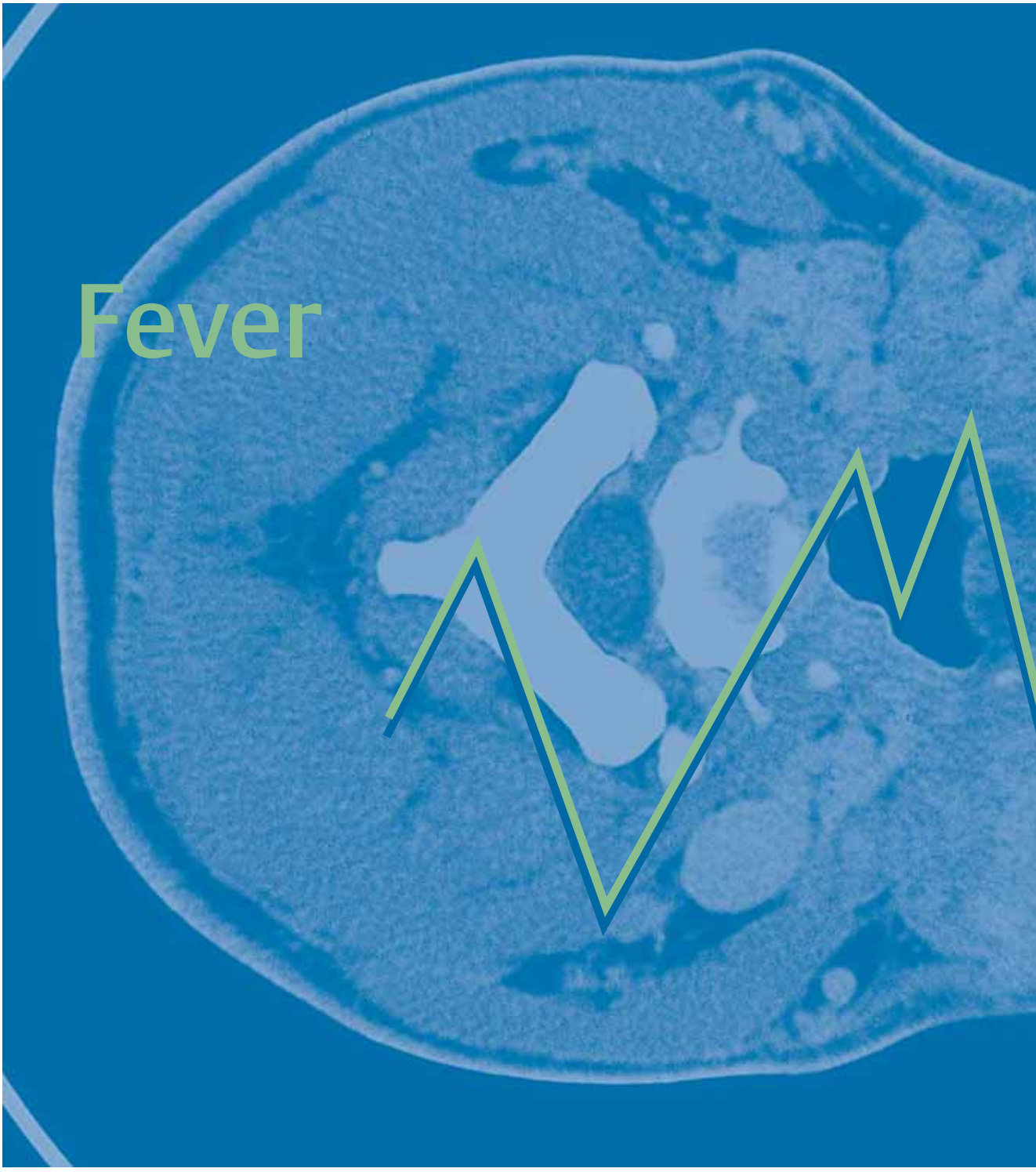

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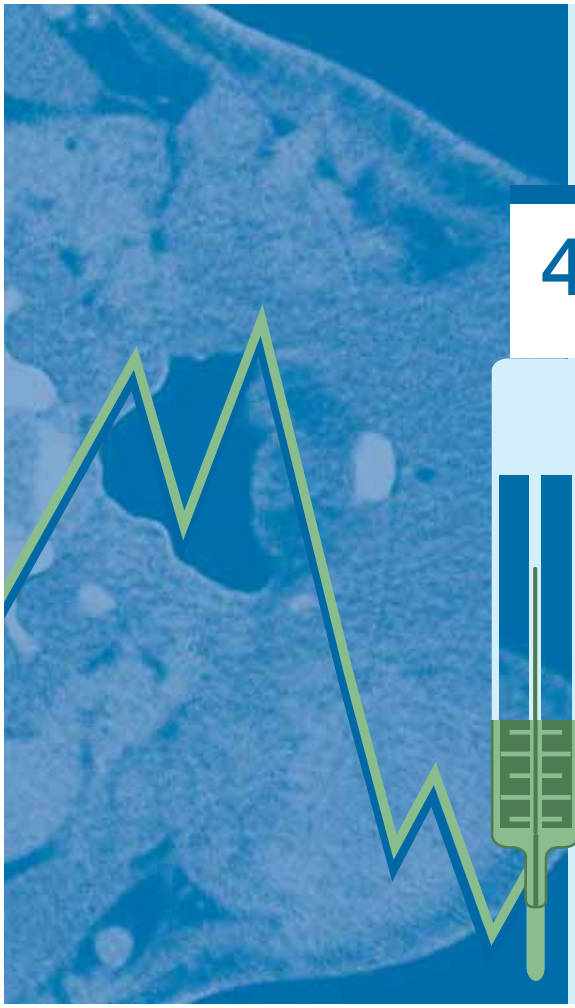

4 Fever

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4.1 General Remarks

Medical History and Clinical Findings

Medical History. The medical history has particular significance. Details about a patient's background, family medical history, occupations, hobbies, participation in sports, international travel (tropical), contacts with animals, insect bites and other injuries, previous illnesses, as well as diagnostic and therapeutic interventions, vaccinations, skin rashes, medications, or illicit (intravenous) drug use can provide important information. A systematic interview concerning the functioning of organ systems and comprehensive information about the present condition are likewise important. The social environment of the patient and his or her sexual preferences should also be discussed.

Clinical Examination. A thorough clinical examination, in combination with the historical information, should lead to a well-founded, tentative diagnosis in most cases. The following parts of the body are occasionally neglected during a physical examination: ocular fundus, temporal arteries, nasal sinuses, thyroid gland, renal beds, spinal column, uterine appendages, and prostate gland. Afflictions of these organs are occasionally clinically asymptomatic, which incorrectly leads to the search for a systemic cause of the fever.

Differential Diagnostic Considerations

Duration of the Fever. The *duration of the fever* is an important differential diagnostic symptom. In outpatients, viral or bacterial infections of the upper and lower respiratory tract or urinary tract infections are the most frequent causes of a brief fever (≤ one week). Fever lasting one to two weeks requires careful evaluation. See Section 4.8, p. 195 for the *fever types*.

Causes of Fever. Aside from *infectious causes*, the physician must consider various diseases with respect to the etiology of febrile conditions (Tab. 4.**1**).

Special Patient Groups. Differential diagnostic considerations also depend on if a fever has occurred *at home* or during the course of *hospitalization* (nosocomial infection). Not only is the spectrum of potential pathogens different in inpatients, but also *iatrogenic* factors must be considered, such as: postoperative infections, pulmonary diseases (atelectasis, pulmonary embolism, pneumonia), urinary tract infections (urinary catheter!), infections of intravasal catheters, as well as phlebitis after parenteral nutrition or therapy.

Patients with *endoprostheses*, *artificial heart valves*, or *intravascular grafts* can experience infections due to these foreign materials perioperatively or thereafter via bacteremia. The clarification of such occurrences can prove to be particularly difficult.

The differential diagnosis of fever in *HIV-infected* or otherwise *immunocompromised* patients (after organ transplants or neutropenia during chemotherapy) also includes opportunistic infections and tumors.

Fever—Definitions and Pathogenesis

Fever. Fever is an elevation of the body temperature > 37.8 °C when measured *orally* or > 38.2 °C when measured *rectally*. Especially in elderly patients, the latter is more reliable than skin or sublingual measurements.
Endogenic and exogenic pyrogens can increase the set point of the body temperature, which is regulated in the hypothalamus. Shivering, trembling, or chills leads to an increased production of heat through muscle work. Simultaneous vasoconstriction reduces the loss of heat through the skin. The most important endogenic pyrogens are interleukin-1, tumor necrosis factor, and interferons. Bacterial endotoxins and exotoxins of Gram-negative or Gram-positive bacteria are typical exogenic pyrogens that stimulate monocytes and macrophages to produce endogenic pyrogens.

Hyperthermia. Hyperthermia (temperature > 41.2 °C) is the consequence of overheating. An adjustment of the set point of the body temperature in the heat-regulating center does not occur, as in the case of fever. The causes of hyperthermia are *exogenic* (e. g., heating pads, sauna, baths) or *endogenic* (muscle work). During this process, the body temperature can rise uncontrollably, whereas the dissipation of heat is disturbed (e. g., as a consequence of unsuitable clothing or high air temperatures with high humidity). Under such conditions *heat stroke* can occur. *Malignant hyperthermia* is a rare complication of general anesthesia in genetically susceptible individuals (autosomal dominant inheritance). It is most frequently caused by succinylcholine and halothane.

Normal Variation in Body Temperature. When evaluating a fever, different normal variations must be considered. Physical exertion or eating an extravagant meal are physiological causes of an elevated temperature. However, body temperature generally does not exceed 37.9 °C. The same holds true for temperatures that can occur in women during the second half of the menstrual

cycle (ovulation to menstruation). The physiological daily temperature fluctuation is around 1 °C.

Fever in Elderly Individuals. The normal body temperature, as well as the physiological daily temperature fluctuation, can be reduced in frail, elderly individuals, although not necessarily in healthy elderly people. Therefore, a recurrent elevation of the oral (> 37.2 °C) or the rectal temperature (> 37.5 °C) indicates fever in this patient group. Additionally, the fever reaction in a severe infection is absent, or only present in mitigated form, in 20–30 % of elderly individuals.

Table 4.**1** Causes of fever

Infectious diseases	– localized pyogenic infections (e. g., abscesses, pneumonia) – systemic infections (e. g., sepsis, typhoid) – relapsing infections (e. g. due to congenital or acquired immunodeficiency)
Tumors and hematologic malignancies	– lymphoma – leukemia – immunoblastic lymphadenopathy – myeloproliferative disorders – solid tumors – atrial myxoma
Vasculitis and collagen vascular diseases	– (see Tab. 4.**21**)
Rheumatic disorders	– (see Chapter 10)
Granulomatous diseases and organ specific autoimmune disorders	– sarcoidosis – Crohn disease – ulcerative colitis – chronic hepatitis – idiopathic, granulomatous hepatitis – primary biliary cirrhosis – malakoplakia – subacute thyroiditis – postmyocardial infarction syndrome
Endocrine and metabolic diseases	– thyrotoxicosis – Addison disease – pheochromocytoma – acute hyperparathyroidism – porphyria – Fabry disease
Primary neurologic disorders	– hypothalamic dysfunction – cerebrovascular accident, bleeding, stroke, epilepsy – heatstroke, hyperthermia – neuroleptic malignant syndrome – peripheral autonomic dysfunction – trauma of spinal cord
Other causes (in alphabetical order)	– alcoholic hepatitis – allergic reactions – Castleman disease – cholesterol emboli – chronic fatigue syndrome – cyclic neutropenia – drug fever – factitious fever – familial Mediterranean fever – graft versus host disease – hemolysis – hemophagocytic syndrome – histiocytosis X – hyperimmunoglobulinemia D syndrome – hypersensitivity pneumonitis (“metal fume fever”) – inflammatory pseudotumor – Kikuchi disease – pancreatitis – PFAPA syndrome (**p**eriodic **f**ever, **a**denitis, **p**haryngitis, and **a**phthous stomatitis) – pulmonary emboli, thrombophlebitis, thrombosis – retroperitoneal fibrosis – sinus histiocytosis with massive lymphadenopathy – sweet syndrome – tissue infarction/necrosis (hematoma, aortic dissection) – **t**umor necrosis factor **r**eceptor-**a**ssociated **p**eriodic fever **s**yndrome (TRAPS)

Fever of Unknown Origin

Definition. The diagnosis "fever of unknown origin" (FUO, prolonged FUO) is used for a fever (with temperatures measured several times ≥ 38.3 °C) of at least three weeks' duration in individuals who are not immunocompromised and who have had a comprehensive, but unsuccessful outpatient or inpatient evaluation. While the definition previously required a minimal period of hospitalization, or a certain number of outpatient examinations, currently a minimal evaluation program is proposed before the term FUO can be used (Tab. 4.**2**). The differential diagnostic spectrum of the causes of fever is changed in the presence of an underlying disease (neutropenia, HIV infection, endoprostheses) or a specific epidemiological situation (nosocomial infection, following a stay in, or return from endemic regions, with specific infectious diseases).

Causes. The further development of imaging techniques and detection methods for infectious agents, as well as the possibilities of fine needle punctation or biopsy, has changed the spectrum of the causes for a FUO during the last 50 years (Fig. 4.**1**). Infectious diseases and malignant tumors as causes of a FUO have become rarer. The proportion of noninfectious, inflammatory diseases has increased. In up to one-third of the cases, a cause cannot be found, despite comprehensive examinations. However, the long-term prognosis in these patients is often benign, as long as new symptoms do not occur (e. g., weight loss).

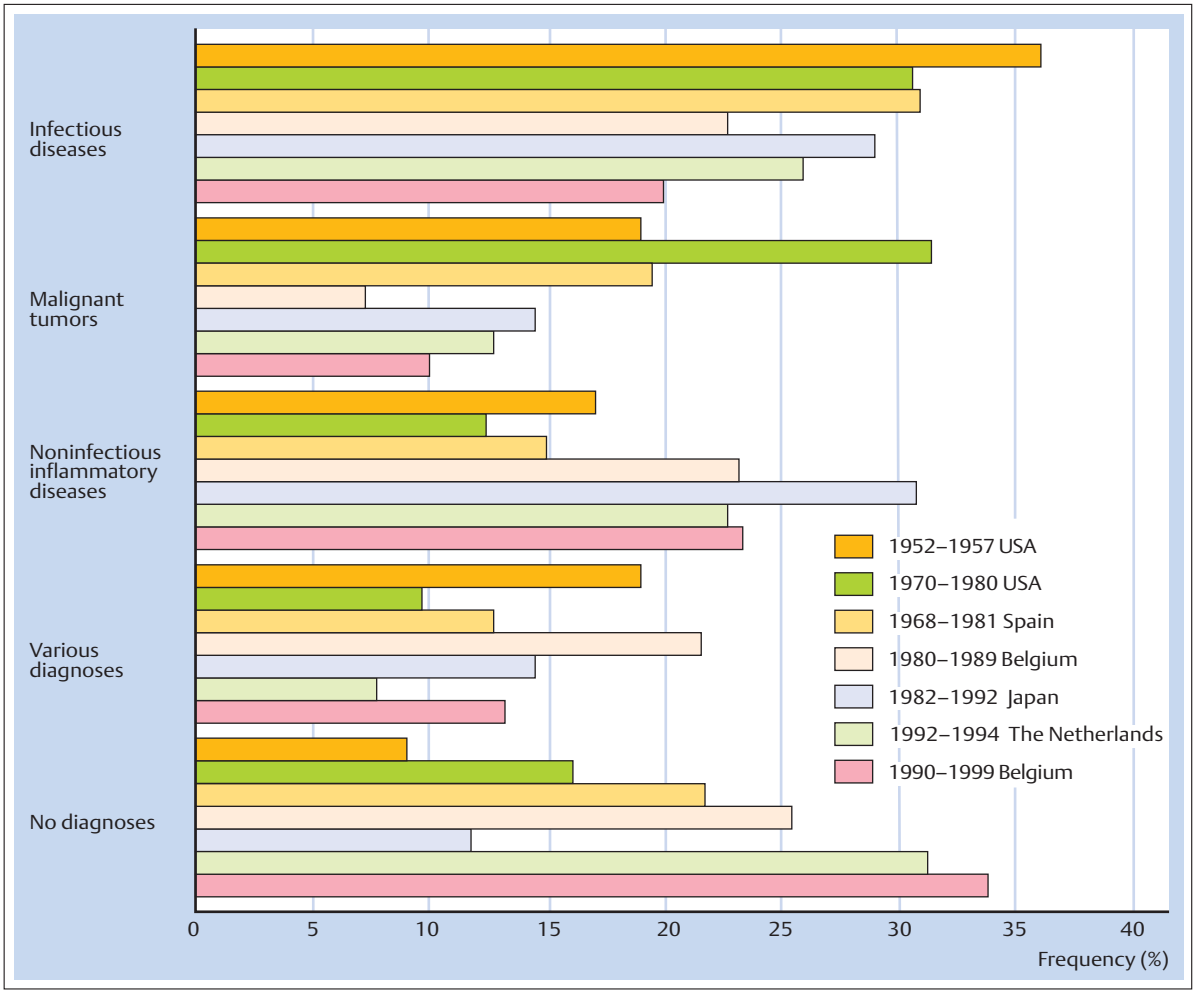

Fig. 4.**1** Final diagnoses in patients with fever of unknown origin (FUO). Time period 1952–1957 (Petersdorf et al., USA); 1970–1980 (Larson et al., USA); 1968–1981 (Barbado et al., Spain); 1980–1989 (Knockaert et al., Belgium); 1982–1992 (Iikuni et al., Japan); 1992–1994 (de Kleijn et al., The Netherlands); 1990–1999 (Vanderschueren et al., Belgium).

Table 4.**2** Minimal diagnostic work-up to qualify as fever of unknown origin (FUO)

- Comprehensive medical history
- Repeated physical examination
- Complete blood cell count and differential?
- Microscopic examination of blood film
- Routine blood chemistry (including lactic dehydrogenase, bilirubin, and liver enzymes)
- Blood sedimentation rate
- Urinalysis and microscopy
- Chest radiography
- Blood and urine cultures (before initiation of antibiotic treatment)
- Antinuclear antibodies
- Rheumatoid factor
- Serologies for cytomegalovirus and Epstein–Barr virus
- Human immunodeficiency virus antibody and antigen tests
- Hepatitis serology (if abnormal liver enzyme test result)
- Computed Tomography scan of abdomen
- Q fever serology (if exposure risk factors exist)
- Examination for specific endemic infectious diseases in returning travelers or persons living in such geographic areas (e. g., systemic leishmaniasis [India, Mediterranean area], etc.)
- Tuberculin test
- Evaluation of any abnormal symptoms and findings

Modified from Arnow et al., 1997 and Mourad et al., 2003.

4.2 Fever without Localized Symptoms

Infectious Diseases

Causes. In some patients with fever it is not possible to determine if a specific organ is affected. Only nonspecific symptoms, such as shivering, sweating, night sweats, fatigue, or weight loss, are present. The clinical examination also does not yield any disease-specific findings. In this situation, the following diagnoses should especially be considered:

- tuberculosis
- endocarditis
- mycotic aneurysm
- septic thrombophlebitis
- spondylitis
- osteomyelitis
- pneumonia
- intra-abdominal abscesses (liver, bile ducts)
- pyelonephritis.

These diseases occasionally take an asymptomatic course, both clinically and with respect to the medical history. Rarer causes are: cat scratch disease, rickettsiosis (which can occur without the classical exanthema), ehrlichiosis, chronic Q fever with hepatomegaly, brucellosis, leptospirosis, Whipple disease, typhoid fever, and rat-bite fever.

The most important *viral diseases* that are not accompanied by localized symptoms, but occasionally by high fever, are cytomegalovirus infection, mononucleosis, HIV infection, and viral hepatitis in an early stage.

Systemic *mycoses* (cryptococcosis, histoplasmosis) are predominantly found in immunocompromised patients. Of the *parasitic diseases*, toxoplasmosis should be considered, as it can occasionally occur without enlarged lymph nodes. Psittacosis or malaria should also be considered, if appropriate exposure has occurred.

Diagnosis. A series of very specific examination methods is available for diagnosis of each of these infectious diseases. In addition to cultures and serological examinations, echocardiography (endocarditis and atrial myxoma), ultrasound, and computed tomography (CT) examinations of the abdomen (intra-abdominal abscesses, lymphomas) play an important role. Computed tomography and magnetic resonance imaging (MRI) are more sensitive than conventional radiographs for the early diagnosis of spondylitis and osteomyelitis. In FUO or fever without localized symptoms, [^{18}F]-fluorodeoxyglucose (FDG)–positron emission tomography (PET) can deliver important additional information and can visualize occult infectious foci and tumors, as well as noninfectious inflammatory diseases (especially vasculitis) (Fig. 4.**2**).

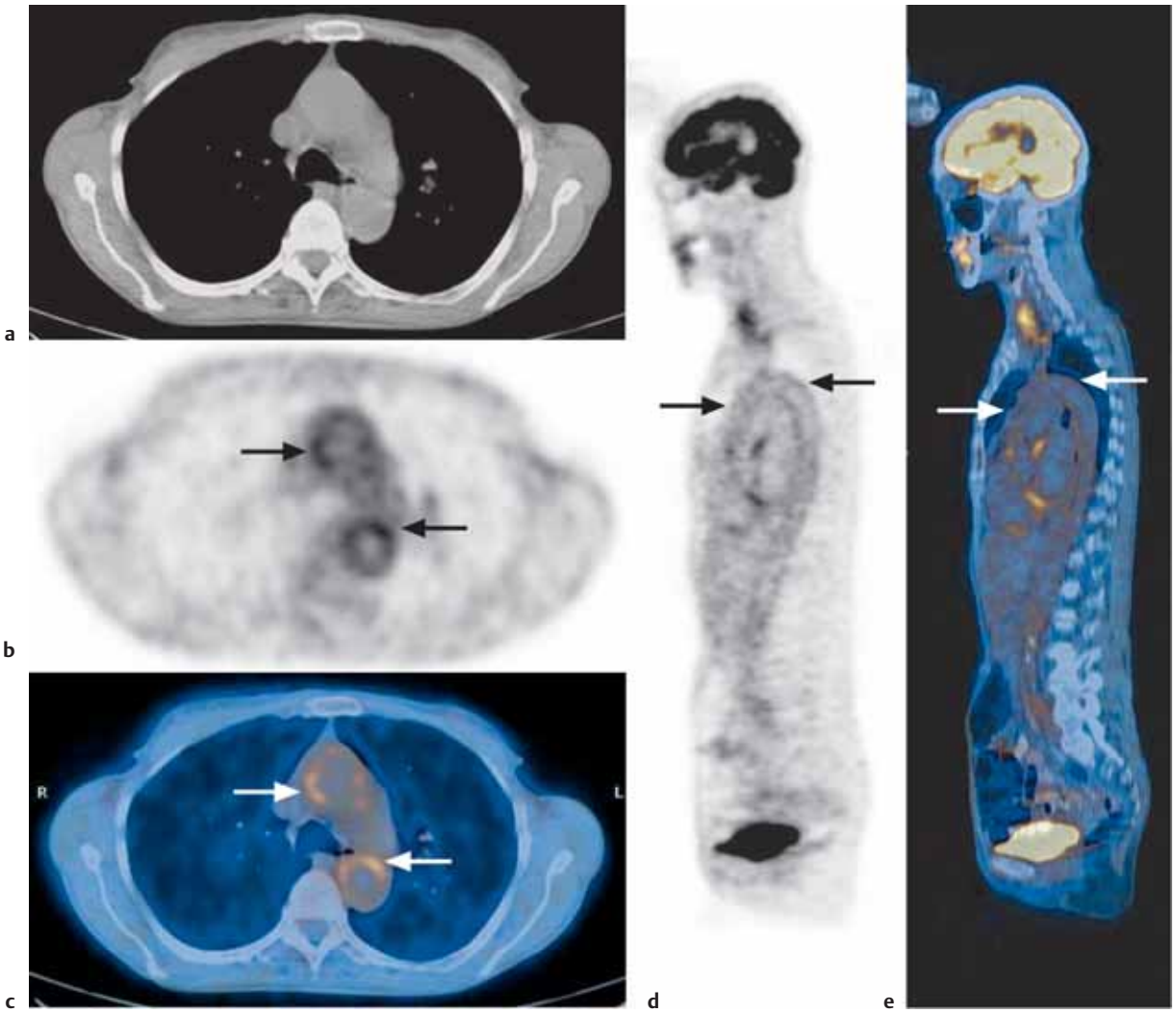

Fig. 4.**2** Vasculitis of large vessels in a 78-year-old woman. [^{18}F]-fluorodeoxyglucose (FDG)–positron emission tomography with integrated CT scan (PET/CT).

a–c Left panel (top to bottom): CT, PET, and PET/CT slice through the aorto-pulmonary region. Increased FDG uptake in the ascending and descending aorta (arrows).

d Middle panel: lateral view of PET scan.

e Right panel: lateral view of PET/CT scans showing increased FDG uptake in the ascending, descending, and abdominal aorta (arrows). The increased FDG uptake indicates the inflammatory process in the aorta (Scans kindly provided by K. Stumpe, Department of Nuclear Medicine, University Hospital Zürich, Switzerland).

Noninfectious Causes

Malignant Diseases. The main noninfectious causes (Tab. 4.**1**) are *malignant lymphomas* and *leukemias*. If peripheral lymph nodes are not accessible to cytological or histological examination, it is frequently possible to make a diagnosis by means of ultrasound-guided fine needle puncture of retroperitoneal lymphomas. The diagnosis of leukemias is primarily based on the peripheral blood count and bone marrow puncture. *Solid tumors* that can be associated with fever include hepatocellular carcinoma, renal carcinoma, hepatic metastases, bronchial carcinoma, pancreatic carcinoma, and atrial myxoma. These tumors generally can be detected with great certainty using imaging techniques.

Vasculitis Syndromes and Connective Tissue Disorders. Among the *vasculitis syndromes* and *connective tissue disorders* (see Tab. 4.**22** p. 177) Polymyalgia rheumatica, nonclassifiable collagen vascular diseases (early form of various collagen vascular diseases), and systemic lupus erythematosus (SLE) must be considered, which at least at the onset of the disease can become manifest without localized symptoms. The adult form of Still disease can also have fever as its only symptom. Whilst antinuclear antibodies are positive in most cases of lupus erythematosus, pathognomonic findings are not available for polymyalgia rheumatica or Still disease.

Other Causes. *Drug fever* is of great practical significance. Concomitant exanthema can occasionally be present transiently. Especially in elderly patients, *recurrent pulmonary embolisms* can occur with a fever, but without notable pulmonary symptoms or radiological changes. Combined perfusion and ventilation scintigrams or CT analyses are diagnostically valuable. Diffuse abdominal pains and fever can also indicate a *mesenteric infarction* in elderly patients. In younger patients, *Crohn disease* can occur without gastrointestinal symptoms. Colonoscopy with intubation of the ileocecal valve confirms the diagnosis. *Cirrhosis of the liver* and *granulomatous hepatitis* are additional causes of a persistent fever. If the abdominal symptoms in *Mediterranean fever* are initially absent, this diagnosis can be suspected but not confirmed based on a positive family history and appropriate origin.

The suspicion that a *fever* is merely being *feigned* is based primarily on discrepancy between the fever and the pulse curves. This is by no means a complete list of diseases associated with fever that primarily can become manifest without localized symptoms.

Possible causes of fever can usually be determined by means of *follow-up observations* and the *associated signs and symptoms*. In this case repeated clinical examinations are of inestimable value.

Hospitalized Patients

If hospitalized patients develop a fever, infectious causes and drug allergies must first be excluded. Intravasal catheters, implanted prostheses, drains, and intubation facilitate access for nosocomial pathogens. Postoperative cholecystitis or sinusitis after intubation can occur initially without localized symptoms.

4.3 Fever with Associated Cardinal Symptoms

Additional *cardinal symptoms* occur together with a fever in many individuals, which makes the differential diagnosis significantly easier. Although, during the development of a febrile illness, various symptoms can overlap and alternate (e. g., arthralgia and skin rash in arthritis–dermatitis syndrome), classification according to different cardinal symptoms has proven to be clinically effective (Tab. 4.**3**).

The following sections will summarize the differential diagnostic possibilities that can occur in the context of one of these cardinal symptoms.

Table 4.**3** Frequent leading symptoms associated with fever

- Rash
- Joint or bone pain
- Lymphadenopathy
- Swelling of face or neck
- Headache and neck stiffness
- Neurological disorder
- Cold or influenza-like symptoms
- Cough and chest pain
- Jaundice
- Splenomegaly
- Diarrhea
- Abdominal pain
- Dysuria
- Sepsis
- Heart disorder

Fever and Skin Rashes

Petechiae and Purpura

Infectious Diseases. Petechiae and purpura can be caused by various bacteria, rickettsia, and viruses (Tab. 4.**4**). Independently of if disseminated, intravascular coagulation is present, a sepsis with Gram-negative pathogens (rarely a sepsis with Gram-positive pathogens) can lead to petechiae. In endocarditis these lesions are generally very discrete. In meningococcemia, lesions are more noticeable due to confluence. In an early stage of bacteremia, gonococci, streptococci, staphylococci, *Pseudomonas aeruginosa*, *Capnocytophaga canimorsus* (after a dog bite), and *Streptobacillus moniliformis* (rat-bite fever) can cause petechiae. However, vesicles and pustules are more frequently present in these infections. Among the rickettsial diseases, typhus and Rocky Mountain spotted fever should be mentioned as rare causes. A petechial skin rash is more frequently observed in viral diseases, including measles, rubella, mononucleosis, hepatitis, dengue fever, and other hemorrhagic types of fever.

Table 4.4 Infectious diseases presenting with rash

Disease	Maculo-papular eruptions	Vesiculo-bullous eruptions	Purpuric eruptions	Nodular eruptions	Erythema-tous erup-tions	Urticarial eruptions	Ulcers
Viruses							
– Adenoviruses	×		×				
– Coxsackie viruses	×	×	×		×	×	
– Dengue virus	×		×				
– Echovirus	×	×	×				
– Epstein–Barr virus	×		×			×	
– Yellow fever virus			×				
– Hemorrhagic fever viruses			×				
– Hepatitis B virus	×					×	
– Herpes simplex virus		×					x
– HIV	×					×	
– Human herpes virus 6	×						
– Measles virus	×		×				
– Parvovirus B19	×				×		
– Rubella virus	×						
– Vaccinia virus		×					
– Varicella-zoster virus		×					
– Cytomegalovirus	×						
– Zoonotic pox viruses		×					
Bacteria							
– *Bacillus anthracis*							x
– *Bartonella* species	×			×			x
– *Borrelia burgdorferi*	× *						
– *Borrelia* species (relapsing fever)	×		×				
– *Capnocytophaga* species			×				
– *Chlamydia psittaci*	×						
– *Corynebacterium diphtheriae*							x
– *Ehrlichia* species	×		×				
– *Francisella tularensis*	×						x
– *Leptospira* species	×						
– *Listeria monocytogenes*		×					
– *Mycobacterium leprae*				x	x		x
– *Mycoplasma pneumoniae*	×	×				×	
– *Neisseria gonorrhoeae*			×				
– *Neisseria meningitidis*			×				
– Nontuberculous myobacteria	×			×			x
– *Nocardia* species				×			x
– *Pseudomonas aeruginosa*	×						x
– Rat-bite fever	×		×				
– Rickettsioses	×	×	×				
– *Salmonella typhi*	×						
– *Staphylococcus aureus*	×	×	×		×		x
– Streptococci	×	×	×		×		
– *Treponema pallidum*	×						x
– *Vibrio vulnificus*		×					
– *Yersinia pestis*							x
Fungi							
– *Blastomyces dermatitidis*	×			×			
– *Candida* species	×			×			
– *Coccidioides immitis*	×			×			
– *Histoplasma* species	×			×			x
– Cryptococci	×						
– *Sporotrix* species				×			
Protozoa							
– *Leishmania* species							x
– Malaria			×				

* Ringlike (erythema migrans).

Noninfectious Causes. The most important *noninfectious* causes include drug reactions, rheumatic fever, Schönlein–Henoch purpura, lupus erythematosus, and other vasculitis syndromes that are associated with antibodies against neutrophilic cytoplasmic antigen (ANCA) (polyarteritis nodosa, Churg–Strauss syndrome, Wegener disease). In chronic hepatitis C infection the vasculitis associated with cryoglobulins, purpura arthralgia nephritis syndrome, should be mentioned. The histology of the purpura in vasculitis syndromes mentioned usually shows an underlying leukocytoclastic vasculitis.

Maculopapular Exanthema

It is usually possible to distinguish maculopapular and vesicopustular rashes, even if morphological transitions from one efflorescence to another are frequently observed (Tab. 4.**4**).

Viral Diseases. A *maculopapular exanthema* usually occurs in measles, rubella, and roseola (exanthema subitum, roseola infantum [human herpesvirus 6]). In infections with coxsackie viruses and echoviruses the rash lasts very briefly. In mononucleosis, the rash is rare and discrete, when present.

> If patients with Epstein–Barr virus infection are given aminopenicillin, they regularly exhibit a very clear maculopapular drug eruption.

In the acute phase of infectious erythema (fifth disease [parvovirus B19]) one observes an erythema of the cheeks that is often associated with an exanthema of the trunk and the extremities. This erythema can reoccur during a one to three week period. In adults, the skin rash often presents atypically or is absent.

Bacterial Diseases. Streptococci and staphylococci have a special affinity for the skin. Erysipelas, scarlet fever, and erythema marginatum (in rheumatic fever) are caused by streptococci. Toxic shock syndrome is caused by an exotoxin produced by staphylococci. The syndrome appears on the skin as an erythema. Later on, scaling develops on the hands and soles of the feet. Group A streptococci can cause a similar clinical picture. A maculopapular exanthema, which occurs on the entire body, but more often on the hands and soles of the feet, is found in secondary syphilis. In typhoid fever, roseolas can develop at the end of the first week of the disease (see Fig. 4.**14**).

Rare Pathogens. Rare causes of maculopapular exanthema are acute HIV infection, infections with adenoviruses, dengue virus, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, *Bartonella henselae* (cat scratch disease), leptospires, rickettsiae, *Streptobacillus moniliformis*, or *Spirillum minus* (rat-bite fever), systemic mycoses (*Candida, Histoplasma,* cryptococci), *Toxoplasma gondii*, as well as Kawasaki disease.

Noninfectious Causes. *Noninfectious* causes of a maculopapular exanthema are drug reactions, serum disease, lupus erythematosus, Stevens–Johnson syndrome, Sweet syndrome, graft-versus-host disease, and, rarely, dermatomyositis.

Sweet Syndrome. This is an acute febrile disease of unclear etiology with leukocytosis and painful red or crimson papules or nodules on the skin. The lesions also can have a vesicular or pustular appearance. In addition, general symptoms, such as arthralgia, malaise, headaches, and myalgia, are also present. Therapy with systemic steroids results in improvement. The fever can precede the skin lesions by days or weeks. A skin biopsy reveals dense neutrophilic infiltrates. Sweet syndrome can be associated with infections (upper respiratory tract, intestinal tract), inflammatory bowel diseases, pregnancy, malignancies, or medications (especially granulocyte colony stimulation factor [G-CSF]).

Vesicles and Pustules

Bacterial and Viral Infections. Vesicles and pustules are typical skin lesions that occur as a result of an infection with herpes simplex and varicella-zoster viruses. Coxsackievirus A16 is most often responsible for *hand-foot-and-mouth disease* (occasionally, coxsackieviruses A4, A5, A7, A9, or A10). Typically the vesicles develop at the named locations on a clearly red background. The skin lesions that occur in *arthritis–dermatitis syndrome* (Fig. 4.**3**) are so characteristic that it is possible to make a diagnosis at a glance in most cases. A vesicopustular rash can also occur in staphylococcal sepsis. The distribution of the skin lesions, over the entire body, usually permits a distinction to be made with respect to disseminated gonococcal infection, in which the vesicles are particularly located on the distal extremities. Rare causes of vesicular skin lesions are rickettsial pox (*Rickettsia akari*), infection with *Vibrio vulnificus*, and diseases caused by *Monkeypox virus* (see Fig. 4.**7**) or *Cowpox virus* (see Fig. 4.**6**).

Noninfectious Causes. Noninfectious causes of vesicles and pustules are drug eruptions, allergic dermatitis, Stevens–Johnson syndrome, and Sweet syndrome.

Nodular Skin Lesions

Nonerythematous nodular lesions can be a sign of candidal sepsis or other fungal infections (blastomycosis, histoplasmosis, coccidioidomycosis, sporotrichosis).

Nocardia species or other nontuberculous mycobacteria (*Mycobacterium marinum*) can cause papular or red nodular skin lesions. Individuals infected with HIV occasionally exhibit papular or nodular skin lesions, which are likewise caused by nontuberculous mycobacteria (*M. fortuitum, M. chelonae, M. marinum*) or by *Bartonella henselae* (bacillary angiomatosis). Bacillary angiomatosis can exhibit a comparable morphology to that of Kaposi sarcoma. Erythema nodosum is described in Chapter 3.

Erythema

A diffuse erythema, with susequent desquamation of the skin possible, can be the main manifestation of acute and foudroyant systemic infections with a high mortality rate, such as streptococci or *toxic shock syndrome* caused by staphylococci. Additionally, a generalized erythema can be the predominant symptom in scarlet fever, enterovirus infections, Kawasaki disease, and noninfectious diseases (allergic reactions, lymphoma, and Sézary syndrome).

Urticaria

Urticarial skin lesions occur frequently and can be associated with infections caused by mycoplasma, enteroviruses, adenoviruses, Epstein–Barr virus, HIV, and hepatitis viruses, as well as febrile, noninfectious systemic diseases (allergy, vasculitis, malignancy).

Ulcers

Infectious Causes. Ulcerous skin lesions can be the primary manifestations of cutaneous leishmaniosis, various sexually transmitted infections, and, in addition, of rare infectious diseases such as anthrax, cutaneous diphtheria, ulceroglandular tularemia, bubonic plague, leprosy, Buruli ulcers (*Mycobacterium ulcerans*), ecthyma gangrenosum (*Pseudomonas aeruginosa*), or tropical ulcers. The primary lesion after a bite by a hard tick (which can carry various types of rickettsiae) is manifested as a small, ulcerous, nonpurulent lesion with a dark base (called eschar or tâche noir, see Fig. 4.**5**).

Noninfectious Causes. Ulcers of *noninfectious* origin are caused by: skin ulcers in peripheral vascular diseases, Behçet disease, vasculitis, cholesterol embolisms, inflammatory bowel diseases, lymphomas, erythema multiforme, primary dermatological diseases, tumors, or toxic skin injuries. The occasionally large ulcers in pyoderma gangrenosum can be associated with various underlying interna diseases.

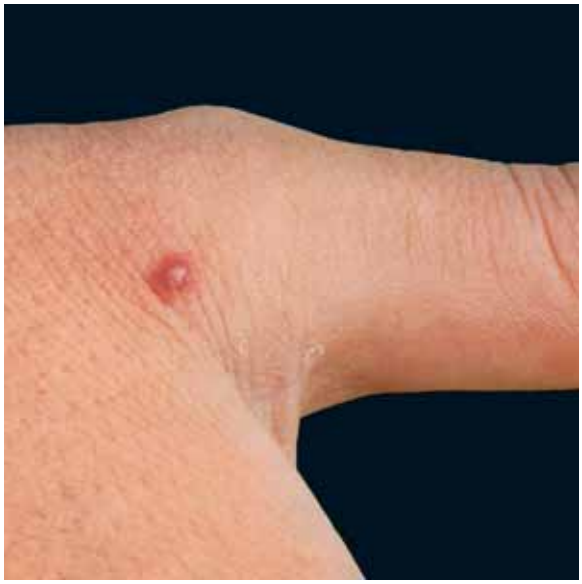

Fig. 4.**3** Skin lesion in arthritis–dermatitis syndrome.

Bacterial Skin Infections

Staphylococcal Infections. Most staphylococcal infections occur on the skin or the soft-tissues and are characterized by pus formation. For example:

- folliculitis
- impetigo
- pyoderma
- sweat gland abscesses
- furuncles
- carbuncles
- paronychia
- wound infections

are characterized by the local findings. Bacteremia occurs in 20–30% of cases of deep, localized infections. Staphylococcal infections of the mucous membranes can also lead to purulent inflammations.

In *toxic shock syndrome* a skin erythema develops, with a characteristic scaling of the palms and soles of the feet occuring approximately one week after infection.

In *pyomyositis* (an acute, localized staphylococcal infection of the skeletal muscles) the collection of pus is initially always intramuscular, such that there is no redness or other visible signs of skin inflammation. The cardinal symptom is localized muscle pain. The disease is mainly observed in tropical regions or in immunosuppressed patients.

Streptococcal Infections. Skin and soft-tissue infections caused by streptococci are:

- *erysipelas* and cellulitis (Fig. 4.**4**)
- contagious impetigo
- necrotizing fasciitis
- surgical wound infections.

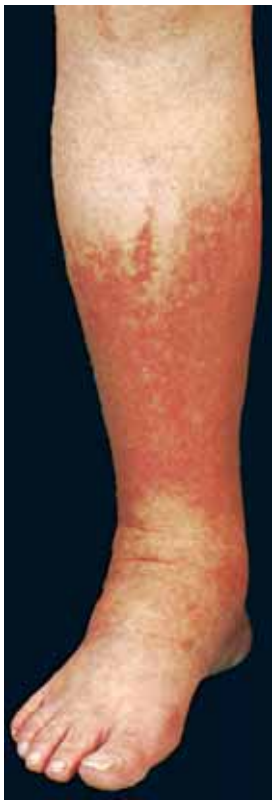

Fig. 4.**4** Erysipelas

A complication of a streptococcal skin infection that can occur two weeks later is *acute glomerulonephritis.*

Toxic shock syndrome, caused by streptococci, starts (usually after a minor trauma) with a soft-tissue infection, whose inflammatory margin, unlike that of the erysipelas, is poorly defined. Locally, the soft-tissues can necrotize rapidly. The general health of the patient is poor and a fulminant shock with multiorgan failure develops.

Arthritis–Dermatitis Syndrome (Gonococci). The skin lesions that occur in arthritis–dermatitis syndrome (1–3% of gonococcal infections) are so characteristic that it is possible to make an instant diagnosis in most cases (Fig. 4.**3**). The exanthema is in its evolution like that of varicella but the number of skin lesions is lower (5–20). For gonococcis, vesicles are mainly located on the distal extremities. A second facultative phase of the disease becomes manifest as tendosynovitis and septic arthritis of the large and medium joints.

Anthrax (*Bacillus anthracis*). Anthrax is a rare, usually occupationally related, zoonosis (e.g., stock farming, processing of pelts, animal hair, and wool). Additionally, anthrax spores have been used in bioterrorism attacks in powder form (skin contact) or as an aerosol (inhalation). In humans, dermatoid anthrax is the most common form (95%); pulmonary anthrax (5%) and intestinal anthrax (< 1%) are very rare. These pathogens can enter through the smallest skin injuries (or by inhalation or ingestion of the spores) and can cause purulent hemorrhagic inflammation with severe edema formation. The typical anthrax carbuncle (covered with a black scab) develops two to three days after infection and is relatively painless. These pathogens can be cultured from the carbuncle (particularly the margins) and from the blood.

Mycobacterial Skin Infections

Nontuberculous Mycobacteria Infection. In immunologically healthy persons *Mycobacterium marinum* can lead to granulomatous skin lesions, especially after exposure to contaminated water (e.g., from an aquarium). In Africa *M. ulcerans* causes ulcerous skin and soft-tissue infections (Buruli ulcers). Soft-tissue infections with *M. chelonae* and *M. fortuitum* are rare.

In *immunocompromised patients* skin lesions can also occur during systemic infections with *M. avium complex*, *M. kansasii*, *M. haemophilum*, *M. scrofulaceum*, *M. xenopi*, and *M. chelonae*.

Leprosy (*Mycobacterium leprae*). Leprosy is a chronic, systemic, infectious disease. Airborne transmission probably occurs between humans. The incubation time is extremely variable (one to 20 years). There are two main forms of leprosy, tuberculoid leprosy and lepromatous leprosy. Transitional forms are common:

- *Tuberculoid leprosy* exhibits a relatively benign course. The skin lesions are limited, depigmented, and manifest as erythematous maculae with a mainly unilateral and asymmetric arrangement. In the immediate surroundings, affected nerves can be palpated as painful cords. Superficial skin sensibility is frequently reduced. In contrast, internal organs are not affected.
- In *lepromatous leprosy,* the course is usually progressive. In addition to the infection of sensory nerves, a significant bacterial multiplication occurs in the skin, mucosa, reticuloendothelial system, liver, spleen, or testes. The facial skin, nose, and ears are significantly infiltrated (lion face) and chronic rhinitis and epistaxis develop. Tissue destruction mainly affects the skin and mucous membranes. Spreading along the trunk and the extremities is usually symmetrical.

The detection of acid–fast rods from cutaneous lesions is straightforward in the lepromatous form. These bacteria are rarely detected in the tuberculoid form.

Rickettsial Diseases

Rickettsiae are transmitted by a variety of vectors (Tab. 4.**5**). These diseases are classified in the spotted *fever group*, *typhus group*, and the *scrub typhus group*, and are manifested through fever and exanthema. Pathogens and vectors are found in specific endemic regions. Additional pathogens belonging to the family *Rickettsiacea* will be discussed under the corresponding primary symptoms: *Ehrlichia* (fever after tick bite), *Bartonella* (cat scratch disease with lymphadenopathy, endocarditis), and *Coxiella burnetii* (Q fever, pneumonia). The diagnosis of rickettsiosis can be confirmed *serologically*.

Spotted Fever. Rocky Mountain spotted fever (*Rickettsia rickettsii*), fièvre boutonneuse (*Rickettsia conorii)* endemic to the Mediterranean area, and the African tick-bite fever *(Rickettsia africae)* are transmitted by *hard ticks*. The clinical picture consists of a maculopapular rash and fever. Rocky Mountain spotted fever frequently presents with petechiae and hemorrhaging. In fièvre boutonneuse and African tick-bite fever, a primary lesion can be frequently found at the location of the tick bite (eschar, tâche noire, Fig. 4.**5**).

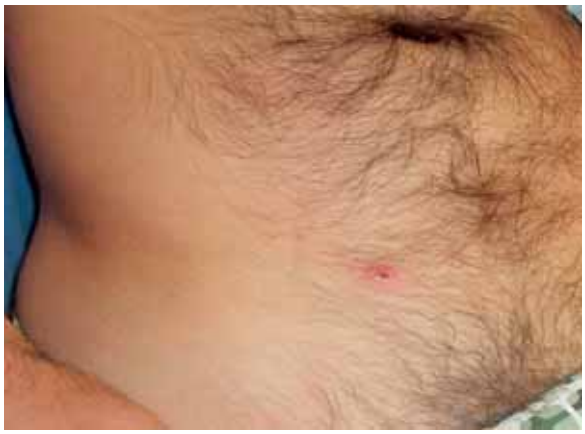

Fig. 4.**5** Eschar on abdominal skin after a tick bite in South Africa. Fever and right inguinal lymphadenopathy due to *Rickettsia africae* infection.

Epidemic Typhus. *Rickettsia prowazekii* is transmitted by lice and has caused epidemics, especially during wars and famines. Humans are the sole pathogen reservoir. The clinical picture (*typhus exanthematicus*) is characterized by a suddenly occurring, high fever, severe head and limb pain, and, beginning on the fourth day, a polymorphous, macular, partially hemorrhagic exanthema, which spreads from the lateral thorax. Typically present are conjunctivitis, a reddened face, and hepatosplenomegaly (approximately 50% of the cases). Simultaneously, the central nervous system can be affected, along with the exanthema. Somnolence, apathy, cranial nerve paralysis (deafness, visual, and speech disorders), tremor, central circulation disorders with hypotension, and tachycardia are observed. In severe courses of the disease, the kidneys are also frequently affected.

Endemic Typhus. The course of endemic typhus (*Rickettsia typhi*) is, in general, more benign and shorter. Rats, mice, and other small mammals are the pathogen reservoir and transmission in rats occurs via *rat fleas*.

Table 4.**5** Rickettsial diseases

Pathogen	Vector	Disease	Epidemiology
Spotted fever group			
R. conorii	hard tick	Mediterranean (fièvre boutonneuse), African and Indian tick-bite fever	Mediterranean, Africa, India
R. africae	hard tick	African tick-bite fever	Africa
R. rickettsii	hard tick	Rocky Mountain spotted fever	North and South America
R. sibirica	hard tick	North Asian tick fever	Asia, Russia, China, Mongolia
R. mongolotimonae	hard tick	Chinese tick-bite fever	East Asia
R. australis	soft tick	Queensland tick typhus	Australia
R. japonica	soft tick	Japanese tick-bite fever	Japan
R. akari	mite, rodents	rickettsial pox	USA, Europe, Korea
R. felis	flea	flea typhus	Mexico, Southern USA
R. helvetica	soft tick	febrile illness	Switzerland, France, Sweden
R. slovacae	hard tick	febrile illness, meningoencephalitis	Slovakia, Switzerland, France, Portugal
Typhus group			
R. prowazekii	body louse	epidemic louseborne typhus fever	worldwide, particularly Africa, South and Central America, Mexico, Asia
R. typhi	rat flea	endemic fleaborne typhus fever	worldwide
Tsutsugamushi fever			
Orientia tsutsugamushi	larval mite	scrub typhus (Tsutsugamushi disease)	East, South, Southeast Asia, Japan, Western Pacific, Australia