

Undifferentiated Febrile Illnesses Amongst British Troops in Helmand, Afghanistan

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Abstract

Objectives: Undifferentiated febrile illnesses have been a threat to British expeditionary forces ever since the Crusades. The infections responsible were identified during the Colonial Era, both World Wars and smaller conflicts since, but nearly all remain a significant threat today. Undiagnosed febrile illnesses have occurred amongst British troops in Helmand, Afghanistan since 2006 and so a fever study was performed to identify them.

Methods: From May to October 2008, all undifferentiated fever cases seen at the British field hospital in Helmand, Afghanistan were assessed using a standard protocol. Demographic details, clinical features and laboratory results were recorded and paired serum samples were sent for testing at the UK Special Pathogens Reference Unit (SPRU).

Results: Over 6 months, there were 26 cases of "Helmand Fever" assessed and 23 diagnoses were made of which 12 (52%) were sandfly fever, 6 (26%) were acute Q fever and 5 (22%) were rickettsial infections. Four cases had co-infections and 7 cases were not diagnosed (mostly due to inadequate samples). The clinical features and laboratory results available at the British field hospital did not allow these diseases to be distinguished from each other. The exact type of rickettsial infection could not be identified at SPRU.

Conclusions: These cases probably represent the "tip of an iceberg" for British and Allied forces. More resources for diagnostic facilities and follow-up of patients are required to improve the management and surveillance of "Helmand Fever" cases; until then doxycycline 100 mg twice daily for 2 weeks should be given to all troops who present with an undifferentiated febrile illness in Helmand, Afghanistan. Patients with acute Q fever should be followed-up for at least 2 years to exclude chronic Q fever. Prevention of these diseases requires a better understanding of their epidemiology, but prophylaxis with doxycycline and possibly Q fever vaccine should be considered.

Introduction

"Undifferentiated fever", "unexplained febrile illness", "acute fever of unknown origin" or combinations of these terms are all used to describe an acute illness of less than two weeks since onset with fever (>38°C) and no specific organ focus. In the tropics and sub-tropics these are mostly caused by the infections listed in Table 1, which may be difficult to diagnose as they usually have non-specific clinical features. Even in developed countries the laboratory diagnosis of these diseases may be limited to serology tests that are often negative in the acute phase and only available from national reference laboratories. Hence the management of undifferentiated febrile illnesses is especially challenging for clinicians and requires a careful assessment of the infectious agents that a patient may have been exposed to. This requires both a detailed travel history and also knowledge of the infectious diseases prevalent in different countries.

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Undifferentiated febrile illnesses have been a threat to British expeditionary forces ever since the Crusades. Nearly all of these remain a significant threat to military personnel deployed in the tropics or sub-tropics and they are the second most common reason for British troops with infectious diseases to be medically evacuated back to the UK [1].

Protozoa

Malaria was a major problem for British troops in Asia and Africa throughout the Colonial Era with too many examples to describe here. During the Kandyan Wars in Ceylon from 1803-18 the majority of British military deaths were due to malaria ("jungle fever") and it led to outbreaks causing approximately 300 deaths in 400 soldiers from one regiment and contributed to an average annual mortality rate of 7.6% in another regiment [2]. Even during peacetime in 1908 there were 16 763 of the 68 522 (24%) British troops in India admitted to hospital with malaria and 91% (234/258) of troops in Western Africa [3]. More recently during the Sierra Leone civil war in 2000 there were 93 British military cases of malaria in less than two months [4]. Visceral leishmaniasis is named after Major (later Major-General Sir) William Leishman RAMC, who identified the parasite responsible in a British soldier from India with "Dum-dum fever" in 1903 [5]. Since 2001 there

Organisms	Diseases [Relevant References]
Protozoa	Malaria [2-4] Visceral leishmaniasis [5,6]
Bacteria	Enteric fever [7-10] Brucellosis [11-13] Q fever [14-16]
Spirochaetes	Leptospirosis [17-21] Relapsing fevers [22-26]
Rickettsiae	Typhus fevers [20,22,27-33] Spotted fevers
Arboviruses	Dengue fever [20,34-36] Sandfly fever [37,38,39,40] Chikungunya [41] Japanese encephalitis [20, 42] West Nile fever [43] Yellow fever [44] Congo-Crimean Haemorrhagic Fever [45]
Other haemorrhagic viruses	Hantavirus infection [46-48] Lassa fever [49]
Other viruses	Infectious mononucleosis [50]

Table 1. Reported causes of acute undifferentiated febrile illness in military personnel

have been British and US military cases from Iraq and Afghanistan and its potential to cause outbreaks is shown by the more than 1300 US military cases of cutaneous disease that occurred in Iraq from 2003-7 [6].

Bacteria

Enteric fever (typhoid or paratyphoid) had a major impact on static British camps in the Boer War and from 556 653 troops, there were 57 684 cases (10%), of whom 8 225 (14%) died, compared to 7 582 killed in action [7,8]. During World War I there were less cases due to vaccination against typhoid and the several thousand cases that occurred amongst British and Commonwealth troops in Gallipoli, Egypt and Mesopotamia were mostly paratyphoid infections [9,10]. Brucellosis is named after Captain (later Major-General Sir) David Bruce RAMC, who identified the bacterium responsible in a British soldier with "Malta fever" in 1887 [11]. It had a long association with British armed forces around the Mediterranean [12] and US military cases have recently occurred Iraq [13]. Q fever outbreaks affecting more than 1000 troops were reported amongst Allied troops in Greece and Italy during World War II [14,15] and have also occurred more recently in Iraq [16].

Spirochaetes

Leptospirosis is probably the most widespread zoonosis in the world and so it is not surprising that military cases have been reported from both World Wars [17], the conflicts in Malaya [18], Borneo [19] and Vietnam [20] and more recently from troops in Germany [17] and the UK [21]. Relapsing fever is a less common spirochaete infection, but the louse-borne form was a major problem during World War I [22] and the tick-borne form previously affected British troops in Palestine [23], Somaliland [24] and Cyprus [25] and military cases are still reported from Israel [26].

Rickettsiae

Typhus has been a threat to British expeditionary forces ever since the time of the Crusades [27]. Louse-borne typhus was a major

problem in Europe during both World Wars [22,28] and scrub typhus was a problem for British troops in South-East Asia during World War II with smaller numbers of murine typhus and spotted fever occurring as well [29]. Military cases of scrub typhus were also reported from the Korean War [30], Malayan Emergency [31], Vietnam War [20] and Hong Kong [32]. More recently outbreaks of spotted fever have occurred during British military exercises in Africa and the USA [33].

Arboviruses

Arboviruses (arthropod-borne viruses) can be grouped into those that cause fever-arthralgia-rash, encephalitis or haemorrhagic fever, but most of these infections will present with non-specific features initially. Dengue fever seemed to be a minor issue during the Vietnam War [20], but emerged as a greater military problem during conflicts in Somalia [34], Haiti [35] and East Timor [36]. Even relatively benign arbovirus infections can have a disproportionate effect on military operations due to high attack rates, diagnostic uncertainty and acute morbidity. Examples include sandfly fever during World War II [37,38] and more recently in Cyprus [39] and Iraq [40] and also an outbreak of chikungunya during an exercise in Senegal [41]. Most arboviruses that cause encephalitis are more likely to present with undifferentiated febrile illnesses rather than encephalitis itself. Examples include Japanese encephalitis, which occurred during the Malayan Emergency [42], the Vietnam War [20] and remains a concern for British troops in Brunei and also West Nile fever, which was diagnosed in a British soldier following an exercise in Canada [43]. Arboviruses that cause haemorrhagic fever include yellow fever, which was a major problem in the Spanish-American War [44] and Congo-Crimean haemorrhagic fever (CCHF), which recently caused the death of a US soldier from Afghanistan [45].

Other Haemorrhagic Viruses

Other (non-arthropod-borne) viral haemorrhagic fevers have also affected British military personnel overseas. Hantavirus was probably the cause of more than 35 000 cases of "trench nephritis" in British troops on the Western Front during World War I [46], it caused more than 3000 military cases of "epidemic haemorrhagic fever" during the Korean War [47] and also affected British troops during the last Balkans Conflict [48]. More recently there have been cases of Lassa fever in military peacekeepers working in Sierra Leone [49].

Other Viruses

Even infectious mononucleosis, which is common in younger troops, is a significant problem due to the small risk of splenic rupture that follows this illness [50]. Diagnosing undifferentiated febrile illnesses in troops overseas may also be complicated by cases of heat illness or other non-infectious causes of fever [51].

Afghanistan's decades of conflict and lack of healthcare facilities mean that relatively little is known about the epidemiology of diseases there. However, a comprehensive review of endemic infectious diseases in Afghanistan was published by the US military in 2002, which included valuable data from the Soviet occupation in 1979-89 [52]. This suggests that malaria, visceral leishmaniasis, enteric fever, brucellosis, Q fever, leptospirosis, relapsing fever, typhus fevers, spotted fevers, sandfly fever, chikungunya, West Nile fever, CCHF and hantavirus should all be considered potential causes of undifferentiated febrile illness in Afghanistan.

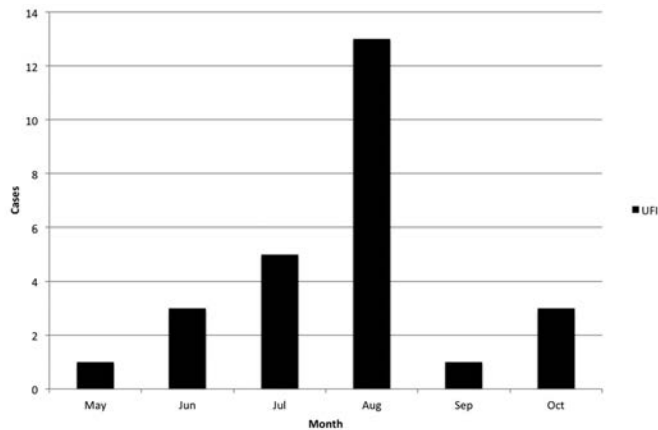


Figure 1. Distribution of Undifferentiated Febrile Illness (UFI or 'Helmand Fever') cases over time

Undiagnosed febrile illnesses have occurred amongst British troops in Helmand, Afghanistan since 2006 [1] and in May to July 2007 there were 14 cases that presented at the British field hospital there. Several of these patients had leukopenia, thrombocytopenia or raised liver transaminases, but no diagnoses were possible using the investigations available, which included blood films, malaria antigen tests, chest radiographs and cultures of blood, faeces and urine. Hence a fever study was planned for 2008, which became known as the Helmand Fever Study.

Methods

A case of "Helmand Fever" was defined as any military person presenting to the British field hospital in Helmand, Afghanistan with an acute (<2 week duration) febrile (>38°C) illness that had no specific organ focus following routine clinical and radiological assessment. Patients were recruited by the deployed consultant physician at the field hospital from May to October 2008 and were managed according to normal clinical practice. However, pre-defined clinical, radiological and laboratory data were collected on admission, which included the results of full blood counts, urea & electrolytes, liver function tests, CRP assays, blood films, malaria antigen tests, chest radiographs and cultures of blood, urine and faeces. All patients had serum sent on admission and (whenever possible) 2-6 weeks later for serology and Polymerase Chain Reaction (PCR) tests at the Special Pathogens Reference Unit, HPA Porton Down. Investigations for Q fever, rickettsial infections, arboviruses (including generic flaviviruses, dengue, West Nile, generic alphaviruses, chikungunya, generic bunyaviruses, phleboviruses and CCHF) and hantavirus were performed and interpreted according to the standard protocols of this UK reference centre [53]. These included an in-house immunofluorescence assay (IFA) for sandfly fever, in-house IFA tests for Q fever using Phase 1 and Phase 2 antigens and commercial rickettsia IFA tests using murine typhus and Rocky Mountain spotted fever antigens (Focus Diagnostics, Cypress, CA, USA).

Results

From May to October 2008 there were 26 military personnel admitted with acute undifferentiated febrile illnesses at the British field hospital in Helmand, Afghanistan. Of these 25 were male, the median age was 23 years (range = 19-32 years) and 23 were British with the remainder being Danish. All the affected personnel had

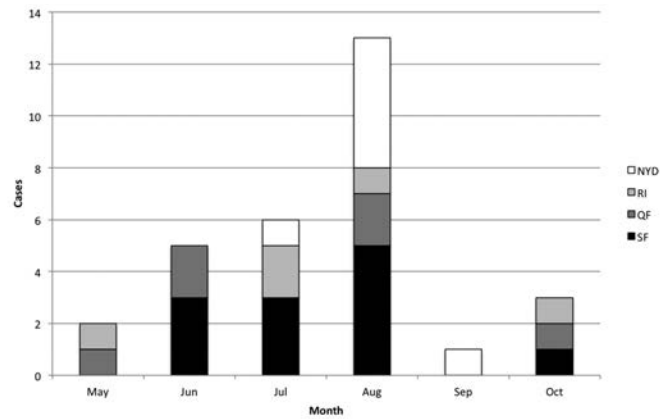


Figure 2. Distribution of final diagnoses over time (SF=sandfly fever; QF=Q fever; RI=rickettsial infection; NYD=not yet diagnosed)

come from remote Forward Operating Bases (FOBs) rather than the main British base at Camp Bastion and 19 (73%) were from a single FOB in the upper Sangin valley (data not shown). The distributions of "Helmand Fever" cases and final diagnoses over time are shown in Figures 1 and 2. A summary of the cases is shown in Table 2 and urea & electrolytes, blood films, malaria antigen tests, chest radiographs and cultures of blood, urine and faeces were negative for all those listed.

Including the four patients with more than one infection, there were 23 diagnoses made of which 12 (52%) were sandfly fever, six (26%) were Q fever and five (22%) were rickettsial infections. All cases of Q fever were acute with no evidence of previous or chronic infection. All cases of rickettsial infection had positive results for both murine typhus and spotted fever antigens and so the exact type of rickettsia involved could not be determined. Four of the 7 cases (57%) with no diagnosis had not provided a convalescent serum sample for serology testing.

Clinical features such as headache and myalgia were almost universal in "Helmand Fever" patients and hence of no value in distinguishing between the final diagnoses. Arthralgia, rash, pharyngitis, diarrhoea and lymphadenopathy were less common, but also not specific to any of the different diagnoses. Conjunctival suffusion was found in 3/12 (25%) sandfly fever cases only, cough was found in 2/6 (33%) acute Q fever cases only and hepatosplenomegaly was found in 2/5 (40%) rickettsial infections only. Laboratory features such as leukopaenia, thrombocytopenia and raised liver transaminases were common in "Helmand Fever" cases, but do not help distinguish between the final diagnoses. CRP tended to be lowest for sandfly fever, variable in acute Q fever and high in rickettsial infections.

Discussion

This study raises issues regarding the epidemiology, diagnosis, treatment and prevention of "Helmand Fever", which is mostly caused by sandfly fever, acute Q fever and unidentified rickettsial infections.

The epidemiology of these diseases in Afghanistan is poorly understood and these cases probably represent the "tip of an iceberg" for British and International Security Assistance Force (ISAF) forces since it is likely that many others would not have presented to the field hospital. This would certainly be true for less severe cases from the most remote or hostile areas, because during this period all medical evacuations from FOBs were carried out

Case	Date	Symptoms & Examination Findings										Laboratory Results				Diagnosis
		Headache	Myalgia	Arthralgia	Rash	Conjunctival suffusion	Pharyngitis	Cough	Diarrhoea	Hepatomegaly	Splenomegaly	Lymphadenopathy	WCC	Plts	CRP	
1	May	Y	?	?	?	?	?	?	?	?	N	Normal	110	90	High	RI + QF
2	Jun	Y	?	?	?	?	?	?	?	?	Y	3.8	101	48-96	Normal	SF + QF
3	Jun	Y	?	?	Y	?	?	?	Y	?	?	1.7	108	<6	Normal	SF
8	Jun	Y	N	N	N	N	N	Y	N	N	N	6.1	270	24-48	High	SF + QF
4	Jul	Y	Y	Y	N	N	N	N	Y	Y	Y	Normal	65	>96	High	RI
5	Jul	Y	Y	N	N	N	N	N	N	N	N	2.4	239	<6	Normal	SF
6	Jul	Y	N	N	N	Y	Y	N	Y	N	N	3.5	141	12-24	High	SF
7	Jul	Y	N	N	N	N	N	N	N	N	N	Normal	240	<6	High	RI + SF
9	Jul	Y	Y	Y	N	N	N	N	Y	N	N	2.9	88	ND	ND	NYD
10	Aug	Y	Y	N	Y	Y	N	N	N	N	N	3.4	Normal	24-48	High	SF
11	Aug	Y	Y	N	N	N	N	N	Y	N	N	Normal	Normal	48-96	Normal	NYD
12	Aug	N	N	N	N	N	N	N	Y	N	N	2.4	118	<6	Normal	NYD
13	Aug	N	Y	N	N	N	N	Y	Y	N	N	Normal	Normal	<6	Normal	QF
14	Aug	Y	N	N	N	N	N	N	N	N	Y	3.4	106	<6	High	SF
15	Aug	Y	Y	N	N	N	N	N	Y	N	N	5.8	Normal	12	Normal	NYD
16	Aug	N	N	N	N	N	N	N	Y	N	N	17.3	156	>96	Normal	NYD
17	Aug	Y	Y	N	Y	N	N	N	N	N	N	Normal	Normal	<6	Normal	SF
18	Aug	Y	Y	N	N	N	N	N	N	N	Y	?	?	?	?	SF
19	Aug	Y	Y	N	N	N	N	N	N	N	Y	?	?	?	?	SF
20	Aug	Y	Y	Y	N	N	N	N	N	N	N	?	?	?	?	NYD
21	Aug	Y	Y	N	Y	N	N	N	N	N	N	2.2	81	48-96	High	QF
22	Aug	Y	Y	N	N	N	N	N	N	N	N	?	?	?	?	RI
23	Sep	Y	Y	Y	N	N	N	N	Y	N	N	10.6	Normal	<6	Normal	NYD
24	Oct	Y	Y	Y	Y	Y	Y	N	N	N	N	2.6	177	24-48	High	SF
25	Oct	Y	Y	N	N	N	Y	N	N	N	Y	7.0	256	24	Normal	QF
26	Oct	Y	Y	N	Y	N	N	N	Y	Y	N	3.3	55	>96	High	RI

Table 2: Summary of clinical and laboratory findings. Y= Yes; N=No; ?=Unknown; WCC=White Cell Count (x10⁹/L); Plts=platelets (x10⁹/L); CRP= C Reactive Protein; LFT = Liver Function Tests; High = liver transaminases >2x upper limit of normal; RI=Rickettsial infection; QF=Q Fever; SF=Sandfly Fever; NYD=Not Yet Diagnosed

by helicopter under the constant threat of enemy attack. Sandfly fever is not life-threatening and has no long-term complications, but affected troops may require up to two weeks off duty [37,39]. Acute Q fever is rarely life-threatening, but up to a quarter of cases may develop “Q fever fatigue syndrome” [54] and 1-5% may develop chronic Q fever with endocarditis [55]. Rickettsial infections may be life-threatening and untreated louse-borne epidemic typhus due to *R. prowazekii* carries a risk of recurrence as Brill-Zinsser disease in later life. A sero-epidemiology study is required to estimate the true burden of disease from these infections in British and ISAF troops.

The diagnosis of these diseases relies on PCR tests (which are not available in British field hospitals) or serology tests on acute and convalescent samples (which are difficult to collect in

deployed military personnel). These limitations contributed to the fact that seven (27%) of the 26 patients in this study did not have a final diagnosis made. In future all military patients with undifferentiated febrile illnesses at the field hospital in Helmand, Afghanistan should have acute and convalescent serum (after 2-6 weeks) sent for “Helmand Fever” tests at HPA Porton Down using the existing military laboratory system. All British cases should also be referred for an out-patient review with the military infectious diseases physician (MSB) at Birmingham Heartlands Hospital (BHH) after their deployment to ensure that a diagnosis is made. More resources for diagnostic facilities and follow-up of patients are required in order to overcome the problem of missed diagnoses and so improve the management and surveillance of “Helmand Fever” cases.

The treatment of these diseases varies from symptomatic relief for sandfly fever to short courses of doxycycline for rickettsial infections and a longer course of doxycycline for acute Q fever. Since it is currently impossible to distinguish between these different diagnoses in Afghanistan, it is recommended that doxycycline 100 mg twice daily (or 200 mg once daily) for two weeks is given empirically to all troops who present with an undifferentiated febrile illness, if bacteriology cultures and malaria investigations are also negative. This regimen remains the most effective for reducing acute Q fever morbidity [56], but patients should be warned that doxycycline may cause gastritis, candidiasis and occasionally severe photosensitivity. Although data on adverse effects is not available for this exact dosage, a meta-analysis of doxycycline 100 mg twice daily for one week to treat genital infections showed that 23% of patients reported adverse effects with doxycycline of which 88% were gastrointestinal [57], but a trial of doxycycline 100 mg daily for several weeks as malaria prophylaxis showed that only 6% had severe adverse events including 2% with photosensitivity [58]. Patients with acute Q fever should have an echocardiogram to look for underlying cardiac defects and be followed-up with serology tests at three months, six months and then every six months for at least two years to exclude chronic Q fever and endocarditis.

The prevention of these diseases requires a better understanding of their epidemiology – especially regarding the reservoirs for Q fever and vectors for rickettsial infections [59]. Improved bite prevention measure should reduce the risk of sandfly fever, rickettsial infections and also Q fever if tick-borne transmission is occurring [59]. Both rickettsial infections and Q fever could be prevented if doxycycline prophylaxis was given to troops at risk [60] and this would then replace the chloroquine-proguanil currently used for malaria prophylaxis with less adverse effects [58]. An Australian Q fever vaccine is also available with good efficacy and an acceptable safety profile [61], although this could not be confirmed on a recent meta-analysis of reported trials [62].

Conclusions

Overall this study raises more questions than it answers and the recommendations summarised in Box 1 should be viewed as just the start of a comprehensive research programme that will be of benefit for this and future deployments.

- A sero-epidemiology study is required to estimate the true burden of these diseases.
- Better diagnostic facilities and follow-up of patients with “Helmand Fever” are required.
- All troops with undifferentiated febrile illnesses in Helmand, Afghanistan should have paired serology tests sent and be treated with doxycycline 200 mg daily for 2 weeks.
- All British troops presenting in this way should also be referred in due course for out-patient follow-up with the military physician at Birmingham Heartlands Hospital.
- Prophylaxis with doxycycline and possibly Q fever vaccine should be considered.

Box 1 Summary of Recommendations

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