Crimean-Congo Hemorrhagic Fever: Epidemiology, Clinical Management, and Control Strategies

Turkish Organisation for Diagnostic Management

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CCHFV, First Step, Case Definition

Clinical Description

At least two of the following 4 clinical criteria must be present in patients suspected of CCHF disease.

- 1. Presence of at least two of the complaints listed below:
  - Fever (≥38°C)
  - Malaise / Fatigue
  - Headache
  - Generalized Body Pain
  - Joint Pain
  - Diarrhea
- 2. Bleeding findings related to skin and mucosa
- 3. Thrombocytopenia and/or leukopenia that cannot be explained by another cause
- 4. Elevated ALT and AST that cannot be explained by another cause

Epidemiological Criteria

Within the last 2 weeks;

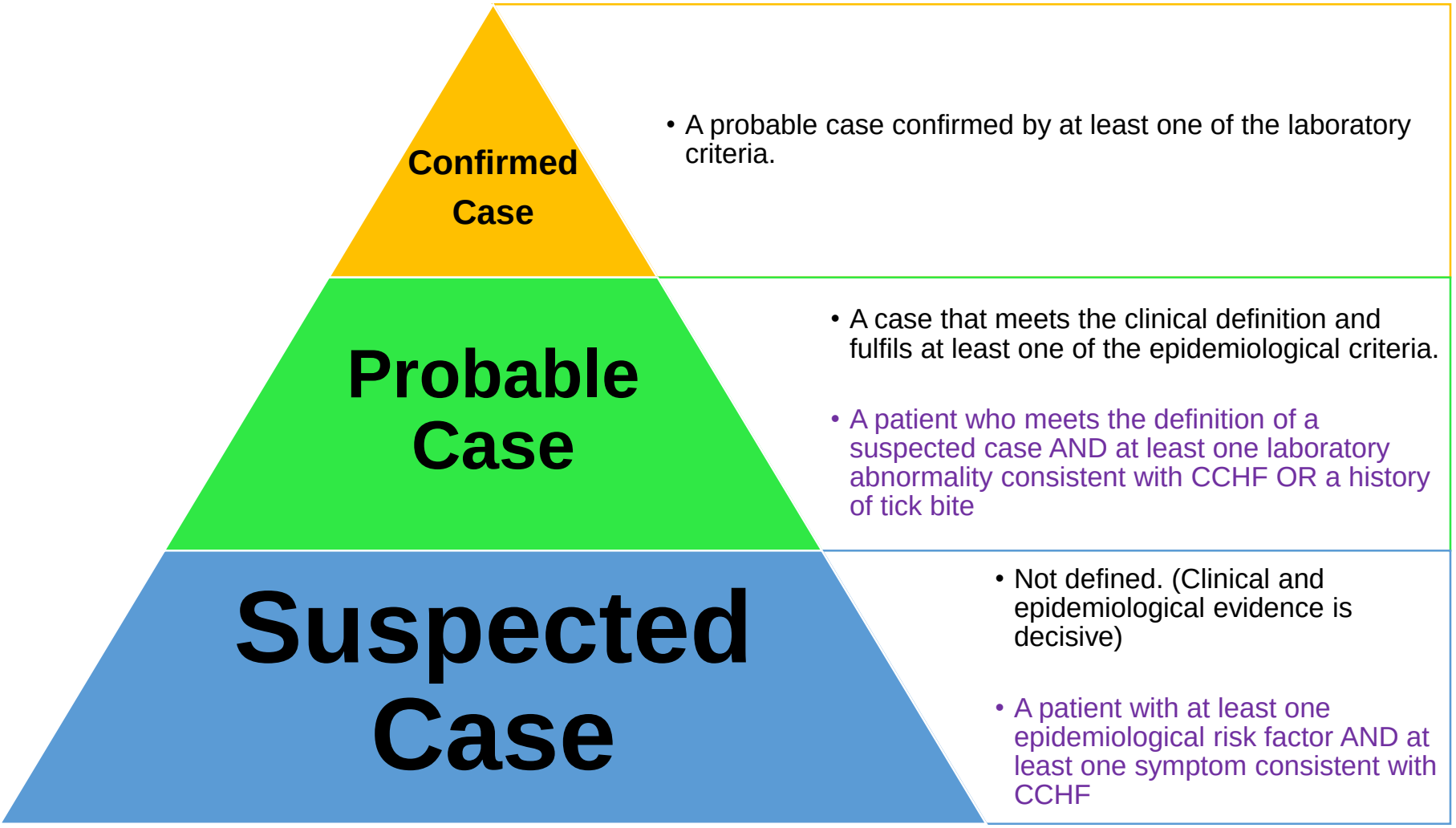
- 1. History of contact with ticks or tick attachment
- 2. History of contact with animal blood, tissue, and secretions
- 3. History of living in a rural area or traveling to a rural area
- 4. History of close contact with a laboratory-confirmed case

Laboratory Criteria

From samples of blood, body fluids, and tissues;

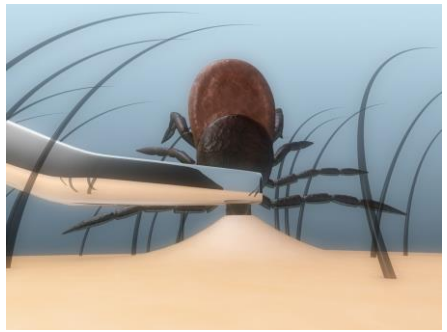
- 1. Virus isolation
- 2. Detection of virus-specific IgM antibody positivity
- 3. Detection of a ≥4-fold increase in virus-specific IgG titer in acute and convalescent phase sera
- 4. Detection of viral nucleic acid

Case Classification



PCR and serological tests should be requested for definitive diagnosis in all suspected and probable cases in endemic areas, and in all probable cases in non-endemic areas.

Algorithm for Managing Patients Presenting with Tick Infestation



1. Carefully remove the tick from the site where it is attached as soon as possible.
2. Clean the area with an antiseptic solution or soapy water.
3. Assess the patient's clinical presentation
   (ask about symptoms consistent with CCHF: fever, headache, generalized body aches, fatigue, joint pain, diarrhea and bleeding)
4. Perform a complete blood count

Blood test results are normal
No complaints

Inform the patient about possible symptoms

Ask the patient to contact a healthcare provider again if any of these symptoms occur within 10 days

If a patient has two symptoms consistent with CCHF,
or
in addition to these symptoms, their platelet count is below 150,000/mm³ and/or their white blood cell count is below 4,000/mm³

they should be assessed in accordance with the case management algorithm.

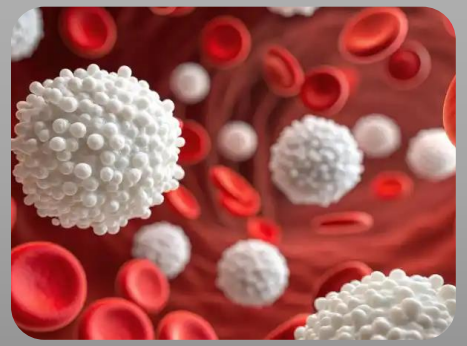
If a person has no symptoms but their platelet count is below 150,000/mm³ and/or their white blood cell count is below 4,000/mm³

they should be assessed by a specialist at a secondary care facility.

Regional centers (RCs) for Patient Management

Regional centres (RCs) have been **established to ensure that patient referrals run smoothly** during periods when the incidence of CCHF is rising and to prevent overcrowding at specific hospitals.

Baseline Biochemical Tests

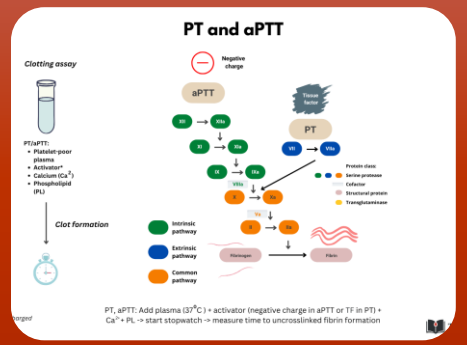


Complete Blood Count

- Thrombocytopenia is a constant feature of the infection.
- Patients present with leukopenia

Elevated Levels of

- Aspartate Transaminase (AST)
- Alanine Transaminase (ALT)
- Lactate Dehydrogenase (LDH)
- Creatine Phosphokinase (CPK)



Haemostasis Tests,

- Prothrombin time (PT) and
- Activated partial thromboplastin time (aPTT) are prolonged
- Fibrinogen levels may be reduced,
- Fibrin degradation products

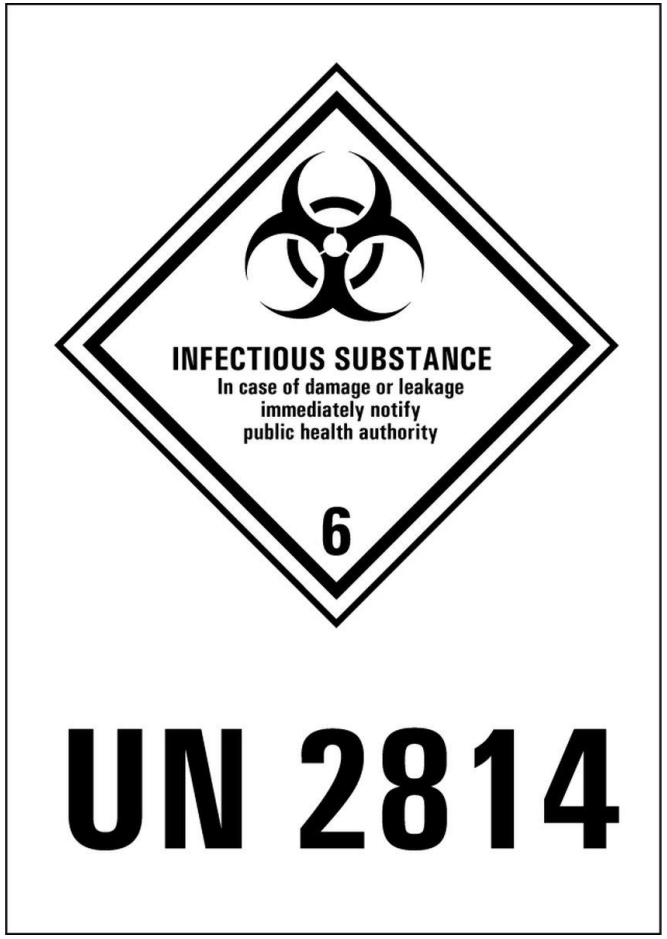
Clinical Samples to be Sent to The Laboratory

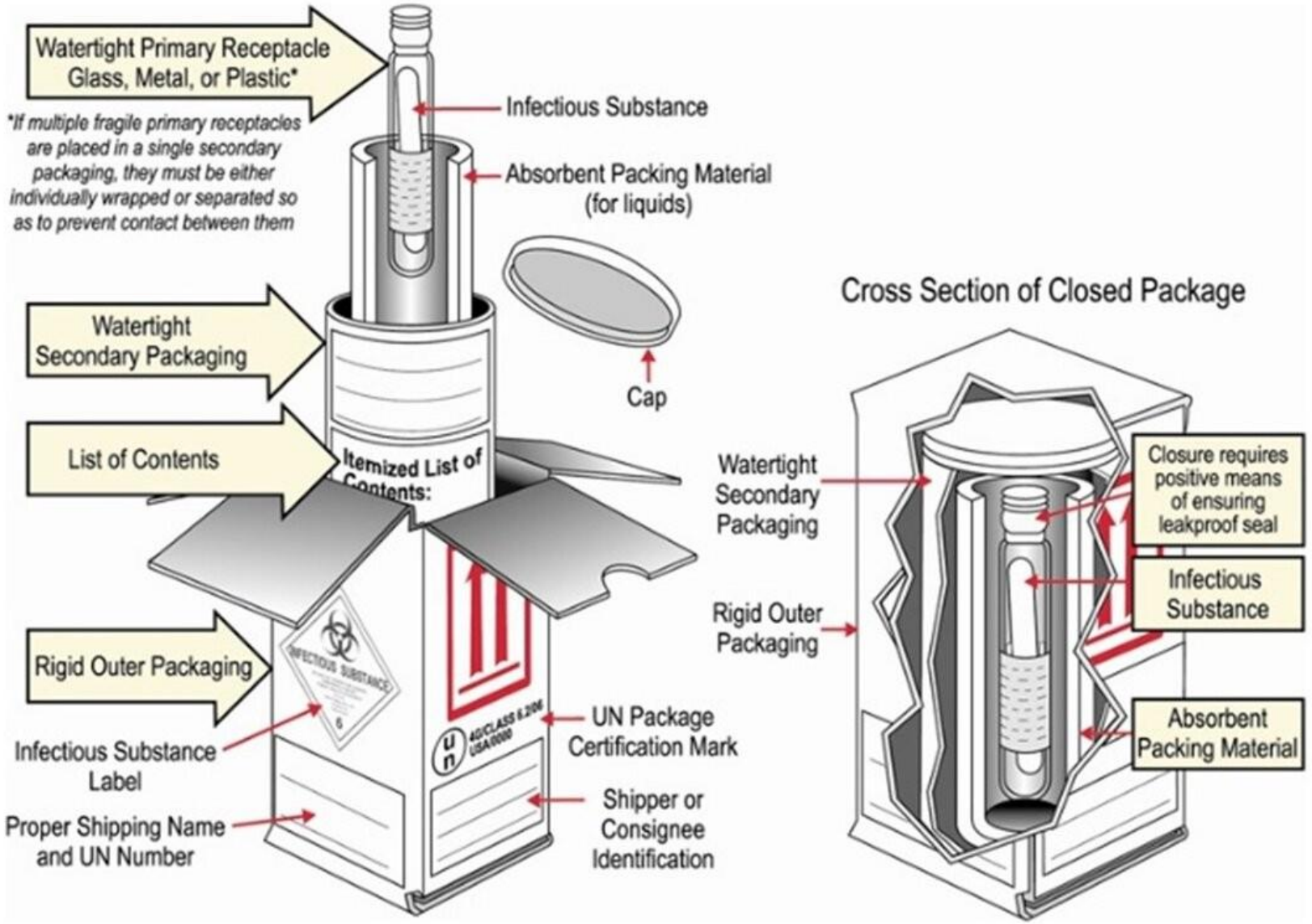
- Blood samples must be taken from the patient on admission (first serum sample) and on discharge (convalescent-phase serum sample) for serological or molecular tests.
- For ELISA tests, a serum sample collected in a centrifuge-compatible gel-lined biochemical tube and centrifuged should be used
- For PCR, a whole blood sample collected in an EDTA-containing tube should be used.
- A blood sample of 5 mL is sufficient for serological tests. Tubes containing blood should be gently inverted 5–6 times to prevent clotting; shaking of the tubes must be strictly avoided.

Clinical Samples to be Sent to The Laboratory

- If the time taken for the sample to reach the laboratory exceeds 48 hours,
  - The serum (or plasma) must be separated into a sterile tube immediately after centrifugation on the day of collection; **it can then be stored at 2–8 °C for up to 5 days**.
  - For nucleic acid analysis, if the blood cannot reach the laboratory within 6 hours of collection, the plasma (or serum) must be separated into a nuclease-free tube using a suitable sterile filter-tipped pipette.
- Sample processing is carried out at the National Arbovirus and Viral Zoonotic Diseases Laboratory under the Directorate of Microbiology Reference Laboratories and Biological Products, General Directorate of Public Health (HSGM), as well as at the Erzurum and Samsun Public Health Laboratories.
- Each province must send the sample to the designated laboratory.
- You must contact the Provincial Health Directorate regarding the collection and dispatch of samples. Clinical samples collected are sent to the reference laboratory via the Provincial Health Directorate using the “Crimean-Congo Haemorrhagic Fever Laboratory Request Form”. The information requested on the form must be completed accurately and in full.

Packaging and Labeling Requirements (Category A)



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Sinop
Samsun
Amasya
Tokat
Ordu
Giresun
Trabzon
Rize
Artvin
Ardahan
Kars
Iğdır
Ağrı
Erzincan
Erzurum
Gümüşhane
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Bingöl
Muş
Bitlis
Van
Elazığ
Diyarbakır
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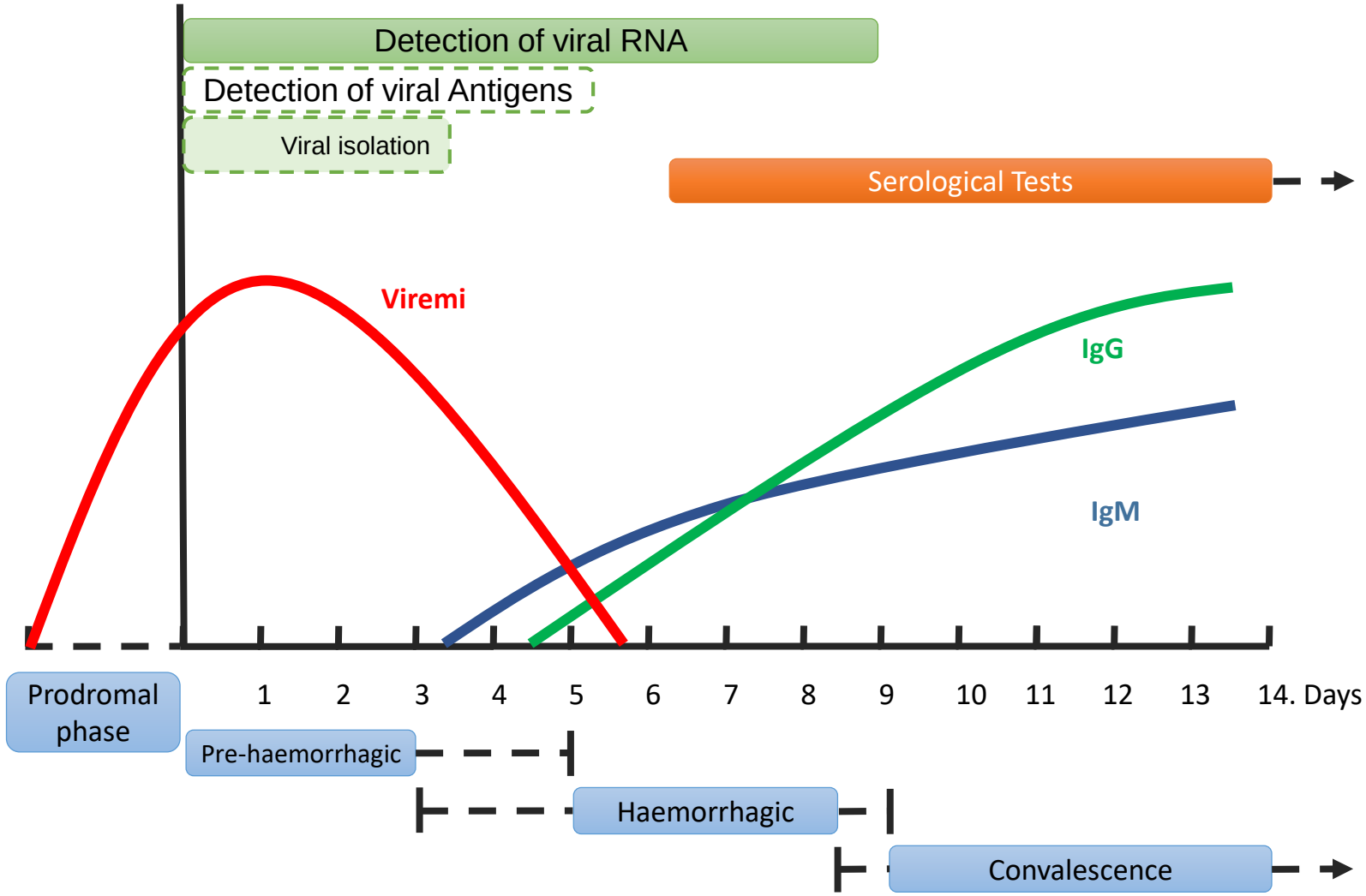
Antalya

Methods Used in Diagnosis



- Early diagnosis is important for public health and to prevent nosocomial transmission.
- A definitive diagnosis is established by
  - The detection of viral RNA in blood, body fluids or tissue samples;
  - The identification of a specific antigen;
    - the presence of virus-specific IgM antibodies;
    - or a ≥4-fold increase in virus-specific IgG titres in acute and convalescent-phase sera.
- In clinical practice, detection of IgM antibodies via ELISA is frequently combined with PCR testing for viral RNA .

Differential Diagnosis of CCHF

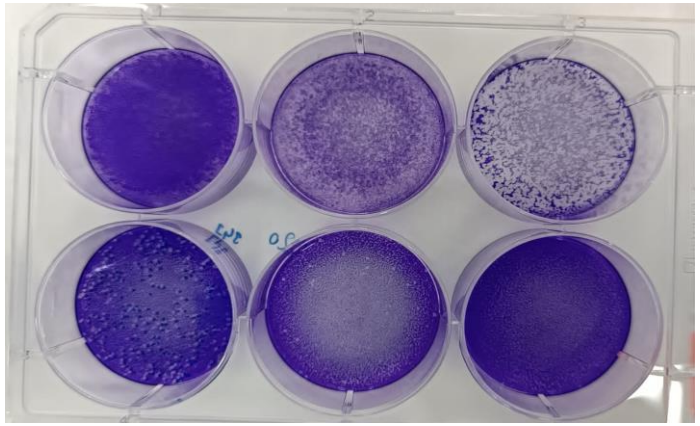
Category	Diseases / Conditions	Clinical & Diagnostic Distinctions
Viral Hemorrhagic Fevers	Ebola, Marburg, Lassa Fever, KFD, Colorado Tick Fever	Clinical presentation is often identical; **travel history** and specific geographical endemicity are key.
Exanthematous Viral Diseases	Measles, Rubella, Hemorrhagic Pox, **Viral Hepatitis**	Presence of Koplik spots (Measles); Hepatitis presents with marked **transaminase elevation** and jaundice.
Vector-Borne & Rickettsial	**Rickettsiosis (RMSF),** Lyme, Tularemia, **Malaria,** Babesiosis	RMSF: Centripetal rash. Malaria: Cyclical fever, splenomegaly, diagnosed via **Giemsa stain** (peripheral smear).
Severe Bacterial & Sepsis	**Meningococcal Septicaemia, Sepsis,** Septicaemic Plague, **Brucellosis**	Meningococcal: Rapid purpura fulminans. Sepsis: Multiorgan failure. Brucellosis: Undulant fever, osteoarticular involvement.
Gastrointestinal & Enteric	**Typhoid Fever**, Shigellosis	Typhoid: Faget's sign (relative bradycardia), "rose spots" on trunk, and positive stool/blood cultures.
Zoonotic & Environmental	Leptospirosis, **Q Fever,** Toxic Hepatitis, Drug Poisoning	Leptospirosis: Conjunctival suffusion and jaundice. Poisoning: History of ingestion, absence of fever (usually).
Hematologic & Malignancies	ITP, TTP, DIC, HUS, Haematological Malignancies	Malignancies (Leukemia): Weight loss, lymphadenopathy, blast cells on smear. TTP: Pentad (fever, anemia, thrombocytopenia, neuro/renal).
Inflammatory & Vascular	Vasculitis, HELLP Syndrome, Other VKA Disorders	VKA (Vitamin K Antagonist) disorders: History of **anticoagulant use**, prolonged PT/INR, absence of infectious prodrome.

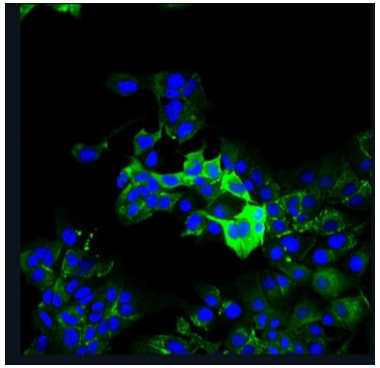
Diagnosis, management, and prevention of Crimean-Congo haemorrhagic fever: a Delphi-based consensus from two decades of experience in Türkiye

Önder Ergönül[1,2], Deniz Güllü[2,3,4], Defne Yigci[3], Aysel Kocagül Çelikbaş[5], Handan Alay[6],

- Very few centers perform PCR and/or serological tests themselves.
  - There are **3 regional reference laboratories in Turkey**, Ankara, Samsun and Erzurum
  - Receipt of results for samples not processed at the same center
    - As early as 3 days, but can take up to 10 days (Median 4.5 days)
    - Serological test results arrive later, (median 6 days)
    - If PCR positivity is detected in samples sent to the central laboratory, serological testing is not performed.
- No additional PCR or serology is requested during follow-up.
  - Clinical course is important at discharge; the PCR result is not considered a criterion for discharge.
  - Some centers send samples to the central laboratory at the time of discharge.

Virus isolation





Virus isolation in cell culture is not routine

Virus isolation is possible within the first 5 days (virus can be detected in the blood using this method up to the 13th day) of the disease, although the sensitivity of cell cultures is low.

Orthonairovirus haemorrhagiae isolate VK4_KUISCID segment L sequence
ACCESSION PV330319
Orthonairovirus hemorrhage isolate VK4_KUISCID segment M sequence
ACCESSION PV330318
Orthonairovirus haemorrhagiae isolate VK4_KUISCID segment S sequence
ACCESSION PV330317

Pfu/ml= 353,75/(10^-4*0,1)=3,54*10^7

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NOTIFICATION & SURVEILLANCE

- Crimean-Congo haemorrhagic fever (CCHF) is a notifiable disease in Türkiye. It is mandatory for all suspected KKKA cases to be recorded in the system via hospital admission.
- It has been actively monitored since 2002.
- Since 2011, the web-based KKKA Information System has been used for the reporting and monitoring of KKKA cases (https://kkka.saglik.gov.tr/giris.aspx).