before the onset of the disease [6,7,24,26,27,31,32].

The HGE agent is transmitted by *I. ricinus*. Small mammals, in particular *Apodemus sylvaticus* (wood mouse), *Apodemus flavicollis* (yellow-necked mouse), *Sorex araneus* (common shrew) and, especially, *Clethrinomys glareolus* (bank vole) have been implicated as reservoirs of granulocytic ehrlichiae in Europe [5,14]. HGE agents have also been detected in mammals such as sheep, lambs, dogs, goats, and horses [5,15,33,34]. As in other TBDs (e.g. Lyme borreliosis (LB)), birds may play a role in the epidemiology and dissemination of HGE [35]. In birds, *Ehrlichia* DNA was detected in none of the larvae, 8% of the nymphs and none of the adult ticks, suggesting that birds are incompetent reservoirs but act as carriers [35].

Depending on the geographic location, the prevalence of the *E. phagocytophila* genogroup in *I. ricinus* ticks ranges from 0.4% to 66.7% [8–12, 14–20,36] (Table 4). Members of the *E. phagocytophila* genogroup have been found more frequently in adult ticks than in nymphs [9,14,15,18,36], although other workers have reported a higher percentage of infection in nymphs [12,16]. This variability could be due to geographic or environmental differences, influencing intermediate host species or reservoirs.

Table 2 Epidemiological and clinical characteristics of the European cases available

Country	**Month**	**Age/Sex**	**Tick-bite/Days**	**Clinical findings and physical examination**
Slovenia [6,24]	June	70/F	Yes/12	Fever (40 °C), headache, nausea, vomiting, malaise, myalgias, arthralgias, conjunctivitis, lymphadenopathy
Slovenia [6]	June	59/F	Yes/21	Fever (41 °C), chills, headache, vertigo, nausea, malaise, myalgias, arthralgia
Slovenia [6]	July	43/M	Yes/7	Fever (40 °C), chills, headache, vertigo, nausea, malaise, myalgias, arthralgia, cough
Slovenia [6]	August	55/F	Yes/30	Fever (39.3 °C), headache, vertigo, nausea, malaise, myalgias, arthralgia, vomiting
Slovenia [32]	August	36/M	Yes/15	Fever (39.2 °C), malaise, headache, chills, lymphadenopathy, hepatosplenomegaly
Slovenia [7]	February	11/F	Yes/9	Fever (38 °C), fatigue, headache, nausea, abdominal pain, conjunctivitis, erythematous throat
The Netherlands [25]	September	58/M	No	Fever (39.8 °C), chills, diarrhea
Spain [26]	August	19/M	Yes/15	Fever (39 °C), malaise, headache, myalgias, abdominal pain
Sweden [27]	August	5/F	NA	Fever, headache, facial palsy
Sweden [27]	October	41/M	NA	Fever, headache, dyspnea, cough, conjunctivitis, rash
Sweden [27]	August	32/F	Yes/>30	Fever, chills, headache, stiff neck
Sweden [28]	October	41/M	No	Fever (39 °C), myalgias, headache, cough, dyspnea, conjunctivitis, rash
Poland [31]	June	40/F	No	Fever (39 °C), malaise, headache, nausea, hepatomegaly
Poland [31]	July	41/M	Yes/7	Fever (40 °C), headache, vertigo, nausea, weakness, hepatomegaly
Poland [31]	July	22/M	Yes/7	Fever (39.2 °C), headache, nausea, vomiting, abdominal pain, diarrhea, splenomegaly

NA, not available.

Table 3 Analytic and microbiological characteristics, and outcome of the European cases available

Country	ESR (mm/h)	Leukocyte ($\times 10^3$/mL)	Platelet ($\times 10^3$/mL)	CRP (mg/L)	AST/ALT (U/L)	Morulae	Morulae	Hospital (admission)	Treatment	Outcome
Slovenia [6,24]	11	6.0	118	58	30/14	No	IFA^+, PCR^+	No	No	Favorable
Slovenia [6]	24	3.4	37	179	38/37	No	IFA^+, PCR^+	Yes	Yes	Favorable
Slovenia [6]	54	10.9	219	83	100/107	No	IFA^+, PCR^-	No	Yes	Favorable
Slovenia [6]	11	1.9	60	12	16/13	No	IFA^+, PCR^+	Yes	Yes	Favorable
Slovenia [32]	8	2.1	86	30	38/109	No	IFA^+, PCR^-	Yes	No	Favorable
Slovenia [7]	NR	2.3	90	39	NR	NA	IFA^+, PCR^+	Yes	No	Favorable
The Netherlands [25]	NR	3.4	24	NR	516/208	Yes	IFA^+, PCR^+	Yes	Yes	Favorable
Spain [26]	NA	3.0	114	NA	72/65	No	IFA^+, PCR^-	No	Yes	Favorable
Sweden [27]	NA	NA	NA	NA	NA	NA	IFA^-, PCR^+	Yes	NA	Favorable
Sweden [27]	NA	NA	NA	NA	Elevated	NA	IFA^+, PCR^+	Yes	Yes	Favorable
Sweden [27]	NR	NR	Decreased	NR	NR	NA	IFA^-, PCR^+	Yes	Yes	Favorable
Sweden [28]	NA	6.3	210	95	27/37	No	IFA^+, PCR^+	Yes	Yes	Favorable
Poland [31]	24	7.7	191	42	39/69	No	IFA^+, PCR^+	Yes	Yes	Favorable
Poland [31]	11	4.9	151	NA	57/122	No	IFA^+, PCR^-	Yes	Yes	Favorable
Poland [31]	3	2.2	74	3	107/75	No	IFA^-, PCR^+	Yes	Yes	Favorable

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFA, indirect fluorescent antibody assay; NA, not available; NR, normal range; PCR, polymerase chain reaction; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

The epidemiology of HGE is very similar to that of LB, and tick bite is the main risk factor for HGE; however patients with no recognized tick bite, such as butchers who cut deer carcasses, and hunters in contact with infected deer blood, also constitute a risk group in the USA [37–39]. Transfusion transmission of ehrlichiosis is biologically plausible [40,41], and perinatal transmission of the agent of HGE to human infants has been documented outside of Europe and may have resulted from transplacental spread [42].

In Europe, human seroepidemiologic surveys of the HGE agent have found prevalences of antibodies of 0–2.9% in blood donors and 1.5–21% in tick-exposed individuals (Table 4) [5,16,23,27,43–55].

The majority of cases in which the authors comment on seasonality (Table 2) occurred between June and August (73%), a period of higher activity of the vector in these areas. In 67% of patients, there was a history of tick bite seven to 30 days before the onset of the disease [6,7,24,26,31,32]. The median age was 38 years (range 5–70 years); nearly 20% of patients were less than 20 years old, and 53% of cases occurred in men. Similar findings have been reported from the USA [22,56,57–60]. In Table 5, we show some differences between two large US series and between these and the cases reported in Europe.

CLINICAL MANIFESTATIONS

After infection, very few individuals develop symptoms, and it seems that HGE cases in Europe are less severe than those in North America. Clinically, Human Monocytic Ehrlichiosis (HGE) can be indistinguishable from HME. In most patients, ehrlichiosis consists of flu-like symptoms (fever, myalgias, arthralgias, and headache). Physical examination reveals a few abnormalities, such as conjunctivitis and lymphadenopathy [6,7,24,27,28,32].

In the USA, a rash occurs in approximately one-third of patients with HME, but is less common in patients with HGE (1–11%) [22,56,58]. In Europe, only two patients with rash have been reported [27,28]. Thus, a difference between tick-borne rickettsiosis and LB is the absence of skin lesions in the majority of cases in the former. Table 5 shows other manifestations that can accompany the illness in a low percentage of patients.

Pulmonary manifestations include dry cough, pneumonia (clinical characteristics of atypical pneumonia) [6], and the presence of pulmonary

Table 4 European seroprevalence in *Ixodes ricinus* ticks and human sera

Country	*I. ricinus* ticks	Human
Bulgaria [43]		9.7%[a]
Denmark [47,54]		3.8% to 21%[a]
England [15]	1.4–9%	
France [5,17]	1.25%	1.6%[a] to 17%[b]
Germany [46]		11.4%[a] to 14%[c]
Hungary [5]		12.5%[c]
Italy [10,48]	24.4%	1.5%[b] to 8.6%[c]
Norway [12,52]	6–11.5%	10.2%[a]
Scotland [8]	0.25–2%	
Slovenia [19,44]	3.2%	15.4%[d]
Spain [9,16]	0–25% of adults; 0.4–66.7% of nymphs	0%[d] to 1.9%[d] to 2.3%[a]
Sweden [20,45,53]	6.6%	8.1%[a] to 11.5%[b]
Switzerland [14,18,23,36,49]	0.4–2.1%	7.4% to 17.1%[c]
UK [50,56]		1.5%[c] to 5%[c] to 7.5%[a]
Wales [11]	7%	

[a]Patients with Lyme borreliosis or neuroborreliosis.
[b]Patients who live in *I. ricinus*-exposed areas.
[c]Tick-exposed individuals (hunters, forestry workers, farm workers).
[d]Healthy individuals.

infiltrates [27,28]. Gastrointestinal manifestations have also been described, and include nausea, vomiting, diarrhea, and abdominal pain [6,7,24–26,31]. Hepatomegaly, splenomegaly or both are occasionally described [31,32].

Although patients can have symptoms and signs that might suggest meningeal involvement (i.e. fever, headache, and nausea) [27,31], no cases of meningitis or pathologic cerebrospinal fluid (CSF) have been reported in Europe. In US patients, there

Table 5 Characteristics, signs, symptoms, outcome and presence of morulae observed in different areas of the USA and Europe

	Europe ($n=15$) [6,7,24–28,31,32]	New York State ($n=18$) [58]	Midwestern USA ($n=41$) [56]
Male sex	53%	61%	78%
Fever	100%	94%	100%
Malaise	47%	NA	98%
Rigors, chills	27%	39%	98%
Myalgias	40%	61%	98%
Weakness	13%	NA	17%
Arthralgias	27%	61%	27%
Sweats	NA	NA	98%
Headache	93%	78%	85%
Anorexia	NA	6%	37%
Nausea	53%	6%	39%
Vomiting	20%	NA	34%
Megalies	20%	NA	NA
Abdominal pain	20%	NA	NA
Diarrhea	13%	17%	10%
Cough	20%	NA	29%
Pneumonia	13%	NA	10%
Confusion	NA	NA	17%
Seizure	NA	NA	2%
Vertigo	33%	NA	5%
Conjunctivitis	27%	NA	NA
Lymphadenopathy	13%	NA	NA
Rash	7%	11%	2%
Death	0%	0%	5%
Morulae	7%	25%	68%

NA, not available.

is no clear evidence of such processes occurring with the HGE agent [56], and when a lumbar puncture is performed, this shows normal CSF [56,61], in contrast to the case with HME [62].

Simultaneous human infections by the HGE agent and other TBD agents, such as the LB agent, babesiosis and tick-borne encephalitis virus, are possible since *I. ricinus* is the common vector [5,10–16,27,30,31,43,45–47,49,50,52–54].

COMPLICATIONS AND OUTCOME

In Europe, the clinical course of the patients is favorable (Table 3). In US series, mortality has been estimated to be 0–5% [21,39,56,58,59]. Most deaths are associated with opportunistic infections due to immunosuppression (ehrlichia-induced neutropenia) or underlying disease [21,56,63]. In Europe, so far, no death has been reported to be associated with HGE.

In the USA, 8.7–56% of patients were hospitalized [38,56,58,60]. In European series, all but three patients (80%) were admitted to hospital. Table 6 shows the complications of HGE infection. These include a sepsis-like syndrome with disseminated intravascular coagulation [21], adult respiratory distress syndrome [29,64], peripheral neuropathies [65,66], uni- or bilateral facial palsy [27,67], vertigo [6,31], pancarditis [63], pericardial effusion and tamponade [61], rhabdomyolysis [25], and severe opportunistic and nosocomial infections [21,56,63]. In the USA, there are no data on the possibility that the HGE agent can cause a chronic disease, and all but two patients recovered successfully [65,66]. A case of reinfection with the HGE agent has been described in the USA [68].

Table 6 Complications reported in Europe and the USA

Europe	USA
Vertigo	Vertigo
Facial palsy	Facial palsy
Severe opportunistic and nosocomial infection	Severe opportunistic and nosocomial infection
Adult respiratory distress syndrome	Adult respiratory distress syndrome
Rhabdomyolysis	Sepsis-like syndrome with DIC
	Peripheral neuropathies
	Plexopathy
	Pancarditis
	Pericardial effusion and tamponade

DIC, disseminated intravascular coagulation.

DIAGNOSIS

Diagnosis requires careful consideration of circumstances and symptoms. Laboratory tests typically show leukopenia, thrombocytopenia, and raised serum hepatic aminotransferase levels. Also, erythrocyte sedimentation rate and C-reactive protein can be elevated [6,56,58,69]. The diagnosis of HGE is easy when the patient remembers a tick bite and presents with a flu-like syndrome with the above analytic findings in an area where LB is endemic.

Physicians should not exclude this illness on the basis of normal analytic parameters [69]. If there is a suspicion of HGE, blood samples must be evaluated with a manual differential leukocyte count, which also permits screening for ehrlichial morulae (intracellular clumps of *Ehrlichia*) within the neutrophils [69].

HGE may be confirmed by culture, examinations of peripheral blood smears (Wright, Giemsa-stained smears), serology, or PCR on an acute-phase blood sample. In Europe, verification of HGE has been based on PCR and the immunofluorescence antibody test (IFA). No isolation from humans has been reported.

The Centers for Disease Control (CDC) established the case definition of HGE in 1997 [70], but this is being revised. Ehrlichiosis is described as an acute illness accompanied by headache, myalgias, rigors and/or malaise for which one of three laboratory criteria must be present: (1) seroconversion (four-fold or greater rise in IFA assay); (2) a positive PCR; or (3) the presence of morulae in blood, bone marrow, or CSF leukocytes, and an IFA antibody titer $\geq$64. Recently, a consensus group of experts [71] has suggested that, because a positive PCR result in the absence of either serologic evidence or the isolation of ehrlichiae could be false positive, the confirmation of a case would require both a positive PCR and detection of morulae. To date, there is no definition approved by consensus in Europe.

Culture

To date, no cultures of the HGE agent have been performed in Europe. Therefore, we will refer to the US experience, since the definitive evidence of infection is isolation of the organism in culture (HL60 leukemia cells) [61]. Cultures show a rapid development of cytopathic effects, and allow the direct visualization of the organism within five to 12 days

after inoculation. Cultures are positive in 34.8% of cases, independent of the incubation period or the characteristics of the initial symptoms [60]. Fever (>38 °C), leukopenia (<4500/mm^3), lymphopenia (<1500/mm^3) and thrombocytopenia (<160 000/mm^3) occur significantly more frequently in culture-positive cases [60]. Detection of morulae, and PCR analysis positive for the HGE agents, are most common in culture-positive cases [58,60].

Morulae

The HGE agent infects the cytoplasm of circulating leukocytes, causing intracellular clumps known as morulae. Test for detection has a high specificity but low sensitivity. The presence of morulae in stained blood, bone marrow or CSF leukocytes is evidence of the presence of ehrlichiae infection, but not for specific species, and supports the diagnosis [21,56,58]. In US patients with HGE infection, morulae are present in 25–68% of cases [56,58,60, 61]. In Europe, morulae have been detected in only one patient [25]. The success in finding morulae varies in accordance with the experience of the microscopist and the duration of the illness [22]. Morulae are usually detected in blood smears only during acute febrile episodes [56,58]. The presence of morulae correlates with the age of the patient (older than 50 years), and a positive PCR [58]. False-positive results could be due to the observation of toxic granulations or Dohle bodies.

Serology

Confirmation by IFA is the most common diagnostic technique [72]. This is a sensitive tool for laboratory confirmation of HGE in acute-phase and convalescent-phase serum samples [73]. The IFA test for HGE can be performed employing the USG3 isolate of the HGE agent grown in HL-60 cell culture as antigen [72], or based on horse granulocytes infected with *E. equi*.

In Europe, serology was positive in 80% of the cases. Of these, all but one had positive serology by the first month. In the USA, among patients with confirmed HGE (detection of morulae in blood smears, confirmation by PCR, blood culture, or a combination of these), all but one (99.2%) tested at the first month were seropositive, 98.7% became seropositive by six months, while 7.3% remained seropositive at 42 months. Neither antibiotic therapy initiated during the first week of illness nor pre-existing immunosuppressive conditions prevented a serologic response [73].

Serology may give false-positive results [74]. Cross-reactivity between the HGE agent and *E. chaffeensis* has been described in 30–53.8% of patients with confirmed or probable HGE [39,59]. To date, in Europe, there are no convincing reports of the presence of types of human ehrlichiosis different from that caused by the HGE agent [1,5–7]. This could be due to cross-reactivity between the HGE agent and other *Ehrlichia* spp., such as *E. chaffeensis* or *E. ewingii* [6,7].

Cross-reactivity to the HGE agent and other rickettsial agents (*Coxiella burnetii*, *Rickettsia rickettsii*, and *Rickettsia typhi*) has also been described [39,75].

At least in relation to other TBD-like LBs, the presence of both *Borrelia burgdorferi* and HGE agent antibodies at the same time may be explained by serologic cross-reaction, co-exposure, or co-infection [13,27,31,42,46,47,76–79]. However, Wormser et al. [80] proposed that active HGE infection could be a cause of false-positive LB serology results when ELISA and immunoblotting were employed. Further observations suggest that, for those patients with HGE, serodiagnosis is insufficient to establish the presence of co-infection with *B. burgdorferi* [81]. However, a mouse model of infection with the HGE agent showed that this infection did not induce *B. burgdorferi* serologic cross-reactions [82].

PCR

Methods based on PCR gene amplification could be useful, sensitive and rapid for the detection and identification of tick-borne pathogens from blood, ticks, and skin biopsy specimens [4,83,84]. PCR was a useful diagnostic tool in 73% of European cases. In four cases (27%), serology was positive but PCR was negative, so a negative PCR result does not exclude the diagnosis [6,26,31,32,56,58,60].

Several PCR-based molecular assays are available for the detection of the *E. phagocytophila* genogroup, and different types of primer can be employed (e.g. ge2, ge9f, ge10r) [4,6,31,53,83–85]. As with serology, the assay is not standardized.

DIFFERENTIAL DIAGNOSIS

In Europe, the differential diagnosis of TBD with acute febrile illness includes a large list of infectious processes (LB, HGE, babesiosis, tularemia,

tick-borne encephalitis, Mediterranean spotted fever, and *Dermacentor*-borne necrosis, erythema and lymphadenopathy or tick-borne lymphadenopathy). This list will depend on the geographic location, season, and presence of the vector in the area. Ehrlichiosis must be suspected in previously healthy individuals who develop fever after outdoor activity, and in patients exposed to ticks who develop fever, leukopenia, thrombocytopenia, or elevated transaminases, or do not respond to treatment with β-lactams or macrolides, especially in an LB-endemic area [23,26,27,69,86].

TREATMENT

In European HE, the outcome is favorable. In some cases, symptoms abate even without the use of antibiotics [6,7,30,32]. In any case, empirical therapy should be started without waiting for microbiological confirmation.

Many antibiotics, including doxycycline, rifampin, and fluoroquinolones (such as ciprofloxacin, ofloxacin, levofloxacin, and trovafloxacin), have demonstrated significant activity against the HGE agent [87,88]. The HGE agent is resistant to clindamycin, trimethoprim–sulfamethoxazole, and imipenem–cilastatin, as well as to ampicillin, amoxicillin, ceftriaxone, erythromycin, clarithromycin, and azithromycin [87,88], although a favorable outcome has been reported with azithromycin [6]. Chloramphenicol and gentamicin have weak inhibitory activity against the HGE agent, and should not be used [87].

The drug of choice is doxycycline (100 mg twice daily) for 7–10 days. In cases of intolerance to doxycycline, rifampin and the quinolones are useful. Rifampin can be reserved for pregnant women. Symptoms resolve by 24–48 h after the start of therapy [56,58]. In the absence of a response, diagnoses other than HGE should be considered.

PREVENTION AND PROPHYLAXIS

General procedures used for preventing other TBDs are recommended. Avoiding exposure to ticks is the best method of prevention of ehrlichiosis and the other TBDs. As for other TBDs, using insecticide sprays or repellents and wearing protective clothing are useful in reducing the risk of tick attachment [1,4,89].

Because the HGE agent can be transmitted during the first hours of tick attachment, prompt removal of the tick does not exclude the infection [90]. We do not have any knowledge of the prevention of HGE with chemoprophylaxis.

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ADDENDA

Since the review was written, new nomenclature (*Anaplasma phagocytophila*) has been proposed; see Dumler JS, Barbet AF, Bekker CP, Dasch GA, Palmer GH, Ray SC, Rikihisa Y, Rurangirwa FR. Reorganization of genera in the families *Rickettsiaceae* and *Anaplasmataceae* in the order *Rickettsiales*: unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia*, and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and 'HGE agent' as subjective synonyms of *Ehrlichia phagocytophila*. Int J Syst Evol Microbiol 2001;51: 2145–2165.

Recently, a new granulocytic ehrlichiosis has been described in Italy from *Ixodes ricinus*. This new specie has been named *Ehrlcihia walkerii* in honor to David H. Walker, see Brouqui P, Sanogo YO, Caruso G, Raoult D. ''*Ehrlichia walkerii*'' a new *Ehrlichia* detected in *I. ricinus* collected from asymptomatic humans in northern Italy. In: Pertrovee & Avsiec-Zupane, eds. International Conference on Rickettsiae and Rickettsial Disease. Lubljana, Slovenia, 2002.

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