# Crimean Congo Hemorrhagic Fever (CCHF)

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# History

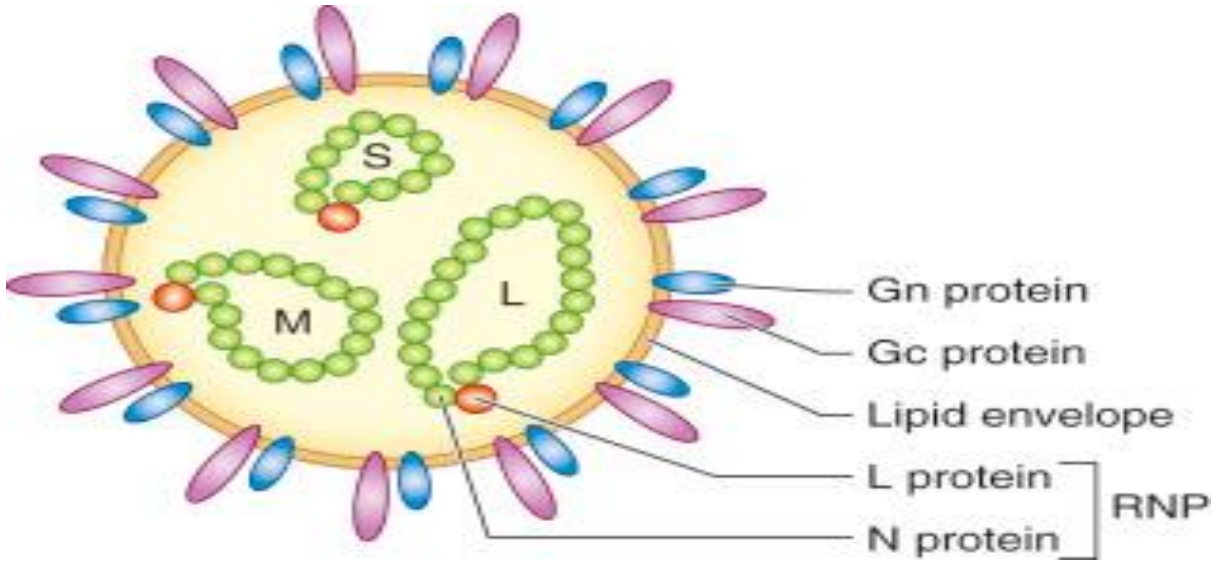
- ١١١٠ : Georgani ( First description of disease)
- ١٩٤٢ : Chomakof ( First medical report)
- ١٩٤٤ : Crime (An outbreak): ٢٠٠ person die
- ١٩٤٦ : Turkmenistan (Nosocomial outbreak): ٧ individuals, ٥ nosocomial
- ١٩٥٦ : Congo (Identification of virus)
- ١٩٦٩ : Same etiologic agent

# Virology

- CCHF virus (CCHFV) is a negative-stranded, enveloped RNA virus
- Order: Bunyavirales
- Family: Nairoviridae
- Genus: Orthonairovirus
- Virus: Crimean-Congo hemorrhagic fever

# Virology

- The genome of CCHFV has three segments:
  - small (S), medium (M), and large (L)
- Based on the CCHFV S-segment sequences, CCHFV strains have seven clades in different geographical locations



# Virology

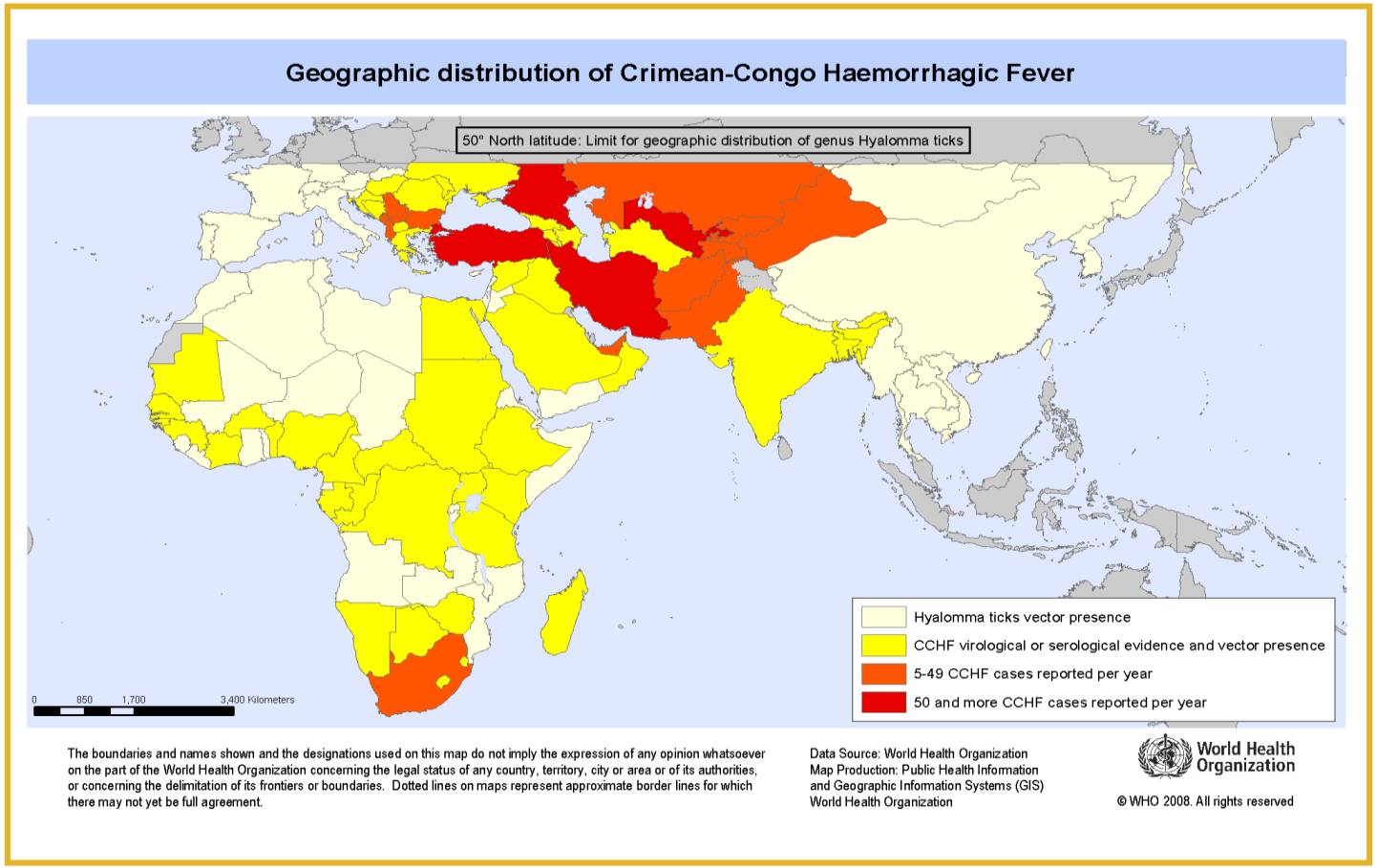
- High viral load up to ٨-١٢ days
- CCHFV can be cultured in  different cell lines
- Culture requires biosafety level ٤ laboratories and is only used for research purposes
- CCHFV is stable in blood and plasma in ٤ °C for ٢-٣ weeks

# Epidemiology

- Geography and season
  - CCHF is endemic in parts of **Africa**, the **Middle East**, **Asia**, and **southeastern Europe**
    - **Africa**: Democratic Republic of Congo, South Africa, Nigeria, Senegal, Uganda, Tanzania, Mauritania, Kenya
    - **Asia**: Pakistan, Afghanistan, Tajikistan, Uzbekistan, Kazakhstan, China
    - **Middle East**: Iran, Iraq, United Arab Emirates, Saudi Arabia, Oman
    - **Southeastern Europe**: Russian Federation, Bulgaria, Albania, Kosovo, Turkey, Greece, and Spain
  - CCHFV is common between **May** and **September**, with a peak incidence in **June** and **July**
  - Seasonal transmission at moderate altitudes, typically around ١٠٠٠ m

# Epidemiology

- Geography and season



# Epidemiology

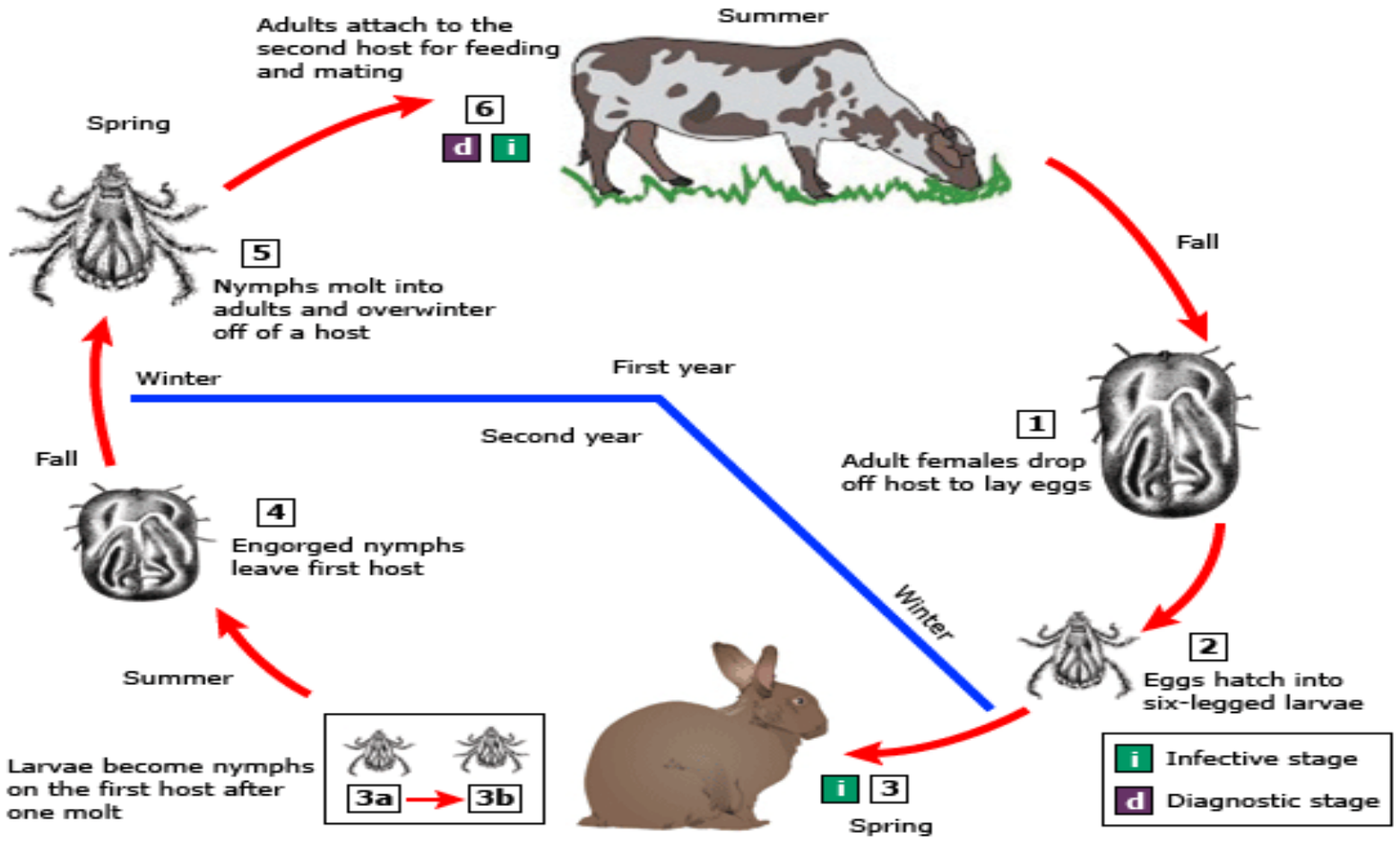
- Ticks
  - CCHFV is primarily transmitted via hard-bodied **Hyalomma** ticks of the family Ixodes, particularly Hyalomma marginatum
  - CCHFV has also been isolated from **Rhipicephalus**, **Boophilus**, and **Dermacentor** spp, which may also transmit the virus

- The most common viral *reservoirs* are domestic livestock (sheep, goat, cattle, and pig), which are infected by **adult ticks**
- **Larvae** and **nymphs** tend to feed on rodents, hares, hedgehogs, and ground dwelling birds, which serve as amplifying hosts for the virus

# Epidemiology

- Ticks

Two-host ixodid tick life cycle



# Epidemiology

- Disease emergence
  - The incidence of CCHF appears to be increasing due to:
    - Changing agricultural practices
    - Climate change
    - Movement of domestic animals
    - Migrating birds
    - Increasing numbers of susceptible animals
    - Increasing tick populations

# Epidemiology

- Transmission
  - Ticks
  - Direct contact with blood or other bodily fluids of infected animals
  - Nosocomial transmission
    - Direct contact with blood and body fluids
    - Needle -stick injuries
    - Splash exposures
    - Aerosol-generating procedures
  - Vertical transmission

# Epidemiology

- Risk groups
  - Agricultural workers
  - Individuals in rural areas engaged in animal husbandry
  - Abattoir workers
  - Veterinarians
  - Leather factory workers in areas with high tick density
  - Campers and hikers
  - Hunters
  - Soldiers
  - Health care workers
  - Travelers to endemic areas

# Pathogenesis

- Primary Viremia
- Replication in RES
- Secondary viremia & endothelial damage

# Clinical manifestations

- Incubation period: ١-١٣ days
  - **Following tick bite**: one to three days; the incubation period
  - **Following contact with blood** and body fluids: three to seven days
  - Relatively short incubation periods have been described in cases due to **nosocomial infection** during later stages of disease, which are associated with high viral loads as well as *diarrhea*, *vomiting*, and *hemorrhage*

# Clinical manifestations

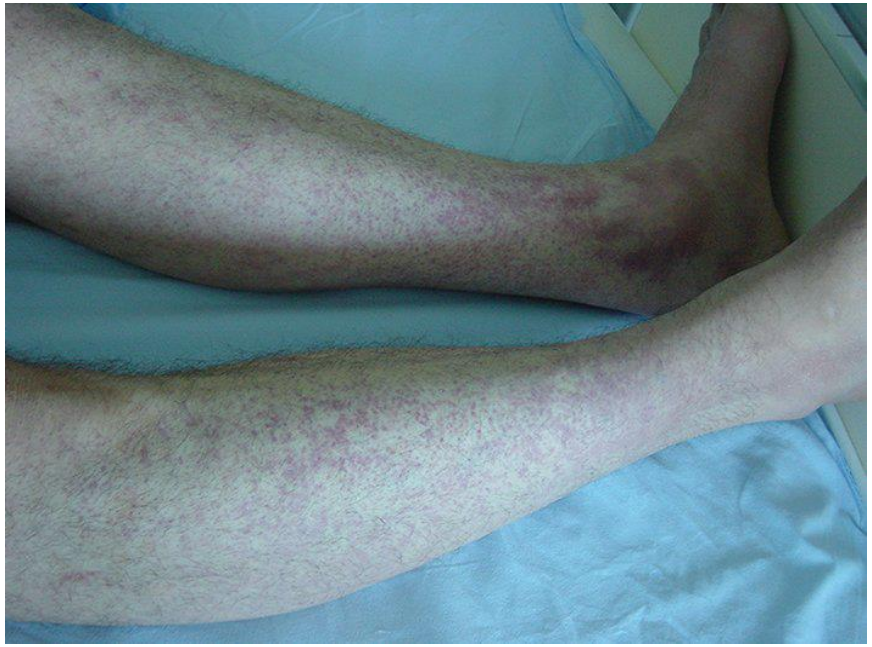
- Prodromal (Prehemorrhagic) stage: ٢-٤ days
  - Sudden onset of fever (٨٩ percent)
  - Headache(٦٨ percent)
  - Malaise
  - Fatigue (٩٢ percent)
  - Myalgia(٧٠ percent)
  - Sore throat
  - Dizziness
  - Conjunctivitis
  - Photophobia
  - Abdominal  pain
  - Nausea
  - Vomiting (٤٣ percent)
  - Diarrhea (٢٥ percent)

# Clinical manifestations

- Hemorrhagic stage: ٣-٧ days
  - Petechiae
  - Ecchymoses
  - Epistaxis
  - Gum bleeding
  - Pulmonary hemorrhage
  - Intra-abdominal bleeding, hematuria
  - Melena
  - Vaginal bleeding (heavy menstrual bleeding or early menstrual bleeding)
  - Rales are generally associated with pulmonary hemorrhage
  - Ocular findings include: subconjunctival and retinal hemorrhage
  - Other clinical findings include: tachycardia, hepatomegaly, lymphadenopathy, and confusion
- Convalescence stage: ٢-٦ weeks

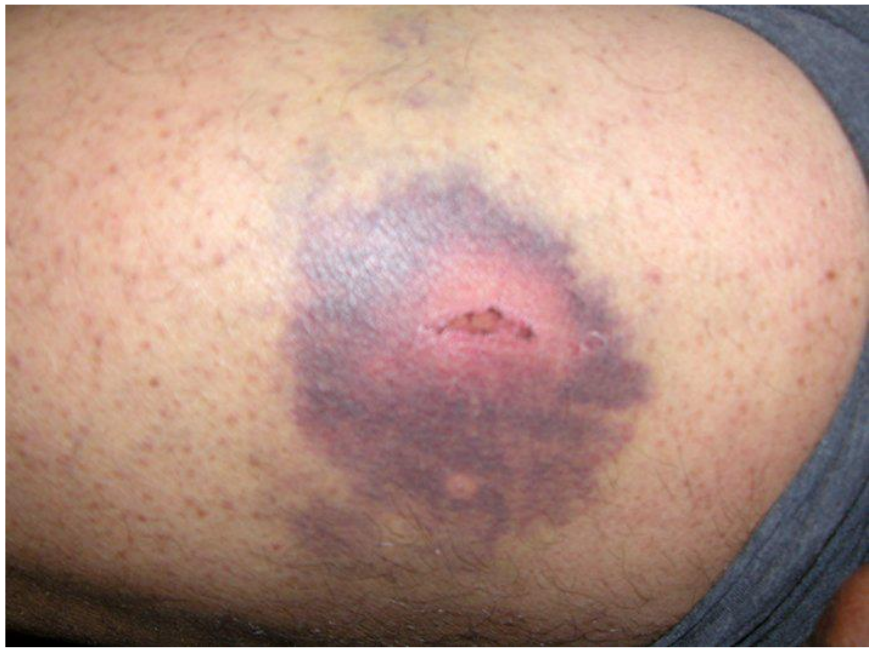
# Clinical manifestations

- Crimean-Congo hemorrhagic fever: Petechiae



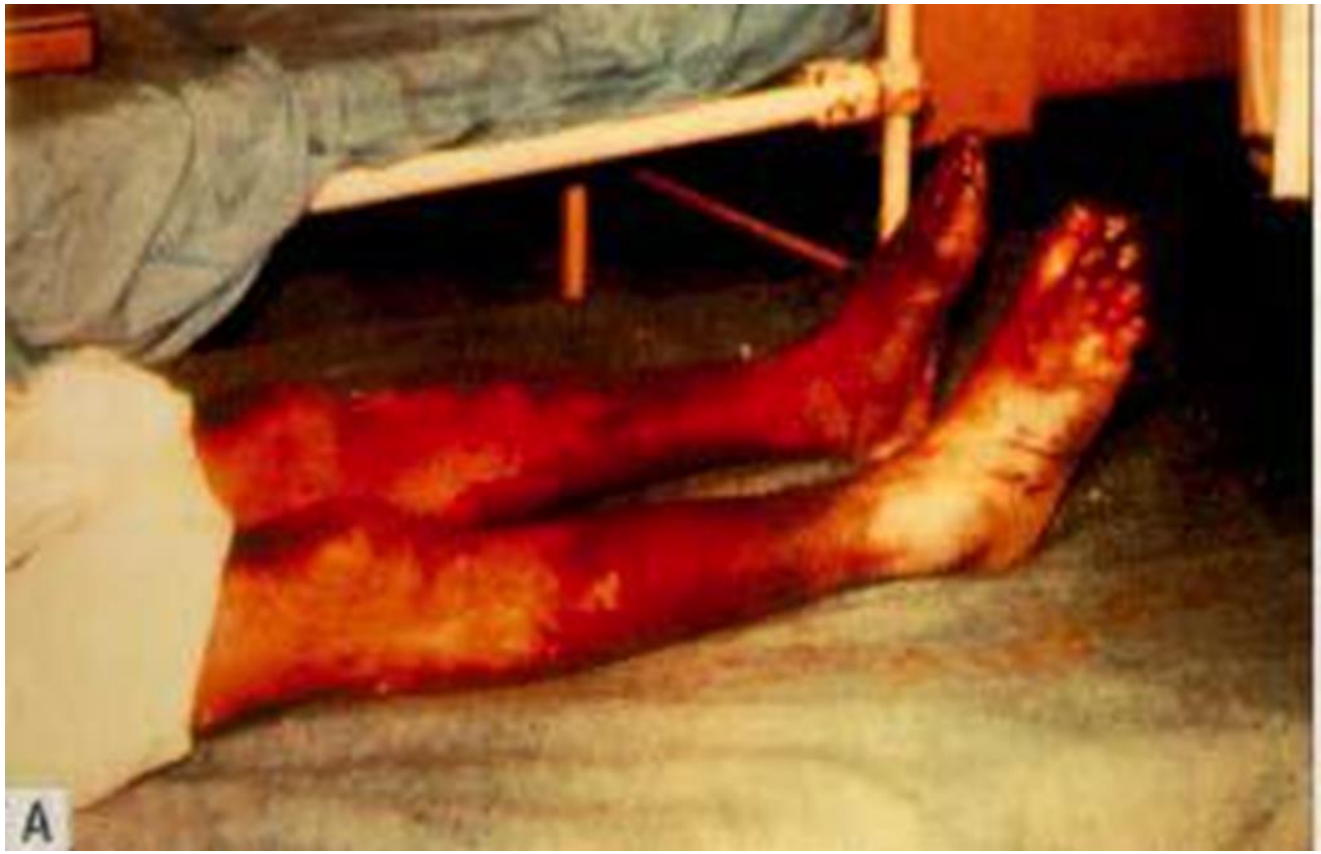
# Clinical manifestations

- Crimean-Congo hemorrhagic fever: Ecchymosis at tick bite area



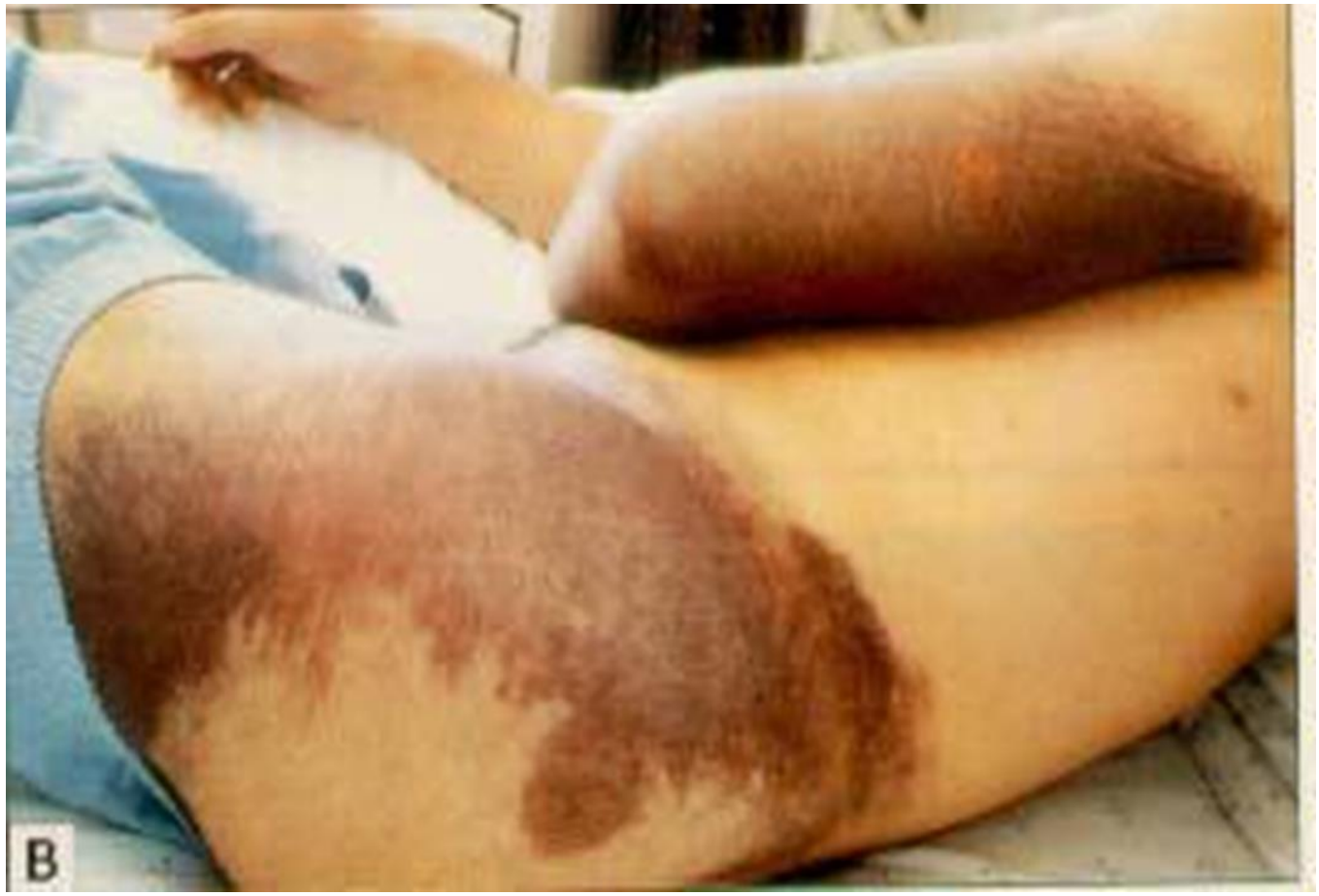
# Clinical manifestations

- Crimean-Congo hemorrhagic fever: Ecchymosis



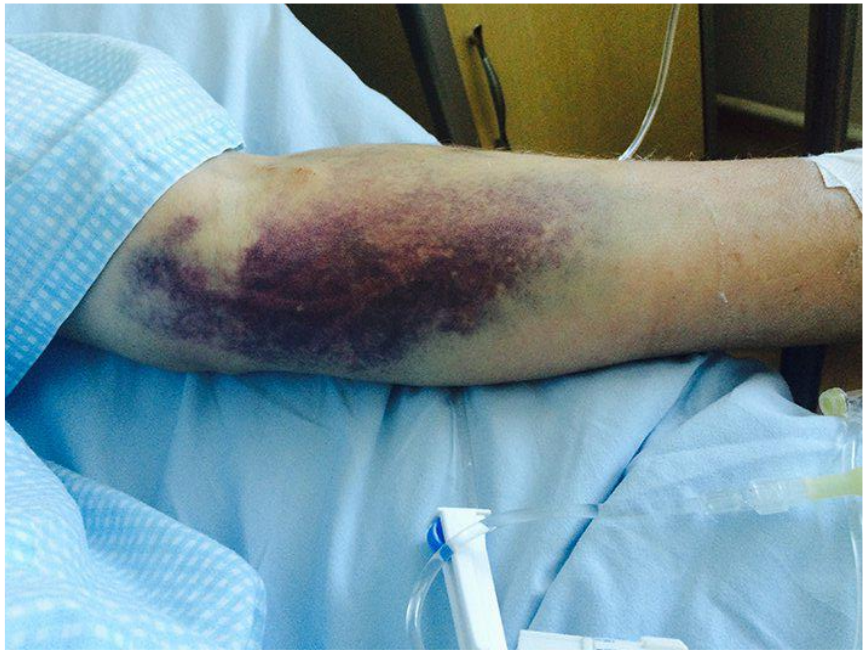
# Clinical manifestations

- Crimean-Congo hemorrhagic fever: Ecchymosis



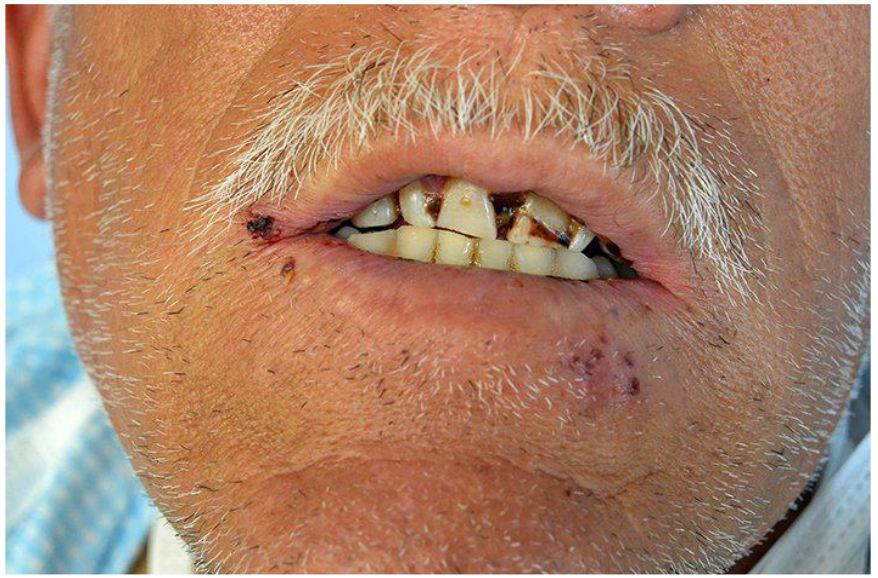
# Clinical manifestations

- Crimean-Congo hemorrhagic fever: Ecchymosis at injection site



# Clinical manifestations

- Crimean-Congo hemorrhagic fever: Gum bleeding



# Diagnosis

- Diagnostic Procedures: Non-Specific & Specific
- Case Definition

# Non-Specific Diagnostic Procedures

- Laboratory findings may include:
  - Thrombocytopenia
  - Leukopenia
  - Hyperbilirubinemia
  - Elevated transaminases
  - Prolongation of PTT, PT, INR
  - Anemia
- In the setting of multiorgan failure:
  - Elevated blood urea nitrogen
  - Creatinine
  - Creatine phosphokinase
- Patients with disseminated intravascular coagulation:
  - Decreased fibrinogen levels
  - Increased fibrin degradation products

# Specific Diagnostic Procedures

- Detection of CCHF virus (CCHFV) RNA by reverse-transcriptase polymerase chain reaction (RT-PCR)
- Specific immunoglobulin (Ig)M and IgG by ELISA
  - Specific IgM and IgG antibodies are detectable **five days** from the onset of symptoms
  - IgG antibodies can remain detectable for at least **five years**
  - Specific IgM positivity in a single sample indicates current infection
  - Seroconversion or fourfold rise of CCHFV IgG antibody levels in paired sera confirm recent or current infection
- CCHFV can be cultured in cell culture (For research purposes only)

# Case Definition

- Suspected Case:
  - Sudden onset of disease with:
  - **Fever** *plus* **Myalgia** *plus* **Bleeding*** *plus* **Epidemiologic** clue**
- Probable Case:
  - **Suspected case** *plus* **Thrombocytopenia** +/- Leukopepia or Leukocytosis
- Definite Case:
  - **Probable case** *plus* **Positive** PCR, Serology or Culture

*Petechia, Purpura, Ecchymosis, Epistaxis, Hematemesis, Melena

**Tick bite, Tick crash, Travel history, Contact with contaminated animals or patients fluids

# Case Definition

نام بیمار یا کد بیمار:
.....

**جدول معیار تشخیص بالینی تب خونریزی دهنده کریمه کنگو**

**چنانچه جمع امتیازات ۱۲ ویا بیشتر شود مورد بعنوان محتمل CCHF تلقی شده و تحت درمان قرار گیرد**

| **۱.سابقه تماس با عفونت به صورت :** | کمتر از یک هفته | بیشتر از یک هفته |
|---|---|---|
| گزش کنه،یا له کردن کنه با دست بدون پوشش (بدون دستکش یا حفاظ) | ۰ ۳ | ۰ ۲* |
| یا<br>تماس مستقیم با خون تازه یا سایر بافتهای دامها یا حیوانات بیمار | ۰ ۳* | ۰ ۲** |
| یا<br>تماس مستقیم با خون ، ترشحات یا مواد دفعی بیمار تایید شده یا محتمل CCHF<br>(شامل ورود سوزن آلوده به بدن) | ۰ ۳ | ۰ ۲ |
| یا<br>اقامت یا مسافرت در یک محیط روستایی که احتمال تماس با دامها یا کنه وجود داشته ، اما بروز یک تماس خاص تصادفی را نمی توان مشخص نمود | ۰ ۲ | ۰ ۱ |

| **۲- نشانه ها و علائم:** | |
|---|---|
| شروع ناگهانی | ۰ ۱ |
| تب بیش از ۳۸ درجه سانتی گرادحد اقل برای یکبار | ۰ ۱ |
| سردرد شدید | ۰ ۱ |
| درد عضلانی | ۰ ۱ |
| حالت تهوع با یا بدون استفراغ | ۰ ۱ |
| تمایل به خونریزی: راش پتشی ، اکیموز ، خونریزی از بینی، استفراغ خونی ، هماتوری ،یا ملنا | ۰ ۳ |

| **۳-یافته های آزمایشگاهی( در پنج روز اول بیماری)** | | |
|---|---|---|
| لکو پنی کمتر از ۳۰۰۰ در میلی متر مکعب یا لکو سیتوز بیشتر از ۹۰۰۰ در میلی متر مکعب | | ۰ ۱ |
| ترمبو سیتو پنی | پلاکت کمتر از ۱۵۰۰۰۰در میلی متر مکعب | ۰ ۱ |
| | پلاکت کمتر از ۱۰۰۰۰۰ در میلی متر مکعب | ۰ ۲ |
| یا کاهش ۵۰ در صد گلبولهای سفید یا پلاکتها در طی ۳ روز | | ۰ ۱ |
| PT غیر طبیعی | | ۰ ۱ |
| PTT غیر طبیعی | | ۰ ۱ |
| افزایش ترانس آمینازها | | |
| اسپارتات آمینو ترانس فراز(AST) بیشتر از ۱۰۰ واحد در لیتر | | ۰ ۱ |
| آلانین آمینو ترانس فراز(ALT) بیشتر از ۱۰۰ واحد در لیتر | | ۰ ۱ |

توضیح اینکه دور امتیاز مربوطه گرد (O) شود . ⊙ ندارد = صفر

* سیاه زخم و تب دره ریفت را باید رد کرد.

** تب مالت ، تب کیو و سیاه زخم را باید رد کرد.

**جمع امتیازات:**

**مهر و امضاء پزشک معالج:**

# Differential Diagnosis

- Infectious:
  - Other viral haemorrhagic fevers: dengue, Ebola, Marburg, Lassa, and yellow fever
  - Malaria
  - Rickettsial infection
  - Q fever
  - Brucellosis
  - Leptospirosis
  - Relapsing fever
  - Viral hepatitis
  - Meningococcemia
  - Severe sepsis
- Non infectious
  - Idiopathic thrombocytopenic purpura (ITP)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Acute leukemia
  - Acute abdomen
  - Vasculitis
  - Aplastic anemia

# Treatment

- Supportive care:
  - Mechanical ventilation
  - Hemodialysis
  - Vasopressor
  - inotropic agents
  - Acetaminophen (ibuprofen and aspirin should be avoided)
  - **Platelet transfusion** is warranted to maintain platelet count >٥٠,٠٠٠/mm٣ **in the setting of bleeding** *and* for **patients with platelet count <٢٠,٠٠٠/mm٣** in the absence of bleeding
  - The need for blood transfusion should be assessed based on the hemoglobin level as well as the general clinical status
  - Unnecessary interventional procedures should be avoided to minimize risk of bleeding

# Treatment

- There is **no proven antiviral treatment** for CCHF infection
  - Studies in vitro and in laboratory animals suggest that **ribavirin** might be effective in the treatment of severe CCHF, and observational clinical experience with the drug in CCHF supports its use:
    - ٣٠ mgr / kg : St
    - ١٥ mgr / kg : QID for ٤ days
    - ٧,٥ mgr/ kg : TDS for ٦ days
- Hyperimmunoglobulin (which is prepared from the plasma of donors with antibody against CCHF) can decrease viral load via direct neutralization, although viral strain variability may be an important determination in the use of this therapy
- Steroids
- Intravenous immunoglobulin
- Plasma exchange

# Prognosis

- The mortality rate varies among countries and ranges from ٢ to ٨٠ percent
- Mortality rates in endemic countries are approximately ٤ to ٢٠ percent
- CCHF is a notifiable disease in Turkey and Iran, and both countries have active surveillance
- **Independent predictors of mortality include**:
  - Presence of hemorrhage (particularly gastrointestinal bleeding and hematuria)
  - Impaired consciousness
  - Central nervous system involvement
  - Diarrhea
  - Splenomegaly
  - Thrombocytopenia
  - Leukocytosis
  - Increased alanine aminotransferase
  - Increased Aspartate aminotransferase
  - Increased Lactate dehydrogenase
  - Decreased fibrinogen levels with a prolonged activated partial thromboplastin time
  - CCHFV RNA level >١٠٧ copies/mL is an important indicator for mortality (positive predictive value ٨٠ percent, sensitivity ٨٩ percent, specificity ٩٣ percent)

# Infection control

- Infection control precautions:
  - **Standard**:
    - Hand hygiene
    - Safe-sharps systems
    - Safe phlebotomy
  - **Contact**:
    - personal protective equipment (an impervious gown, gloves, mask, and eye/face protection)
  - **Droplet**:
    - (N٩٥ mask or FFP٣ respirator) is required during aerosol-generating procedures
- Patients with suspected or confirmed CCHF should be treated in isolation rooms
- If this is not possible, cohorting of patients is appropriate
- The number of health care personnel entering patient rooms should be minimized
- Precautions may be discontinued for patients with:
  - No signs and symptoms of disease for at least three days
  - Platelet count >٥٠,٠٠٠/
  - Normal coagulation tests
  - If possible, a negative blood polymerase chain reaction for viral hemorrhagic fever should also be documented

# Infection control

- Postexposure management
    - Two-week period of monitoring:
        - **Daily** temperature measurement
        - **Weekly** assessment of complete blood count
        - **No quarantine** is required
    - Development of a febrile illness during the monitoring period should prompt diagnostic testing
    - The role of **ribavirin** for prevention of clinical illness when given as postexposure prophylaxis is uncertain:
        - **٢٠٠ mg/BD for ٥ days**

# Infection control

- Environmental cleaning
  - CCHF virus (CCHFV) can be inactivated by disinfectants including:
    - ١% sodium hypochlorite (household bleach)
    - ٧٠% alcohol
    - ٢% glutaraldehyde
    - Hydrogen peroxide
    - Peracetic acid
  - The virus is susceptible to high **temperature** at ٥٦°C (١٣٣°F) for ٣٠ minutes or ٦٠°C (١٤٠°F) for ١٥ minutes
  - Areas contaminated with CCHFV can be disinfected with an approved hospital disinfectant or bleach
  - Housekeeping staff should use personal protective equipment when cleaning

# Prevention

- Avoiding tick exposure
  - Wearing light-colored clothing allows easy detection of ticks
  - Tucking shirts into pants and pants into socks is helpful to minimize exposure
  - The use of a ٢٠ to ٣٠% N,N-diethyl-m-toluamide (DEET) repellant for skin
  - Permethrin-treated clothes
  - Grassy areas should be avoided in warm seasons when ticks are most active
- Manage tick bite properly
  - Ticks should not be handled with bare hands and should not be crushed or squeezed
  - Skin and clothes should be examined regularly for presence of ticks
  - Attached ticks should be removed with tweezers
  - Following tick removal, the skin should be cleaned with antiseptic
- Avoiding contact with animal bodily fluids
  - Control of CCHF in animals is difficult
  - Restricted areas should be established for slaughtering
  - To reduce the risk of human infection during slaughtering, **animals should be quarantined for ١٤ days before slaughtering**
  - Quarantine could also be applied to imported cattle
- Issues related to prevention of nosocomial transmission are discussed above

# What a physician should know about control and prevention of CCHF

١- Methods of transmission
٢- Clinical features
٣- Reporting & referring of suspected cases
٤- Strict isolation
٥- Universal precautions ( Blood tissue , ..)
٦- Diminished invasive procedures
٧- Decontamination
٨- Sending serum samples at the following times :
Clinical diagnosis : ٥ days later : ٥ days later
٩- Ribavirin therapy
١٠- Ribavirin prophylaxis