CCHF

Dr.Shiva shabani

FLLOWSHIP OF INFECTIOUS DISEASES IN IMMUNCOPROMISED PATIENTS AND TRANSPLANT

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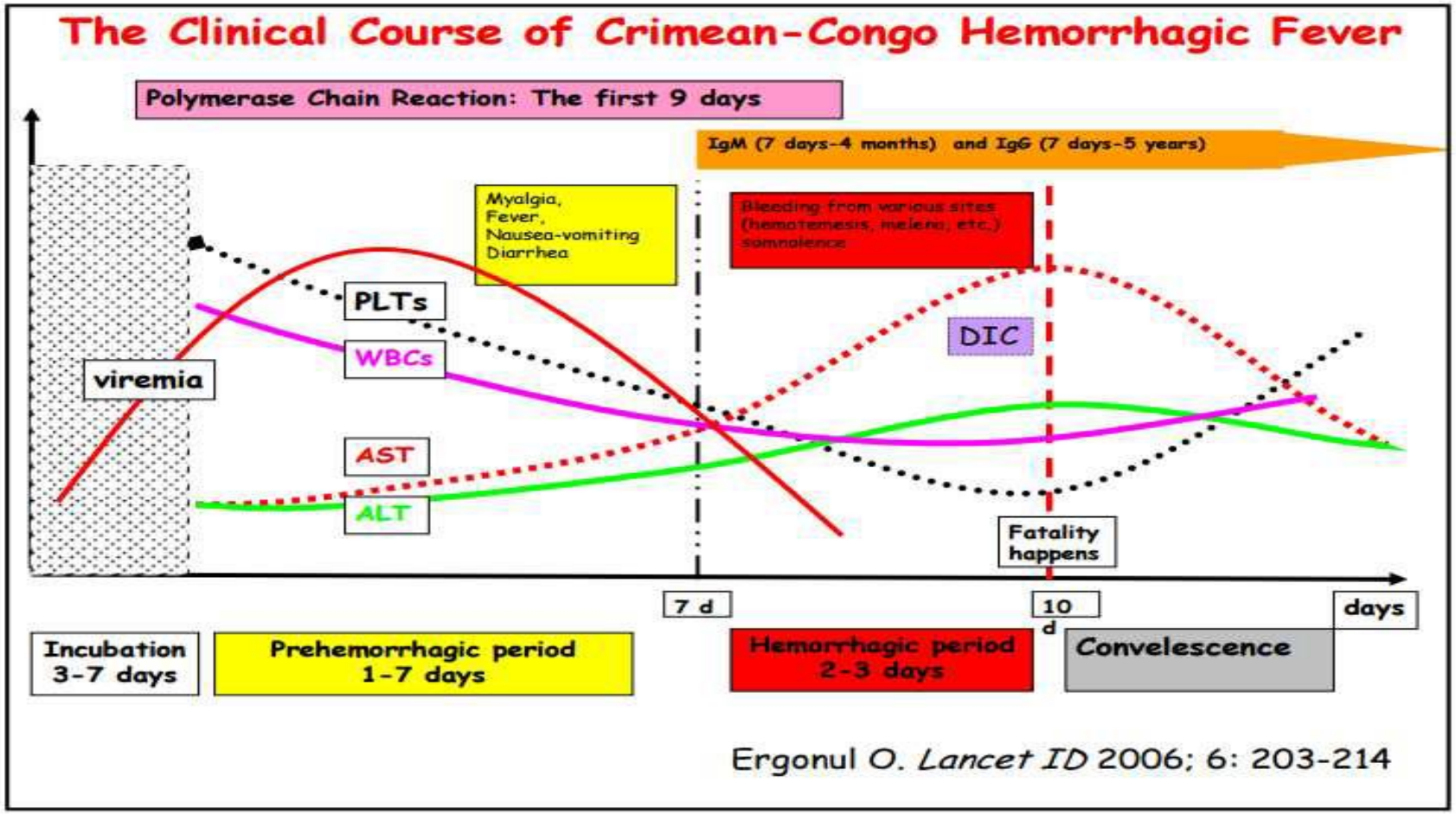
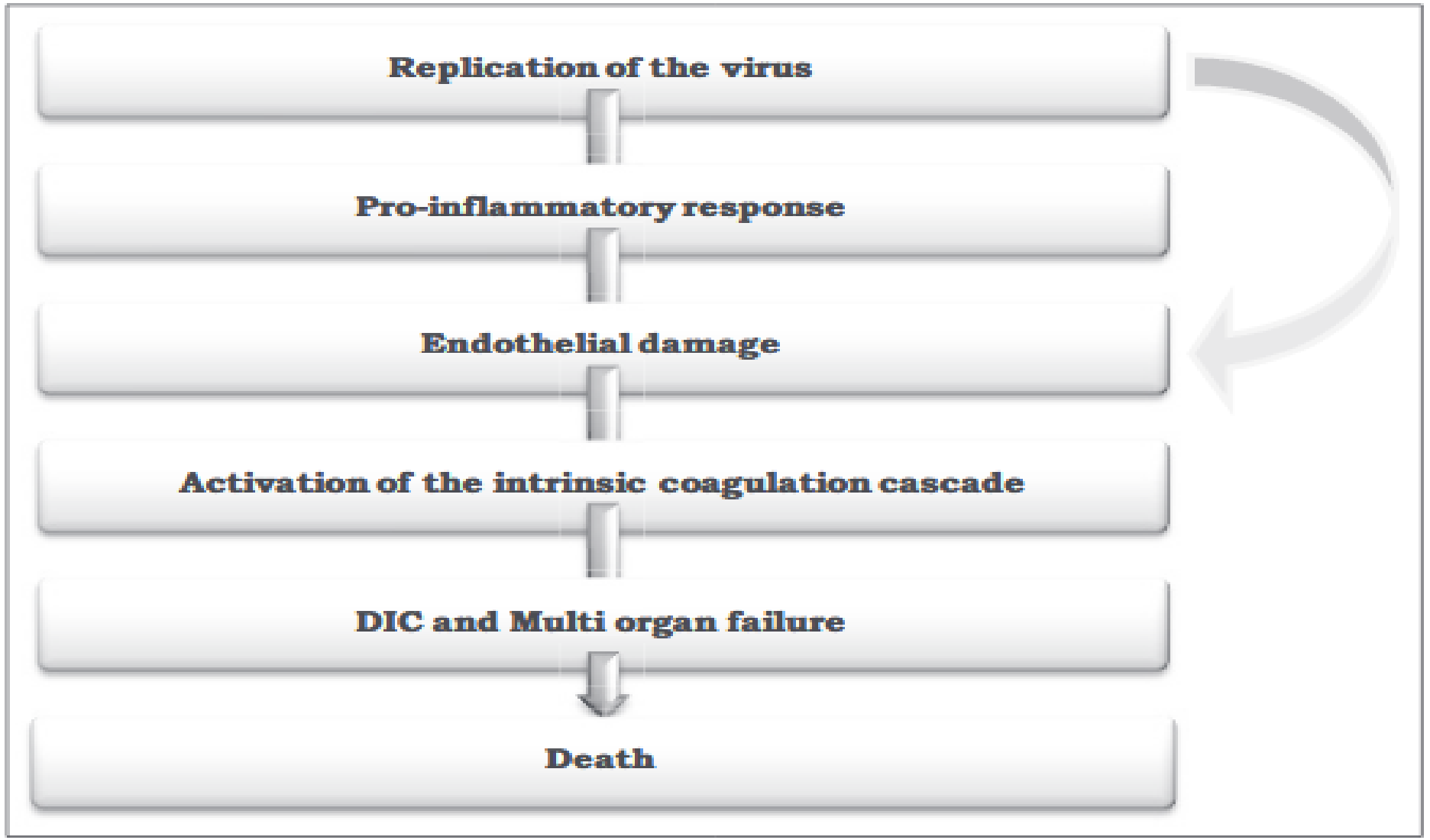

The Clinical Course of Crimean-Congo Hemorrhagic Fever
Polymerase Chain Reaction: The first 9 days
IgM (7 days-4 months) and IgG (7 days-5 years)
Myalgia,
Fever,
Nausea-vomiting
Diarrhea
Bleeding from various sites
(hematemesis, melena, etc.)
somnolence
PLTs
WBCs
viremia
DIC
AST
ALT
Fatality
happens
7 d
10
d
days
Incubation
3-7 days
Prehemorrhagic period
1-7 days
Hemorrhagic period
2-3 days
Convelescence
Ergonul O. Lancet ID 2006; 6: 203-214

- Incubation period
- Prehemorrhagic phase
- Hemorrhagic phase
- Convalescent phase

PATHOGENESIS



NATURAL HISTORY

- **Death** occurs in **2nd week** of illness.
- **Recovery starts** on **9th or 10th day of onset of illness**.
- **Complications: (after 5th day)**

• Hepatitis (tender hepatomegaly)
• rapid kidney deterioration,
• sudden liver failure or
• pulmonary failure
• DIC and Shock

In case of diagnosing a probable case, the sampling guideline is as such, 3 samples:

- First sample: upon clinical diagnosis
- Second sample: 5 days after taking the first sample
- Third sample: 10 days after taking the first sample

- All samples are taken under observation of Provincial Health Center and Provincial Reference Lab then are sent to Pasteur Institute of Iran

Treatment

The current approach to treatment of CCHF is based on :

-General supportive measures

-Monitoring of the patient’s hematologic and coagulation status

-Use of Ribavirin.

Almost all therapy has employed the oral form of the drug.

Ribavirin in Hemorrhagic Fevers

- Ribavirin is **the only antiviral drug** that has been used to treat viral hemorrhagic fever syndromes, including CCHF and Lassa fever.

Clinical use of Ribavirin

No randomized clinical trials of the efficacy of ribavirin against CCHF have been performed

-The efficacy has been described in several observational studies.

- A report published in South Africa in 1985 described the use of intravenous Ribavirin for both therapy and postexposure prophylaxis in a small number of patients in a nosocomial outbreak

CCHF Treatment in Heath care Workers

- In 1994, in Pakistan, Fisher Hoch et al reported **three health workers infected with CCHF virus who were treated with oral ribavirin**. All the three patients were severely ill.
- **The patients became afebrile** within 48 hours of treatment with Ribavirin.
- All the three patients made a complete recovery

- In a historical cohort study, in Iran, in 2003, we compared the mortality rate among patients suspected of having CCHF who received treatment with oral Ribavirin and those who did not
- The efficacy of oral Ribavirin was 80% among patients with confirmed CCHF and 34% among patients suspected of having CCHF.

Post exposure prophylaxis

- Prophylaxis is suggested after a high-risk contamination, such as a needle stick injury

Daily follow-up by checking complete blood count and biochemical tests for the exposed individuals is highly recommended.

Ribavirin prophylaxis is generally well tolerated, potentially useful and should therefore be recommended for health care workers who are at risk of exposures such as percutaneous injuries.

Prophylaxis protocol

- In case of known direct with the blood or secretions of a probable or confirmed case such as needle stick injury or contact with mucous membranes such as eye or mouth.

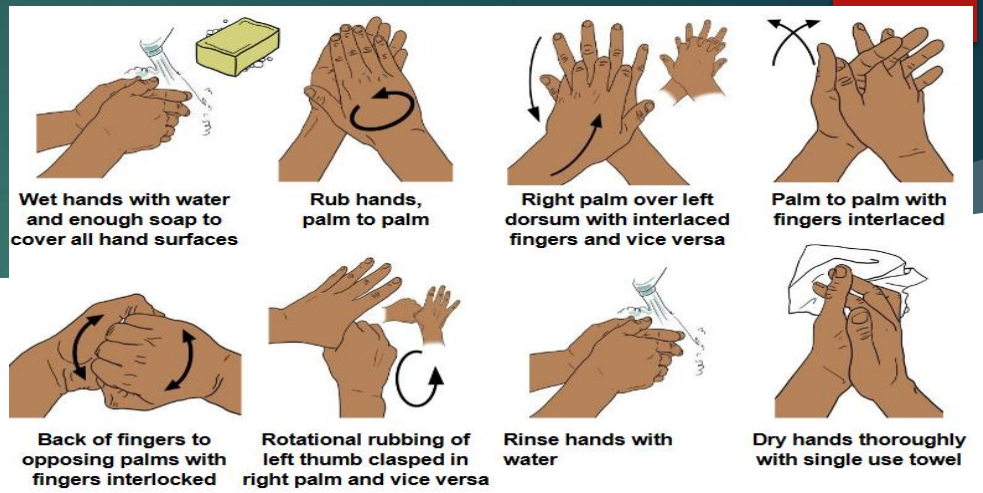
Prevention and control: Hospitals and Health Facilities

1- the patient should be treated in a **separated room** under strict barrier nursing.

2- **only designated medical/para-medical staff and attendants should attend the patient.**

Non – essential staff and attendants should not be allowed to enter the room.

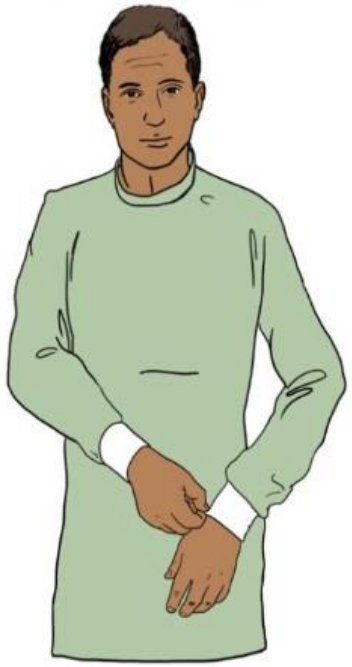
Entering patients room



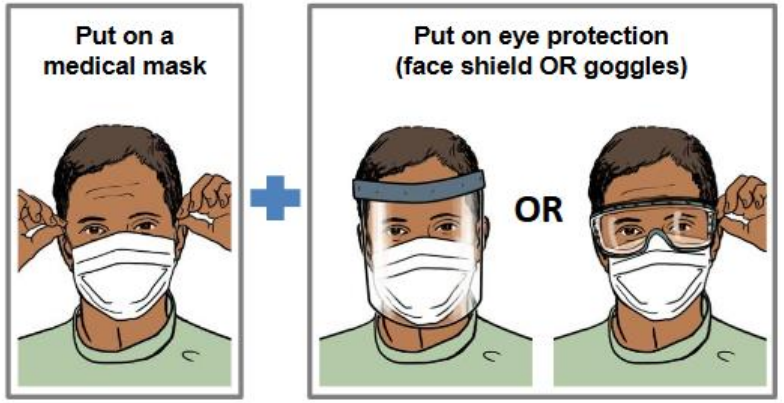
Before entering: Perform hand hygiene. Duration of the entire procedure: 40-60 sec if hand washingwith soap and water; 20-30 secif handrubbingwith an alcohol-based solution

Put on all personal protective equipment (PPE)

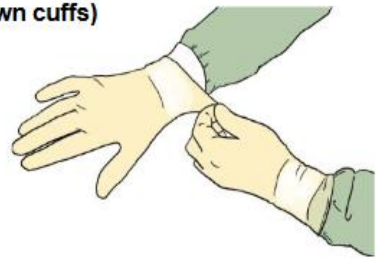
Step 2b: Put on a gown



Step 2c: Put on face protection



Step 2d: Put on gloves (over gown cuffs)



Prevention and control: Hospitals and Health Facilities

3-All secretions of the patient and hospital clothing in use of the patient should be treated as infectious and should be autoclaved before incinerating.

4- all medical and para-medical staff and attendants should wear disposable gloves, disposable maskes and gowns (gowns should be autoclaved before sending to the laundry or incineration).

5- safe sampling:

every effort should be made to avoid spills, pricks, injury and accidents during the management of patients.

Needles should not be re-capped but discarded in proper safety disposal box.

Safe sampling

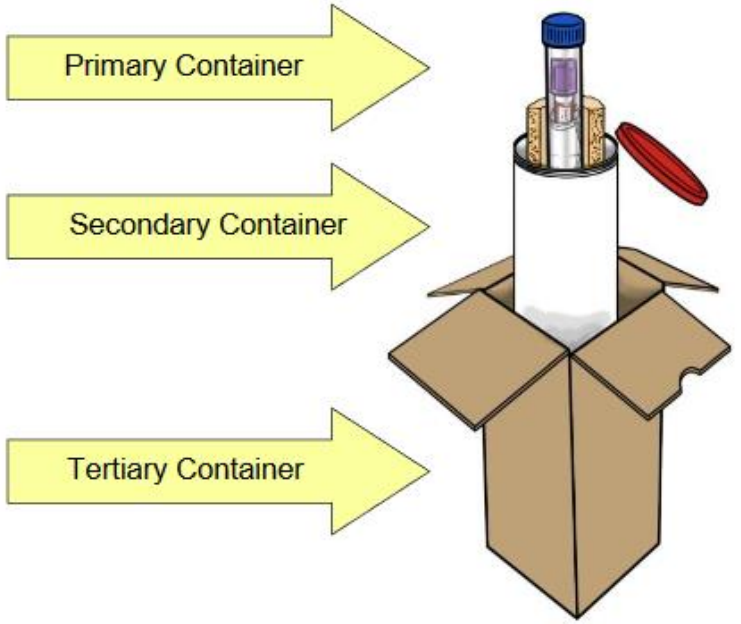
If the sharps container DOES NOT HAVE a needle remover:

- ✓ Put the needle and holder into a sharps container
- ✓ Do not remove the needle from the holder
- ✓ **Do not reuse the needle**

If the sharps container DOES HAVE a needle remover:

- ✓ Remove the needle following instructions on the sharps container
- ✓ Put the holder into the infectious waste bag for disinfection

- Samples for laboratory testing should be properly collected, labelled, sealed,and decontaminated from outside with liquid bleach and **packed in triplecontainer packing**
- Designated laboratory should be informed about the sample and should be transported to the designated laboratory with great caution, ensuring there would be no breakage or spills.



6- **All use material** e.g. syringes, gloves, canulla, tubing etc, should be **collected in autoclave-able bag** and **autoclaved before incinerating.**

7- **all instruments** should be **de-contaminated and autoclaved before re-use.**

8- all surface should be de- contaminated with liquid bleach.

9- after the patient is discharged, room surface should be wiped down with liquid bleach to kill the virus and the room should be fumigated.

Importance of Lab Diagnosis of CCHF

- Since the pathologic features of the disease resemble those of other infections, **unequivocal diagnosis can be made only by laboratory confirmation.**

The differential diagnosis include:

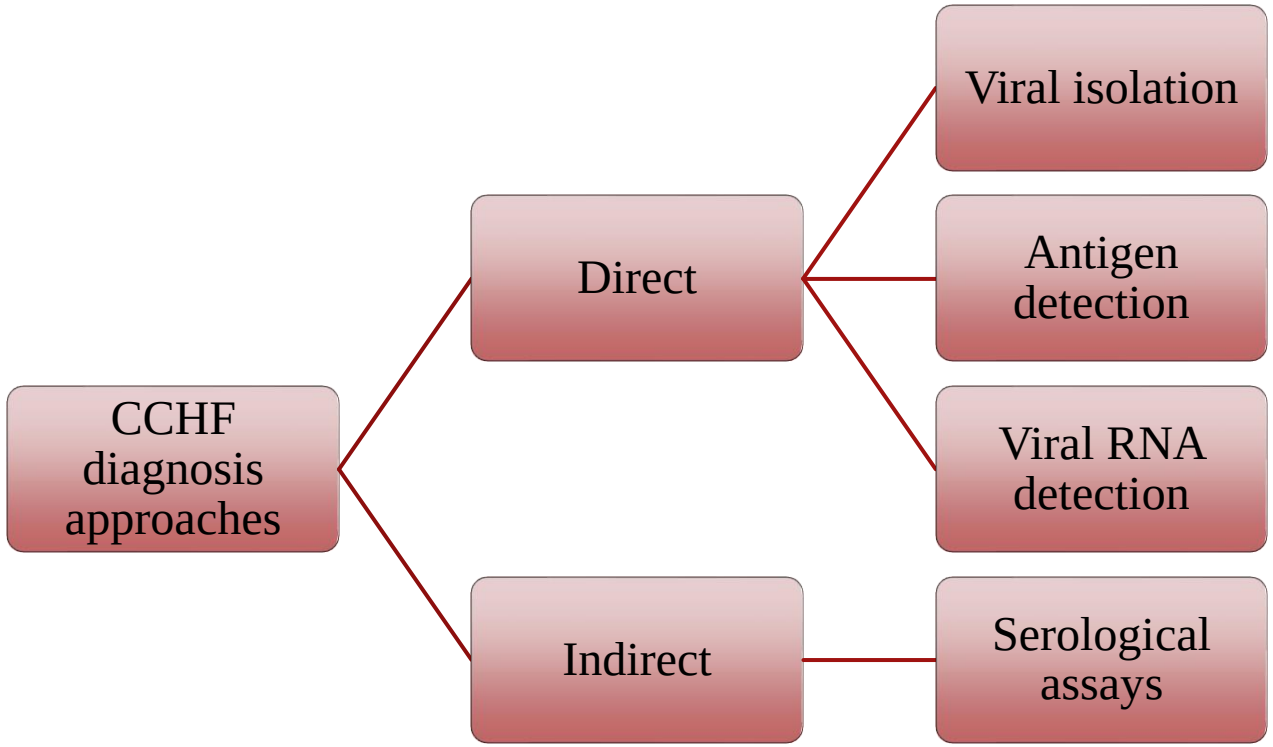
- Other Viral Hemorrhagic Fevers
- Rickettsiosis,
- Leptospirosis,
- Borreliosis,
- Meningococcemia,
- Malaria,
- Some non-infectious medical conditions

Nevertheless, no diagnostic kits have been licenced by the WHO

Laboratory Diagnosis of CCHF

Laboratory Diagnosis of CCHF


up
up
up
up


CCHF diagnosis approaches
Direct
Indirect
Viral isolation
Antigen detection
Viral RNA detection
Serological assays

Laboratory Diagnosis of CCHF

Virus isolation: In Acute phase (optimum: up to 1 week after illness)

- **Virus isolation methods:**
  - **Intracranial** or **intraperitoneal** inoculation of an **acute phase** sample to **newborn mice**.
  - **Isolation in cell culture** is far **simpler** and provides a more **rapid** result, **but** is generally considered **less sensitive** and can generally **only detect high concentrations of virus.**
    - CCHF virus replicates in a wide variety of primary cell and line cell cultures, including **Vero, CER, SW13 , LLC-MK2 and BHK21** cells

Viral isolation is seldom used for diagnosis because **1-it has to be done in BSL4 lab**, **2-it is time consuming**, **3-it needs highly expert technicians, 4- CCHFV may not produce CPE in cell culture**

Antigen detection: In acute phase (Optimum: 5 days post illness)

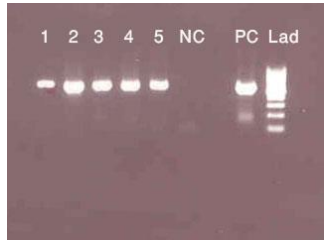
- The detection of CCHFV antigen is a useful rapid technique for the diagnosis **of acute infections**

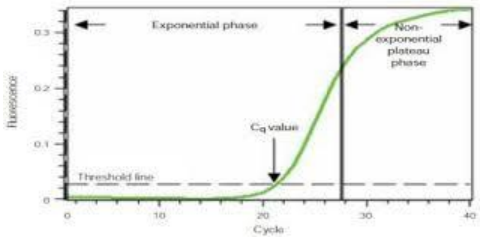
- **Ag detection methods:**
  - Immunocapture enzyme-linked Immunosorbent assay (ELISA)
  - Immunochemistry
  - Immunofluorescence (IF)

Viral RNA detection: In acute phase (Up to 9 days after illness)

- Highly specific
- High sensitivity
- Rapid
- Perquisite for Genetic Analysis

- **Methods for detection of Viral RNA :**
  - Conventional RT-PCR
  - Real-time RT-PCR



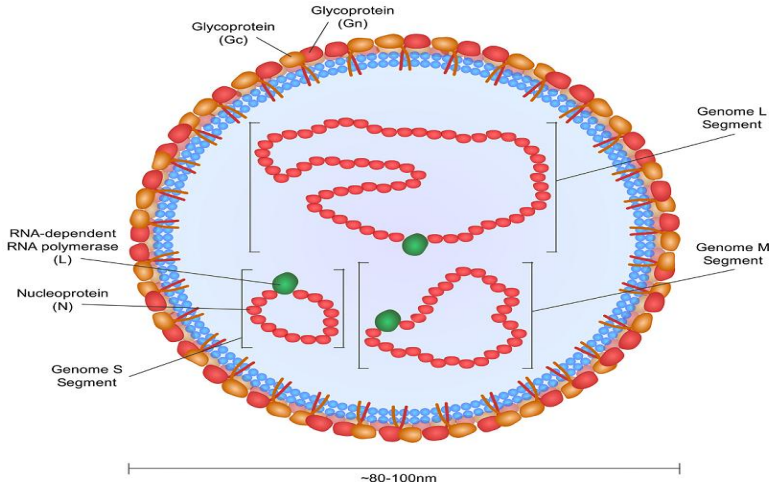


Viral RNA detection: In acute phase (Up to 9 days after illness)

- Although **commercial** assays were in use in some countries, many countries relied on **in-house** molecular tests.
- The **regional genetic** diversity of CCHFV probably explains why the majority of international laboratories use in-house assays.
- It has also been suggested that some commercial tests may be **too expensive**, **difficult to order**, or **not available to international customers.**

CCHFV displays the greatest degree of sequence diversity of any arbovirus

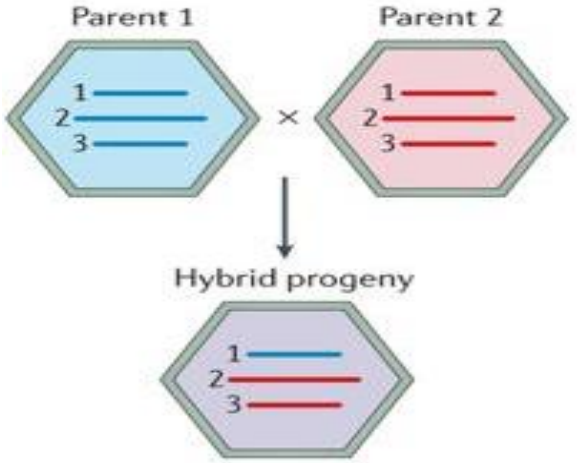
- CCHFV has 3 segments of viral RNA



Nucleotide sequence differences among isolates:

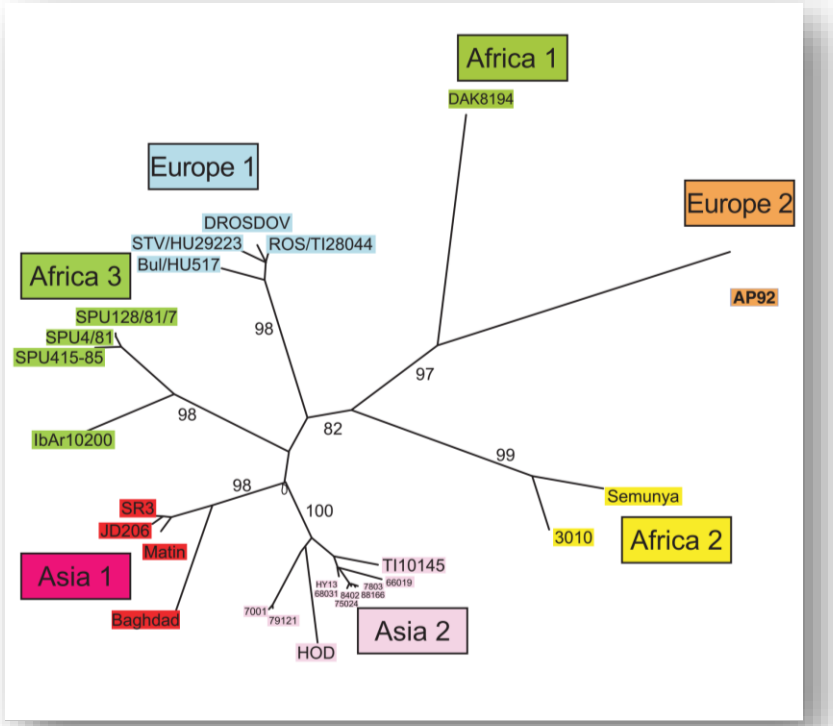
- 20% for the viral S segment
- 22% for L segment
- 31% for the M segment

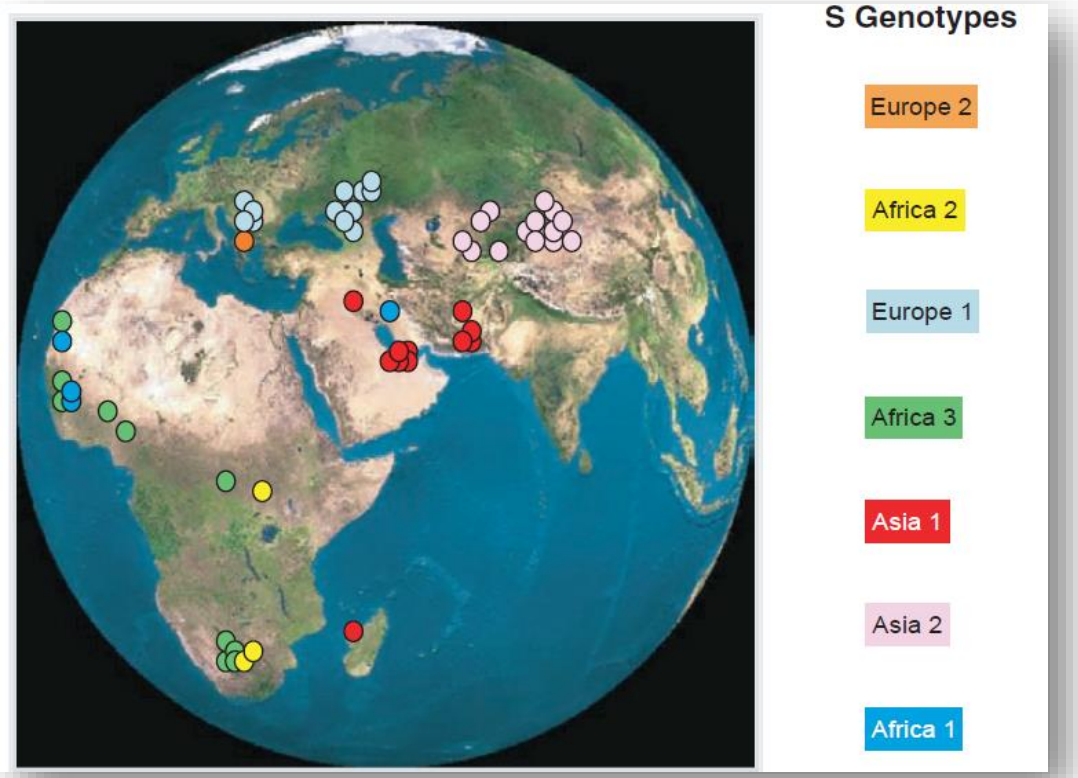
Reassortant



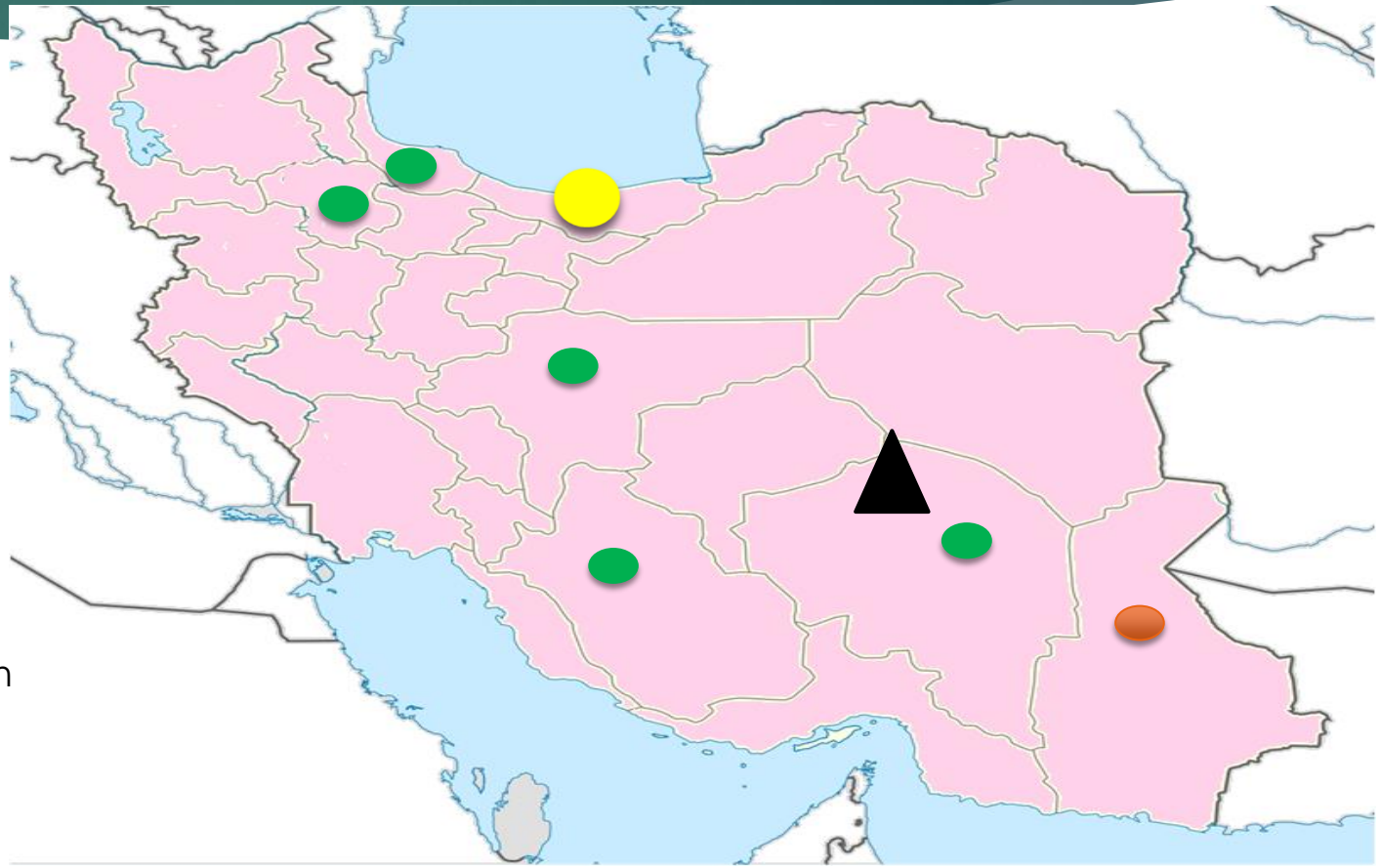
Reassortant progeny can have different phenotypes

CCHFV is the most genetically diverse of the arboviruses with 7 distinct genotypes





The most genetic diversity of CCHFV has been observed in Iran



Asia-1 (Clade IV)

Europe 1 (Clade V): in ***5*** provinces

Asia-2 (Clade IV): only in Sistan and Baluchistan

Europe 2 (Clade VI): only in Mazandaran

Out-group: Only in Kerman

Laboratory Diagnosis of CCHF

- **Serological assays**

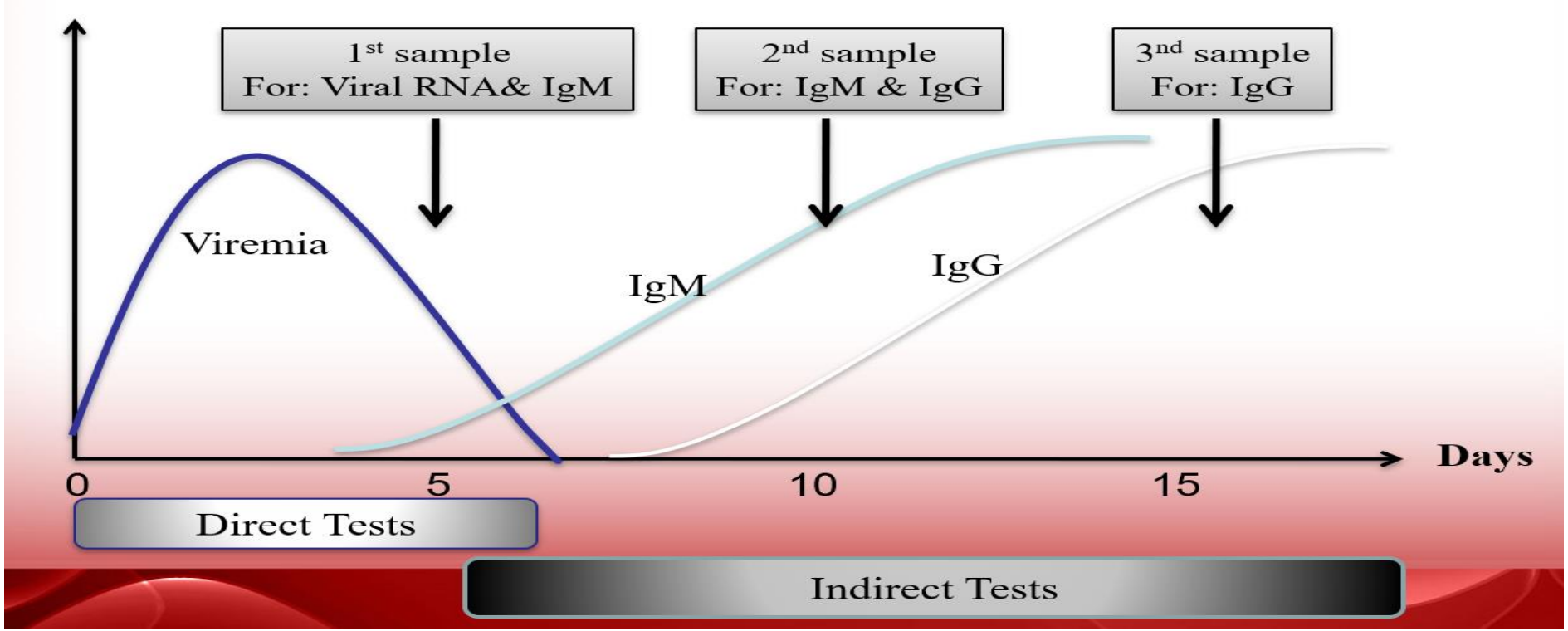
- Used to detect IgM and IgG antibodies against CCHFV.
- **Serological assays:**
  - Immunofluorescence assay
  - ELISA
- IgM can be detected on the 5^{th}-7^{th} days after onset of symptoms
- IgM remains detectable about 4-6 months after onset of symptoms
- IgG can be detected on the 7^{th}-9^{th} days after onset of symptoms
- IgG remains detectable about 5 years after onset of symptoms

- In fatal and sever cases, antibodies response may be weak or undetectable
- There is possibility of cross reaction between CCHF antibodies and other Nairoviruses' antibodies.

Laboratory Diagnosis of CCHF In National Ref Lab, IPI

- **CCHF diagnosis kinetics**

Specimen: Serum



Treatment of CCHF

- The main stay of Treatment is Conservative Management including Transfusion of Pack cell, FFP, Platelet
- Monoclonal Antibody
- Steroids
- Anti viral drug like **Ribavirin & Favipiravir**
- **TREAT DURATION :30mg/kg stat ,15mg /kg q6hr for 4 days and fallow 7.5mg/kg q8 hr 6 days.**

Ribavirin in Hemorrhagic Fevers

Ribavirin is the only antiviral drug that has been used to treat viral hemorrhagic fever syndromes, including CCHF and Lassa fever. The application in 2006 in the WHO model list of essential medicine as threatment of CCHF.

Clinical use of Ribavirin

No randomized clinical trials of the efficacy of ribavirin against CCHF have been performed,

-The efficacy has been described in several observational studies.

-A report published in South Africa in 1985 described the use of intravenous Ribavirin for both therapy and postexposure prophylaxis in a

small number of patients in a nosocomial outbreak.

CCHF Treatment in Heathcare Workers

- In 1994, in Pakistan, Fisher Hoch et al reported three health workers infected with CCHF virus who were treated with oral ribavirin. All the three patients were severely ill. The patients became afebrile within 48 hours of treatment with ribavirin. All the three patients made a complete recovery

In 1999, in Pakistan, Sheikh AA et al evaluated the efficacy of oral Ribavirin in CCHF cases. CCHF were confirmed in 39 out of the 94 cases by the CDC.

After a mean period of 2.30 ± 0.69 days of starting the 10-day course of treatment with oral Ribavirin, the patients improved and the laboratory parameters returned to normal levels

In a historical cohort study, in Iran, in 2003, we compared the mortality rate among patients suspected of having CCHF who received treatment with oral Ribavirin and
Ninety-seven (69.8%) of 139 treated patients suspected of having CCHF survived, and 61 (88.9%) of 69 treated patients with confirmed CCHF survived.

The efficacy of oral ribavirin was 80% among patients with confirmed CCHF and 34% among patients suspected of having CCHF

In another study, for eight critically ill patients with severe hemorrhagic manifestations & GI bleeding, we administered oral Ribavirin by nasogastric tube.

Only one out of the eight patients died.

So it is recommended that

in severe and comatose forms of CCHF, ribavirin can be administered via this route

In 2003, in Turkey, Önder Ergönül et al described the role of ribavirin in treating 35 patients who diagnosed as having CCHF.

All of the eight patients who were given oral ribavirin **survived**, while the overall mortality among the untreated cases was 4.5%.

In 2006, in Turkey, Ozkurt Z et al demonstrated that mean recovery time in the cases treated with Ribavirin was shorter than those of controls.

But the **need for blood and blood product, mean length of hospital stay, fatality rates, and hospital expenditure values** were not significantly different between the group treated with ribavirin and the controls.

Two Systematic Reveiew analyzing Efficacy of Ribavirin

The first (Soares-Weiser et al. 2010), analysed twelve studies from Iran, Pakistan, Turkey and Russia which provided data on mortality outcomes between ribavirin treated and untreated patients [one Randomised Control Trial (RCT) and eleven observational studies]. Results from the single RCT (136 participants; (Koksal et al. 2010)) suggested no benefit from ribavirin treatment, with a mortality risk ratio (treated vs. untreated) of 1.13. Analysis of the pooled observational studies (9955 patients) suggested that ribavirin reduced mortality by 44% when compared to no ribavirin treatment. However, the quality of all the data was judged to be low (RCT) or very low (observational studies) with a high risk of bias and the study concluded that the benefit of ribavirin suggested by the observational study was confounded and these data alone are not reliable.

The Second Systematic Review

The second systematic review (Ascioglu et al. 2011) included one randomised trial and 7 published observational studies that included an untreated comparison group in the study design. Compiling the data from all 8 studies, survival following ribavirin treatment was found to be only 1.06 times better than no treatment, suggesting no significant benefit from ribavirin

Meta-analysis was systematically performed to assess the effectiveness of ribavirin administration regarding CCHF patient survival and to explore the
most important influential parameters for its efficacy.

Administration of ribavirin to CCHF patients significantly decreased the mortality rate (by 1.7-fold) compared with those who did not receive this medication. Furthermore, it was found that the prescription of ribavirin in the initial phase of disease was more effective, and a delay in the start of treatment resulted in a 1.6-fold increase in mortality rate. In addition, interventional therapy resulted in an ~2.3-fold reduction in the mortality rate of those who received ribavirin .

Table 3

Experience with the treatment of CCHF with ribavirin in Iran from 1999–2011. In Column 2, some studies compared the outcome of cases treated with ribavirin, beginning at different time points in the disease course. Column 3 lists the number of patients in each study who were treated with ribavirin and the total number of confirmed cases of CCHF. Column 4 lists the number of deaths among patients who were treated with ribavirin.

Years	Study type	Treated/confirmed	Deaths among treated cases	Province	Reference
1999–2001	Historical comparison	61/69	8/61 (13.1%)	All involved provinces	(Mardani et al., 2003)
1999–2004	Historical comparison	236/255	37/236 (15.7%)	Sistan and Baluchestan	(Alavi-Naini et al., 2006)
2000–2005	Comparison to evaluate	184/184	38/184 (20.65 %)	Sistan and Baluchestan	(Metanat et al., 2006)
2000–2006	Comparison to evaluate timing	63/63	16/63 (25.4%)	Sistan and Baluchestan	(Izadi et al., 2009)
2004–2006	Observational	6/6	0/6 (00.0%)	Golestan	(Jabbari et al., 2006)
2009	Observational	6/6	2/6 (33.3%)	Khorasan	(Naderi et al., 2011)
	Total of all 7 studies	679/706	120/679 (17.67%)		

The Journal of Infectious Diseases

IDSA Infectious Diseases Society of America

hivma hiv medicine association

ACCEPTED MANUSCRIPT

Ribavirin has a Demonstrable Effect on Crimean-Congo Hemorrhagic Fever Viral Populations and Viral Load during Patient Treatment

Nicole Espy, Unai Pérez-Sautu, Eva Ramírez de Arellano, Anabel Negredo, Michael R Wiley, Sina Bavari, Marta Díaz Menendez, María Paz Sánchez-Seco, Gustavo Palacios ✉

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Abstract

The use of ribavirin to treat infections of Crimean-Congo Hemorrhagic Fever virus (CCHFV) has been controversial based on uncertainties on its antiviral efficacy in clinical case studies. We studied the effect of ribavirin treatment on viral populations in a recent case by deep sequencing plasma samples taken from a CCHFV-infected patient before, during, and after a five-day regimen of ribavirin. CCHFV viral load dropped during ribavirin treatment and subclonal diversity (transitions) and indels increased in viral genomes during treatment. Although the results are based on a single case, these data demonstrate the mutagenic effect of ribavirin on CCHFV *in vivo*. (Word Count: 100)

Favipiravir (T-705)

T-705 (6-fluor-3-hydroxy-2-pyraxinecarboxamide) is a pyrazinecarboxamide derivative that inhibits the replication of various RNA viruses. The drug is intracellularly phosphoribosylated to its active form, favipiravir-RTP, which interacts with the viral RNA-dependent RNA polymerase thus inhibiting viral replication (Furuta et al. 2017). T-705 and other derivatives of pyrazinecarboxamide (T-1105 and T-1106) have demonstrated good activity in treating viral infections in laboratory animals caused by various RNA viruses, including influenza virus, arenaviruses, bunyaviruses, West Nile virus, yellow fever virus and foot-and-mouth disease virus

In 2014, the efficacy of favipiravir, ribavirin and arbidol (umifenovir) was tested *in vivo* in CCHFV-infected transgenic (IFNAR-/-) mice. Results indicated good efficacy of T-705, some beneficial effect from ribavirin (survival time was prolonged but survival rate did not increase) and no effect from arbidol (Oestereich et al. 2014). Favipiravir also shows potential efficacy against other bunyaviruses, notably Severe Fever with Thrombocytopaenia Syndrome virus (SFTSV) inhibiting

Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulin (IVIG) is a non-specific immunoglobulin G preparation that has immunomodulatory activities (Stangel and Pul 2006). It is used to treat various autoimmune, infectious and idiopathic diseases. A study in Iran compared the outcome of 28 lab-confirmed CCHF cases treated with ribavirin alone with that of 12 cases treated with a combination of ribavirin and 30-50g IVIG. No significant differences were found between the groups in terms of mortality rate but the time taken for white blood cell counts and liver function tests to return to normal levels was significantly shorter in the patients who received IGIV (Salehi et al. 2013).

Steroids

One study demonstrated that the use of steroids was beneficial particularly among patients with severe disease (Dokuzoguz et al. 2013). Among 24 patients with severe CCHF, 16 received steroid treatment. Eight of the case group died (fatality rate 50%) but all 8 patients in the control group died (fatality rate 100%; P = .014). Further studies are needed to determine the value of steroid treatment for severe CCHF, specifically to assess whether the anti-inflammatory effect of steroids and their ability to stimulate hematopoiesis in the bone marrow outweigh the negative effects associated with immunosuppression. There may also be a need to investigate the potential to combine corticosteroids such as high-dose methylprednisolone with ribavirin, based on promising findings from two studies (Sharifi-Mood et al. 2013); (Jabbari et al. 2006).

Therapeutics: Gap analysis

The only antiviral available for the treatment of CCHF infection in humans is ribavirin. However, evidence about its efficacy is inconclusive and in some affected countries it is no longer recommended for CCHF treatment. In the absence of ribavirin, supportive care remains the mainstay of CCHF management.

Crimean-Congo Hemorrhagic Fever in Children and Adolescents

A total of 34 non-adult confirmed CCHF patients were studied. The mean age of the studied subjects was 13.3 ± 4.6 (range: 5.0 – 18.0) years. All the patients except two were receiced oral Ribavirin for treatment for 10 days.

The case-fatality rate was 26.5% (9/34). Those who survived received treatment with Ribavirin sooner (initial 3 days of illness) than those who did not survived.(85.5% versus 24.8%)

B. Sharifi-Mood, M. Mardani;… et al,Pediatric Infectious Diseases Journal 2008.

CCHF in pregnant women

-We report a series of six pregnant women with confirmed CCHF who were admitted to BooAli hospital in a time period of 5 years from 2000 to 2005.Due to the severity of the illness all patients were treated by Ribavirin.

-All the patients except one were survived.(83.3%).

-Abortion was observed in 3 patients and stillbirth in one patient.

-Unfotunately one pregnant woman died due to DIC and multiorgan failure.In fact,66.6% of pregnant women had fetal loss.

Sharifi Mood.B,Mardani.M,….et al , Annual meeting of IDSA,Oct 2007,San Diego,USA, Abstract#750

Observational versus controlled trials

1-Limitations: Ethical considerations prevent the performance of placebo-controlled trials.

2- Unavailability of IV formulation of Ribavirin in endemic areas.

3- No Comparison study between IV and Oral formulation.

Evidence of efficacy is therefore limited to observational studies, which have been criticized

Post exposure prophylaxis

Prophylaxis is suggested after a high-risk contamination, such as a needle stick injury.

Daily follow-up by checking complete blood count and biochemical tests for the exposed individuals is highly recommended.

Ribavirin prophylaxis is generally well tolerated, potentially useful and should therefore be recommended for health care workers who are at risk of exposures such as percutaneous injuries.

(Tarantola et al., 2007).

Household Contacts

In our experience we suggest prophylactic use of oral Ribavirin in context of household contacts with a recommended dosage of 200 mg daily for 5 days.

-We recommend twice daily temprature monitoring in household contacts and early initiation of therapy in whom CBC & Biochemical tests become abnormal.

Research Priorities of CCHF

1- Development of Rapid Diagnostic Test (RDT)

2- Full genome sequencing of CCHF virus isolates in different parts of Iran to determine the circulation of various genotypes (based on all 3 genome segments) in the country.

3-Surveillance of CCHF in wildlife (Ticks and amplifier host like small mammals) to better understand the ecology of the virus

4-Development of monoclonal antibodies for diagnostic and therapeutic purposes.

5- To become a WHO collaborating center to help other endemic countries in the Region.

6-Development of Pseudotyped Lentivirus for CCHF Neutralization test

Thanks