

## Epidemiology of Rickettsiosis in Children of Almarj in East of Libya - Feb 2022

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### Abstract

### Original Research Article

**Background:** The most important tick-borne infectious disease in North Africa is Mediterranean spotted fever, which is endemic in Libya's green mountain region, with dogs serving as the main domestic reservoir. **Aim** of this study is to identify the epidemiological, clinical, and laboratory profile of spotted fever in children in the Almarj region, as well as the treatment response. **Materials and Methods:** A cohort study with prospective data collection of 60 patients visiting Almarj teaching hospital as outpatients or admitted from January 1<sup>ST</sup> 2018 to December 31<sup>ST</sup> 2019. **Results:** The median age of the 60 children was 3.3 years. The 55% were males. A tick-bite history were given in three cases. Majority of the cases had direct contact with domestic animals, all had a high-grade fever and rash (purpuric in 29% and 71% maculopapular). Arthralgia, myalgia affect the joints and muscles of the lower limbs in the majority of cases. One case with Hepatomegaly. In our sample, white blood cell count 56% was normal and thrombocytopenia in 37% of the patients. A mild hyponatremia was the most common electrolyte disturbance 56.9%. High liver enzymes in three cases. The antibiotics used in treatment were well tolerated and there were no deaths. **Conclusions and Recommendations:** Spotted fever group Rickettsiosis (most likely type is Medritanian spotted fever) is common in Almarj area, and it is curable. Rickettsia should be considered as a possible diagnosis of any febrile disease in summer or spring even before the rash appearance, or when there is no rash at all, particularly in those living in rural areas. The oral antibiotics (doxycycline and azithromycin) had a great response.

**Keywords:** Almarj teaching hospital, epidemiology, East of Libya, tick-borne, Mediterranean spotted fever.

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## I. INTRODUCTION

Rickettsiosis is a treatable tick-borne disease caused by rickettsiae belonging to the tick and mite-fever group (SFG) rickettsiae [1]. There are over twenty species and different forms of rickettsiae [2]. Based on serology and the presence or absence of the outer membrane protein A gene, divided to the typhus group (TG) and the spotted fever group (SFG) [3]. Rocky Mountain spotted fever (RMSF) is caused by Rickettsia rickettsii, while Mediterranean spotted fever (MSF) or Boutonneuse fever (BF) is caused by Rickettsia conorii; Oriental spotted fever is by Rickettsia japonica; African tick bite fever is by Rickettsia africae; mite-transmitted rickettsialpox is by Rickettsia akari; and cat flea-borne rickettsial pox by Rickettsia felis [4]. The genus is gram negative, an intracellular bacterium, between April and September [5, 6]. Ticks Habitats as wooded areas, stray dogs and rodents are the focus of infection in rural and urban areas [7]. Is highest among males and all ages [8].

The clinical features in the epidemiologic setting, symptoms in an endemic area in the spring or summer diagnostic [9]. Symptom on 2 -14 days of tick bitten [10]. The dose of the inoculum and the longer the tick is attached risk of transmission [11, 12]. Humans infected when remove an attached tick, because fluids rubbed into bite wound or conjunctivae by contaminated fingers [13]. A host factors increase in severity; older people, male gender, glucose-6-phosphate dehydrogenase (G6PD) deficiency [14]. Race linked to death, it is difficult to rule out that, a delay in finding or antimicrobial plays a role in death [15], have a broad spectrum of severity, RMSF is the most virulent, young and healthy people may die, while BF is milder [16]. Vaccines are still a low priority due to of successful antibiotics [17]. Rickettsiosis is highly prevalent in poor countries, and antibiotic resistance [18, 19]. Ticks require 4-6 hours before transmitting infection, proper

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tick removal technique, bathing soon and immediate cleaned are effective [20, 21].

Mediterranean spotted fever (MSF) common in North Africa and transmitted by brown dog tick [22] is endemic to the Mediterranean basin among the European countries with high *R. conorii* rates Middle East [23, 24].

The incubation period 1-16 days, with high fever, a maculopapular rash, myalgia/ arthralgia, vomiting, or diarrhea. Regional lymphadenopathy in children [9]. The case fatality rate 9% of children and can be severe [10]. Immunofluorescent tests (IFA), PCR, serologic positive within the 1<sup>st</sup> week are diagnosis of MSF [28]. The IFA is the gold standard test [12]. Treatment started empirically within the first week in suspected cases without waiting for laboratory result, as morbidity increases with the delay (doxycycline) [13]. Fever persisting beyond 48 hours of initiation of doxycycline should consideration of alternative diagnosis, and medication stopped 2-3 days after the patient is afebrile [14]. Sulfonamides increased mortality [15], azithromycin effect because achieves higher intracellular concentrations [16]. No role of antibiotic prophylaxis [17]. Spotted fever group rickettsiosis is common in the Almarj region of northeast Libya, but the true incidence of childhood Rickettsiosis disease is uncertain. Since scarce our country's resources, no serological confirmation so the diagnosis based on epidemiology, clinical symptoms and nonspecific investigations.

## II. OBJECTIVE

1. To determine the clinical, laboratory, and epidemiological characteristics of rickettsia in the patients being studied.
2. To determine the treatment's clinical effectiveness.

## III. MATERIALS AND METHODS

Patients who visit Almarj teaching hospital (in eastern Libya, about 100 kilometers from Benghazi) as outpatients or as inpatients were studied in a cohort study with prospective data collection (January 1<sup>st</sup> 2018

and to December 31<sup>st</sup> 2019). Diagnostic management services for common paediatric health conditions are available in the pediatric department. Seasons, age, sex, residency, and animal contact. Every patient's long-term diseases, such as diabetes mellitus, G6PD, and immunodeficiency were all taken into account. The appearance of fever, rash, headache, and vomiting are consider. Data for WBC, platelet count, and sodium levels collected using a questioner. Therapies types and outcomes were assessed. Clinical response to antibiotic evaluated on the basis of body temperature and clinical improvement. Patients admitted if, unwell, dehydrated, under two, reside far away or no caregiver. The time to defervescence was defined as the time from the beginning of antibiotic therapy to the first achievement of persistent defervescence (i.e., an axillary body temperature  $\leq 37$  °C for at least three consecutive days). Analyzed Data using SPSS version 22. Descriptive statistics; mean, standard deviation and median were used. The data was presented in the form of tables and figures.

## IV. RESULTS

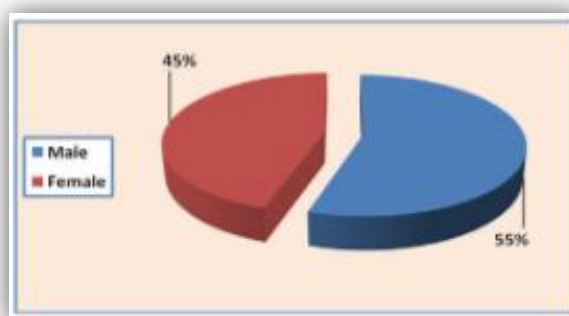
During that time, sixty cases of Rickettsia infection were clinically diagnosed, between April and September (peaking in June), indicating a strong annual seasonal pattern.

The median age was 3.3 (5 months -12 years). About 91.1% from Almarj farms, 55 % were males, 45% were admitted, 5.5 % had tick bitten and 75% having direct animals contact.

**Table 1: Distribution of patients according to age**

Age in years	N0	%
<1	3	5
1-5	39	65
6-10	15	25
>10	3	5
TOTAL	60	100

Mean age = 4.2 years. STD .Deviation = 3.1 years. Median= 3.3 years. Minimum age=5 months. Maximum = 12 years.



**Fig 1: Distribution of patients according to age**



**Fig 2: Distribution according to the months of the year**

**Table 3: History of animal contact**

History of animal contact	No.	%
Yes	45	75
No	15	25
Total	60	100

**Table 4: Source of patients**

Source of patients	No.	%
Admitted patient	27	15
From out patients department	33	55
Total	60	100

From 1 –5 days after the onset of fever, the patients were seen in the emergency department. The 100% present with a fever and rash, exanthema in 89% within 1-4 days of the fever onset as a macular on the wrists and ankles, hands, soles, then to a maculopapular on the trunk in 33.3% and face in 66.7% of cases, 29% petechial and 71% maculopapular headache and nausea in 13.3%. One patient was admitted to the hospital with mental confusion, hypertonia and facial palsy (1.7 %). The arthralgia / myalgia of the lower limbs joints and muscles, with ankle swelling 6.7%, respiratory symptoms 6.7 percent, abdominal pain, 10%, 15% had diarrhea and red eyes 21.7%. Hepatomegaly in 1.7%.

**Table 5: Distribution of clinical feature**

Clinical features	NO	%
Fever	60	100
Rash	60	100
History of tick bites	3	5
Myalgia /arthralgia	58	96.6
Conjunctivitis	13	21.7
Headache	8	13.3
Diarrhea	9	15
Vomiting	8	13.3
Abdominal pain	6	10
Respiratory symptoms	4	6.7

**Table 6: Distribution of patients according to the residency**

Residency	NO	%
Almarge farms	20	33.3
Frzoga	9	15
Bata farm	5	8.3
Sas farm	4	6.7
Almarge city	4	6.7
Aloylya	3	5
Taknis	3	5
Albnya	3	5
Tokra	2	3.3
Jardes	3	5
Temytha	2	3.3
Albyada	2	3.3
Total	60	100

**Table 7: Duration of fever before hospital visit**

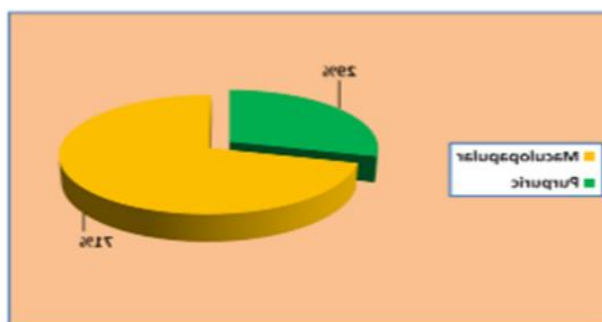
Duration of fever/days	NO	%
≤7	54	93.1
>7	4	6.9
Total	58	100

Mean duration= 4.6 days. STD .Deviation=days.  
Median= 4 days. Minimum = 1 day. Maximum = 10 days.

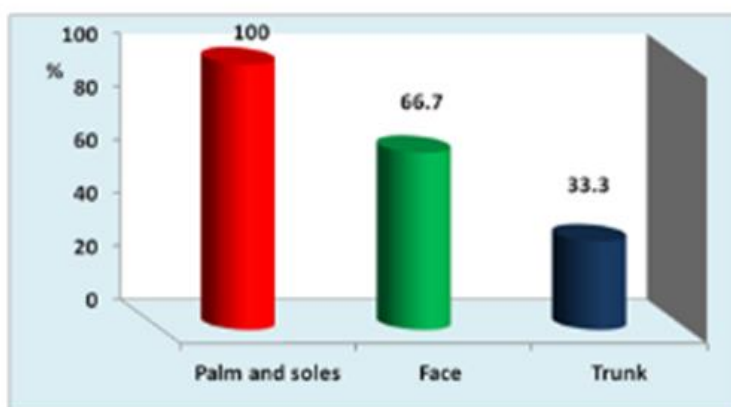
**Table 8: Duration of appearance of rash after fever**

Appearance of rash after fever/days	NO	%
1-4	49	89
5-8	6	11
Total	55	100

Mean duration= 2.6 days. Std .Deviation = 1.3 days.  
Median =2 days. Minimum = 1 day. Maximum = 7 days



**Fig 3: Type of rash**



**Fig 4: The rash sites**

In current study, 19.6% white blood cell count > 10,000/mm<sup>3</sup>, 23.5% < 5000 cells/mm<sup>3</sup>, with mild to moderate, thrombocytopenia, 15.6% platelet count < 100,000/mm<sup>3</sup>, 21.5% with 100 - 150/mm<sup>3</sup> and 78%

was a normal, with mild hyponatremia, 14.6% had a Na level 125-130 mEq/L, 130-135mEq/L, in 65.8% and 19.5% was a normal, 5% had Elevated liver enzymes.

**Table 9: White cell count (WBC)**

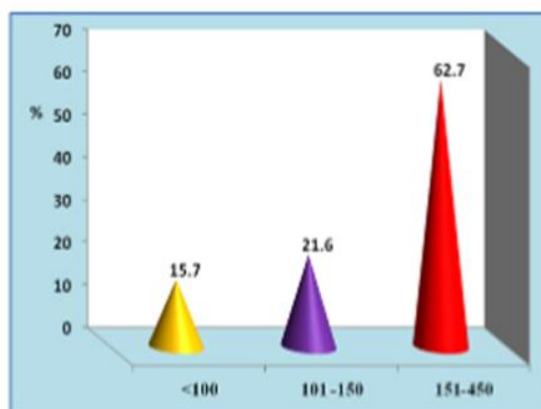
White cell count (WBC/ 10 <sup>9</sup> /L	NO	%
Leucopenia	12	23.5
Normal WBC count	29	56.9
Leukocytosis	10	19.6
Total	51	100

Mean =9.4/10<sup>9</sup>/L. Std .Deviation =9.8/10<sup>9</sup>/L. Median= 7.5/10<sup>9</sup>/L. Minimum =1.6/10<sup>9</sup>/L. Maximum =17/10<sup>9</sup>/L

**Table 11: Serum sodium level**

Serum sodium level	NO	%
<130	6	14.6
130-135	27	56.9
136-145	8	19.5]
Total	41	100

Mean =135.6. Std .Deviation =16.2. Median=132.6. Minimum =126.2. Maximum=145.



**Fig 5: Platelet count**

Both of the antibiotics used in the procedure (azithromycin and doxycycline) were well tolerated, with no signs of toxicity or serious side effects, three cases of admitted patients not respond to azithromycin and switched to doxycycline.

There were no statistically significant differences in defervescence time, in the admitted cases

(27 cases) after a mean (SD) of (46.2± 36.4 hrs.), (median, 32 hrs.); in the azithromycin group, after a mean (SD) of (39.3±31.3 hrs.), (median, 28 hrs.); in the doxycycline group. The discrepancies not statistically significant (p = 0.34). All of our patients recovered completely.

**Table 13: Time of Fever Defervescence in Admitted Cases, based on antibiotics**

Fever defervescence	Azithromycin group(10 cases)	Doxycycline group (17 cases)	p-value
Median hours	32	28	0.34***
Standard deviation	46.2±36.4	39.3±31.3	

\*\*\*statistically not significant value.

**V. DISCUSSION**

MSF is endemic to the Mediterranean region, which includes northern Africa and southern Europe. Season (summer), animals contact and travel to an endemic area are -important epidemiological factors to make a diagnosis.(22) A larger study, including both hospitalized and ambulatory patients, is needed to ascertain the true prevalence of rickettsia in our area. Disease notification by physicians is mandatory for correct epidemiologic surveillance, allowing the adoption of preventive measures. Furthermore, our study lacks data on specific laboratory test results for MSF diagnosis so some cases with no or atypical rash are expected to be missed and we depend on epidemiological criteria (season, animal interaction, and outdoor activities), a nonspecific laboratory investigation, and good response to treatment. Based on the results of the clinical trial, believed that rickettsial diseases are common in Almarj and the surrounding areas.

We reported 60 pediatric cases of spotted fever rickettsiosis in our region over 24-months, with an incidence rate that not recorded but appears to be high and higher than in Sicily, Karak Province, and Portugal. Comparing our findings to previous studies.

In our sample the age group of 1-5 years most affected; 3.3 years the median age in Sicily and Jordan was 6 years; while in Portugal and Algeria was about 4-5 years [19, 20, 23, 26]. The youngest case in our study was a 5-months, while in Sicily, was one month old.

According to other surveys, the majority of cases occurred in the summer, and 78 % of cases in rural areas. No cases during the winter. All the cases had a high-grade fever (39°C-40°C) no rigors or sweating and responded to antipyretics and the headache in older.

Arthralgia /or myalgia of the lower limbs joints and muscles in 96%, two infants were unable to articulate their discomfort, in Sicily three cases reported [19].

While a rash is a common symptom but not in all patients in the early disease stages, in our study, maculopapular the most common form while 29% was petechial, its appearance constitute an indirect measure of the delay in diagnosis and initiation of antimicrobial therapy.



In comparison to studies, maculopapular rash was in about 5% of the 415 cases without rash in Sicily with 10% of the cases in the Mexican without rash [19, 21]. In Indian, petechial in 9 and papulovesicular in 3 cases [25].

Rickettsia serology tests were positive in both cases in southern Jordan's Karak province presented with high-grade fever, seizures but no rash [23]. In Algerian and Indian studies, the main type of rash was maculopapular [23, 25]. While in Australia maculopapular, vesicular 10% and purpuric 3 % [24].

In a Portuguese report, maculonodular in 50% of cases by the third day of fever, in our study appears 1-5 days after a fever, as a macular on the wrists and ankles, palms and soles, then into a maculopapular on trunk and less to the face, in Australia the rash is global.

One case was the tache noire and the history of tick bite reported in 3 cases, compared to Mexican study, 69% in urban and 92% in poor areas, in the American study 49% had ticks bitten [21, 22]. Mild to moderate abdominal pain registered in 10% in our study, 15% in Sicily, 25% in Portugal, and 26.7% of cases in India [19, 20, 25]. Bulbar, non-exudative, non-itchy conjunctivitis red eyes were noted in 21.7 % cases, with no photophobia, No slit lamp or fundoscopy examinations. Conjunctivitis reported in 6% in Sicilia, and 10% in India. No local or generalized lymphadenopathy in our sample, 46.9% in Portuguese study, 49% in the Sicilian. In our sample, X-ray was normal, the changes from mild pleural effusion to basal consolidation, with cough and dyspnea in 28% in the Australian study [24].

In current study one patient was admitted to the hospital with mental confusion, hypertonia and facial palsy ( high grade fever and purpuric rash all over his body), thrombocytopenia, hyponatremia, leukopenia, high ESR and normal cranial MRI , recovered fully on 2wks [16]. NO CNS involvement in Indian and Australian and Portugal studies [20, 24, 28]. Furthermore, thrombocytopenia in all Jordanian sample. Our sample with a PLT count of <100,000/mm<sup>3</sup> in 15.6% [23]. While 13% in a Sicilian sample. In Indian study of meningoencephalitis, the PLT count was 17,000 cells/mm<sup>3</sup>. Low in more than half of the patients in USA and Australia [22, 24].

Our sample leukopenia in 23.5%, 56% in the Jordan and 27% in Sicily, in Algeria was in > half of cases. White blood cell count >10,000/mm<sup>3</sup> in about 19.6%. Leukocytosis were in Sicily and India. Lymphopenia in the 69% in Australia.

In our study, mild to moderate hyponatremia, with 14.6% Na level < 130mEq/L; was 52% in America. High rate of hyponatremia in Jordan. The ESR was elevated in 81.8% of our cases with 3 cases

had elevated AST and ALT compared to a Sicilian study, liver enzymes were high in 11% of cases, 61.8% in Jordan and in 89% of the Australian study.

In treatment terms, the antibiotic protocol was random, as medical schools advise using both doxycycline and azithromycin in the treatment of MSF. In 20 cases, azithromycin was given. Despite the fact that 37 of the cases were given doxycycline. Both of the medications well tolerated. Azithromycin syrup, is more practical in younger. All of the cases in our study were fully cured. Furthermore, no statistically significant difference in the time of fever defervescence between admitted patients treated with azithromycin or doxycycline.

However, in the cases when patients were treated as outpatients, showed an excellent response to treatment. The resolution of fever after two days of azithromycin therapy in Sicilian study as those treated with doxycycline and 107 cases were treated with iv chloramphenicol who could not tolerate the oral without evidence of toxicity [19].

Furthermore, no statistically significant difference in Italy study comparing azithromycin and doxycycline in the treatment of Mediterranean spotted fever in children [29]. In Portugal no statistically significant difference in the number of days with fever after starting doxycycline in 15.6% and azithromycin in 84.4% of children (20). In Jordan, India, America and Australia studies, doxycycline was used with clinical improvement within 48 hours [21-25].

In mortality terms, our sample no deaths recorded, because (young, healthy, patients arrive early at the hospital, suspicion index and timely implementation of treatment). In contrast, in Jordan studies; causes of death, thrombocytopenia, and multiorgan failure and late admission [23]. The 20% fatality rate in the Mexican study because delay therapy > fifth day of illness [21]. The 3 patients died and 13 had neurologic deficits in USA case [22]. Complete recovery in all cases in other studies [19, 20, 24-29].

## VI. CONCLUSIONS

1. Spotted fever group Rickettsiosis is a common disease in the green mountains Libya, it is curable.
2. The transmission is through contact with animals during the summer, spring, and seasons.
3. Characterized by a high-grade persistent fever, myalgia, arthralgia, headache,
4. Maculopapular or purpuric rash involving the palms, soles, may-red eyes, feet swelling and neurological involvement are uncommon.
5. Simple laboratory tests may aid in the diagnosis when used in conjunction with clinical features as leukocyte count, thrombocytopenia, hyponatremia.

6. Treatment that is specific and accurate i.e oral antibiotics (doxycycline and azithromycin) had a great response.
7. We a comparison of epidemiological, clinical, and laboratory characteristics of our study with studies from neighboring Libyan countries, and the lack of specific laboratory studies that aid in diagnosis and verification, that the most likely type in our region is the (Mediterranean spotted fever group).

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