Case Report

Ebola virus disease: Case management in the Institute of Infectious Diseases, University Hospital of Sassari, Sardinia, Italy

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Abstract
Since the onset of the worst epidemic of Ebola virus disease in December 2013, 28,637 cases were reported as confirmed, probable, or suspected. Since the week of 3 January 2016, no more cases have been reported. The total number of deaths have amounted to 11,315 (39.5%). In developed countries, seven cases have been diagnosed: four in the United States, one in Spain, one in the United Kingdom, and one in Italy. On 20 July 2015, Italy was declared Ebola-free.

On 9 May 2015, an Italian health worker came back to Italy after a long stay in Sierra Leone working for a non-governmental organization. Forty-eight hours after his arrival, he noticed headache, weakness, muscle pains, and slight fever. The following day, he was safely transported to the Infectious Diseases Unit of University Hospital of Sassari. The patient was hospitalized for 19 hours until an Italian Air Force medical division transferred him to Rome, to the Lazzaro Spallanzani Institute. Nineteen people who had contacts with the patient were monitored daily for 21 days by the Public Health Office of Sassari and none presented any symptoms.

So far, neither vaccine nor treatment is available to be proposed on an international scale. Ebola is considered a re-emerging infectious disease which, unlike in the past, has been a worldwide emergency. This case study aimed to establish a discussion about the operative and logistic difficulties to be faced and about the discrepancy arising when protocols clash with the reality of facts.

Key words: EVD; Italy.


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Introduction
Ebola virus disease (EVD) is a severe multi-organ hemorrhagic fever caused by Ebolavirus, belonging to the Filoviridae family. Fruit bats act as a reservoir of the infection, passing it to big mammals, including monkeys. The risk of contracting the disease for humans is proportional to the exposure to killing and preparing animals. Once a human being contracts the infection, the virus is transmitted through an inter-human pattern by contact between infected body fluids (sweat, tears, blood, semen, feces, and urine) and mucous membranes or non-intact skin. The disease begins with non-specific symptoms such as fever, muscle pains, and nausea. Progressively, it affects the gastrointestinal tract, causing vomiting and diarrhea, and it ultimately provokes bleeding disorders [1].

Since the beginning of the largest outbreak of Ebola in Guinea in December 2013, up to 6 January 2016, there have been 28,637 confirmed, probable, and suspected EVD cases, resulting in 11,315 deaths (39.5%). The most affected countries, Sierra Leone, Guinea, and Liberia, interrupted the human-to-human transmission and were declared Ebola-free on 7 November 2015, 29 December 2015, and 14 January 2016, respectively. They are all in a 90-day period of heightened surveillance. There have been 881 confirmed cases of EVD among health workers, with 513 reported deaths (58.2%) [2,3].

The infection was diagnosed in Western countries in only seven cases; all other patients were safely repatriated once they had tested positive for EVD in Africa. Furthermore, among these cases diagnosed in developed countries, just four patients were working in the epidemic area and returned to their hometowns (two in the United States, one the United Kingdom, and one in Italy) before the outbreak of symptoms. Other confirmed cases (two in the United States and one in Spain) were among the nurses who had provided
treatment for the repatriated patients. These individuals who returned were uncertain that they had developed the disease, so they had contact with the community. For this reason, a person who resulted positive for EVD in the European Union, as in this reported case, has an important impact with respect to disease management. Additionally, being on an island could be a cause of delay in diagnosis and treatment, as hospitals designated as national reference centres are overseas, and a proper interconnection has not yet been established.

At this time, the threat of Ebola seems to be over, but the international community should remain on the alert in case of unexpected late-onset complications. Recently, on 6 October 2015, a health worker who was infected in Sierra Leone in 2014 and treated in the United Kingdom, was again hospitalized in London after developing late EVD-related complications. The patient was discharged on 15 November 2015. None of the 62 contacts under follow-up presented any symptoms [4,5].

Case Report

On 9 May 2015, an Italian health worker 37 years of age came back to Sassari, via Casablanca, Morocco, after a long stay in Sierra Leone where he worked for a non-governmental organization (NGO). At home, the nurse self-monitored his body temperature daily.

On 10 May, during the night, the nurse noticed headache, weakness, muscle pains, and fever. On the following morning, he reported a higher body temperature, up to 39°C. The health worker, therefore, isolated himself immediately to avoid any contact with his family, and he immediately referred his clinical conditions to the medical personnel of the Public Health Office and, secondly, to the Infectious Diseases Unit of University Hospital of Sassari.

The emergency protocol of the operating unit was activated. At about 2 p.m., the nurse was safely transported from his home directly to the infectious diseases unit, without stopping in the emergency room. During transportation, the patient was lucid, alert and cooperative; he was in a febrile state and he complained of a headache, but he did not report any other severe clinical manifestations.

He arrived at the ward at 3 p.m., and he was admitted to an isolation room. He was taken through a dedicated path, as the specific area of the building had been previously evacuated, and the room, connected by a corridor to the elevator and to the dressing room, was isolated by fire doors (Figure 1).

A team comprising a doctor and a nurse evaluated the patient’s clinical conditions; a second doctor was outside. Two healthcare professionals equipped with personal protective equipment (PPE) entered the room, and the third waited in the anteroom. The doctor and the nurse first took vital parameters (body temperature was 38°C, mean arterial pressure was 130/85 mmHg). A peripheral venous access was inserted and blood samples were taken to be sent to the Lazzaro Spallanzani Institute in Rome and to the medical laboratory for analysis in Sassari. Paracetamol (1,000 mg; one oral tablet), levofloxacin (500 mg; two oral tablets per day), and physiologic salt solution (500 cc; continuous IV) were administered. Due to the patient’s broad spectrum in antimicrobial activity, levofloxacin was included to prevent any clinical hypothesis of pneumonia until a definitive diagnosis was available.

The doctor performed a rapid test for malaria, which resulted negative. The nurse, in the decontamination room, inserted the samples into rigid containers. The containers were properly disinfected with sodium hypochlorite and placed in another biohazard box. Finally, they were delivered outside the critical area. The three operators, in sequence, proceeded to take their PPE off.

At 6 p.m., the patient reported productive cough and fever (body temperature of 38°C). During the night, he did not require further medical interventions. A permanent visual communication was ensured. Due to technical problems related to the laboratory, it was possible to perform only the complete blood count (CBC): red blood cell count (RBC), 5,800,000/μL; hemoglobin (Hb), 16.6 g/dL; hematocrit (HCT), 48%;
white blood cell count (WBC), 5,240/μL; neutrophils (NEUT), 4,100/μL (77.8%); lymphocytes (LYMPH), 500/μL (9.7%); monocytes (MONO), 500/μL (10.2%); eosinophil (EOS), 0/μL (0.3%); basophil (BASO), 0/μL (0.6%); large unstained cells (LUC), 100/μL (1.5%); and platelets (Plt), 126,000/μL.

At 6 a.m. of the following day, 12 May 2015, the patient was still in a febrile state (39°C); paracetamol (1,000 mg; one oral tablet) was administered. At 9 a.m., stationary clinical conditions were reported: body temperature of 37°C, mean arterial pressure of 115/70 mmHg, and regular diuresis. The patient still complained of a productive cough without any other symptoms. Levofloxacin was switched to moxifloxacin (400 mg; 1 oral tablet). As a confirmed diagnosis was not still available, moxifloxacin was administered due to its longer half-life. The tendency was to favor a once-daily single tablet regimen to reduce the risk of exposure to the personnel in charge of administering the therapy. At 12 p.m., the patient was still febrile (body temperature of 38°C); paracetamol (1,000 mg; one oral tablet) was administered. The CBC, after 24 hours, showed that platelets were halved: RBC, 5,260,000/μL; Hb, 14.9 g/dL; HCT, 43.7%; WBC, 3,000/μL; NEUT, 2,200/μL (72.4%); LYMPH, 600/μL (18.8%); MONO, 200/μL (5.6%); EOS, 0/μL (0.5%); BASO, 0/μL (1%); LUC, 100/μL (1.7%); Plt, 75,000/μL (Table 1).

At 3 p.m., the Lazzaro Spallanzani Institute confirmed the positive diagnosis of the investigation. Following the national protocol, the Italian Air Force medical division was charged to transport the patient from Sassari to the Lazzaro Spallanzani Institute in Rome.

The patient’s clinical conditions seemed to worsen. At 5 p.m., he was still febrile (body temperature of 38.5°C); paracetamol (1,000 mg; one oral tablet) was administered. At 6:30 p.m., he appeared to be suffering and complained of moderate dyspnoea. The vital parameters were: body temperature, 38.9°C; mean arterial pressure, 90/60 mmHg; heart rate, 87 bpm; oxygen saturation, 92% in AA; and regular diuresis. At 7 p.m., a team comprising a doctor and a nurse, assisted by a third operator in the anteroom, equipped with PPE, entered the isolation room. The health worker appeared alert and cooperative, but in a state of agitation. He received therapy with Ringer’s lactate at 500 cc IV continuously and oxygen with a Venturi mask at 31% 6 L/min. The three operators, in sequence, proceeded to take their PPE off. At 10:30 p.m., the patient’s mean arterial pressure normalized (110/60).

### Table 1. Comparison of two complete blood counts, on admission and at 24 hours.

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>At 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHITE BLOOD CELLS</strong></td>
<td>5,240/μL</td>
<td>3,000/μL</td>
</tr>
<tr>
<td><strong>RED BLOOD CELLS</strong></td>
<td>5,800,000/μL</td>
<td>5,260/μL</td>
</tr>
<tr>
<td><strong>HEMOGLOBIN</strong></td>
<td>16.6 g/dL</td>
<td>14.9 g/dL</td>
</tr>
<tr>
<td><strong>HEMATOCRIT</strong></td>
<td>48.0%</td>
<td>43.7%</td>
</tr>
<tr>
<td><strong>MEAN CORPUSCULAR VOLUME</strong></td>
<td>82.8 fL</td>
<td>83.0 fL</td>
</tr>
<tr>
<td><strong>MEAN CORPUSCULAR HEMOGLOBIN</strong></td>
<td>28.7 Pg</td>
<td>28.3 Pg</td>
</tr>
<tr>
<td><strong>HOMOLOGIN CONCENTRATION</strong></td>
<td>34.6 g/dL</td>
<td>34.1 g/dL</td>
</tr>
<tr>
<td><strong>RED CELLS DISPERSION WIDTH</strong></td>
<td>12.8%</td>
<td>12.2%</td>
</tr>
<tr>
<td><strong>HEMOGLOBIN DISTRIBUTION</strong></td>
<td>2.5 g/dL</td>
<td>2.4 g/dL</td>
</tr>
<tr>
<td><strong>PLATELETS</strong></td>
<td>126,000/μL</td>
<td>75,000/μL</td>
</tr>
<tr>
<td><strong>MEAN PLATELET VOLUME</strong></td>
<td>8.5 fL</td>
<td>7.8 fL</td>
</tr>
<tr>
<td><strong>NEUTROPHILS%</strong></td>
<td>77.8%</td>
<td>72.4%</td>
</tr>
<tr>
<td><strong>LYMPHOCYTES%</strong></td>
<td>9.7%</td>
<td>18.8%</td>
</tr>
<tr>
<td><strong>MONOCYTES%</strong></td>
<td>10.2%</td>
<td>5.6%</td>
</tr>
<tr>
<td><strong>EOSINOPHILS%</strong></td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>BASOPHILS%</strong></td>
<td>0.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>LARGE UNIDENTIFIED CELLS%</strong></td>
<td>1.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td><strong>NUCLEATED RED BLOOD CELLS%</strong></td>
<td>0%</td>
<td>---%</td>
</tr>
<tr>
<td><strong>NEUTROPHILS#</strong></td>
<td>4,100/μL</td>
<td>2,200/μL</td>
</tr>
<tr>
<td><strong>LYMPHOCYTES#</strong></td>
<td>500/μL</td>
<td>600/μL</td>
</tr>
<tr>
<td><strong>MONOCYTES#</strong></td>
<td>500/μL</td>
<td>200/μL</td>
</tr>
<tr>
<td><strong>EOSINOPHILS#</strong></td>
<td>0/μL</td>
<td>0/μL</td>
</tr>
<tr>
<td><strong>BASOPHILS#</strong></td>
<td>0/μL</td>
<td>0/μL</td>
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<tr>
<td><strong>LARGE UNIDENTIFIED CELLS#</strong></td>
<td>100/μL</td>
<td>100/μL</td>
</tr>
<tr>
<td><strong>NUCLEATED RED BLOOD CELLS#</strong></td>
<td>0/μL</td>
<td>---/μL</td>
</tr>
<tr>
<td><strong>MYELOPEROXIDASE INDEX</strong></td>
<td>-1/μL</td>
<td>-7/μL</td>
</tr>
</tbody>
</table>
The patient remained stationary. At 12:30 a.m., the Air Force medical division arrived at the Infectious Diseases Unit of Sassari. They safely transported the patient in a dedicated biobag to the airport of Alghero, about 25 kilometers away from the hospital.

The patient was admitted at 15 hours from the onset of symptoms. The positive diagnosis was communicated after 60 hours. After 90 hours, he was transferred to the Lazzaro Spallanzani Institute, where a specific therapy with specific monoclonal antibodies was commenced.

After the patient was discharged, the Public Health Office of Sassari was tasked with monitoring all the patient's contacts for 21 days. Three family members were identified as code pink because they had been in contact with the confirmed case of EVD without using PPE. As an intermediate level of control, their body temperature was monitored twice daily (8 a.m. and 8 p.m.) by an officially registered call. They were banned from being in public places and having contacts with other people, and they were required to remain in isolation in their countryside house. A committed person left food and drinkable water outside of their gate. Sixteen workers, including the emergency responders (three people), infectious disease personnel (five people), and laboratory personnel (eight people) were identified as code green because they had been in contact with the confirmed case of EVD, although they were protected by PPE. The healthcare workers’ body temperatures were monitored once daily (8 a.m.) by an officially registered call. Even if the risk of exposure was low, they were advised to avoid public places. Their work activities were temporarily suspended.

Results

Operative and logistic difficulties

When an emergency occurs, the implementation of guidelines helps to foresee all the possibilities. A list of unpredictable obstacles is proposed in order to set up a debate in the scientific community. It is important to learn from mistakes, mainly to prevent other healthcare facilities that might face this emergency from repeating the same errors.

Operative and logistic difficulties encountered during the case management are hereby reported:

(i) No agencies were indicated in protocols as being in charge for certified disinfection of contaminated rooms; as a consequence, a delay occurred in disinfecting the patient's house, the medical laboratory, and the infectious disease unit after the patient's transfer. This is because private agencies for the decontamination were available only from outside the island.

(ii) The medical laboratory was not equipped with closed-loop instruments, so it was only possible to perform the CBC.

(iii) Another delay occurred in the diagnosis; blood samples to be sent to the Lazzaro Spallanzani Institute were taken at 3 p.m., but they were shipped only at 6 a.m. the following day by the civil aviation flight that first took off. This happened because the emergency protocol foresaw the patient's transport to be assigned to the Italian Air Force, but biological samples could not be transported promptly from the island by dedicated vehicles.

(iv) The Air Force medical division was not allowed to transport the patient from Sassari to Rome if health conditions were severe. Fortunately, a worsening of the patient’s condition occurred later when he was already in Rome; if the patient became unstable, he would have had to stay in Sassari without receiving appropriate intensive care treatment.

(v) Although 16 of the 19 people under follow-up, including emergency responders, health workers from the infectious disease unit, and laboratory personnel were classified as code green and were defined by the World Health Organization (WHO) to be at low risk of exposure, were not allowed, as a precaution, to go to work and attend public places for 21 days, mainly to prevent being exposed to any other infection. This resulted in a lack of personnel in the facilities involved.

(vi) Training was essential, but a strict selection of the personnel in the infectious disease unit was not performed. The result was that a nurse who was to attend the patient had a panic attack while he was getting dressed with the PPE and he was immediately replaced, but he caused a higher stress condition [6].

Discussion

Worldwide emergence

Ebola is a re-emerging zoonosis first identified in 1976. After the initial epidemic, numerous and self-limiting outbreaks occurred. On the one hand, the most affected countries where the recent epidemic occurred had never had cases of Ebola and political willingness [7]. On the other hand, the catastrophic dynamics of the spread witnessed a complete subversion in transmission, mainly due to globalization. Goods, travelers, services and sometimes diseases, are now free to move worldwide. This is the reason that the international community should ensure effective global monitoring and approve public measures. Thus, operational protocols should deal with infection when it...
is still in its place of origin. The last epidemic started in December 2013 in Guinea, and after 10 months, all but one district in Liberia and all districts in Sierra Leone reported at least one confirmed or probable case of EVD. Underestimating the extent of the infection caused the accumulated delay responsible for the epidemic [8].

As a consequence, worldwide communities have been seriously threatened by Ebola; the lack of approved guidance has also spread the epidemic to developed countries. On 8 August 2014, the WHO declared Ebola a public health emergency of international concern; consequently, all nations prepared. Numerous keys to combat the virus were highlighted into operative protocols, based on both control and prevention, but also on management of suspected or confirmed individuals. The global strategies include tracking travelers’ movements from an affected country to a naive one; effective recognition and monitoring for 21 days of suspected cases; rapid medical care in dedicated isolation rooms if symptoms occur; and rapid and accessible diagnostic tests, waste disposal, and burials.

In order to prevent epidemics, a deep, comprehensive, national awareness of screening and monitoring incoming passengers is vital. This goal can be successfully achieved by training health workers and educating the community. Ensuring prompt medical care can decrease the mortality rate of patients; in fact, as it has been reported, renal failure and rhabdomyolysis occur frequently and relatively early in severe EVD cases. Due to infection severity, patients tested positive and in stable health condition should be admitted to specific centres where an intensive care unit dedicated to highly contagious infectious diseases is operational [1,9,10].

**Italian and regional protocols for dealing with the infection**

Based on the Italian national protocol, individuals coming back to Italy from endemic areas must land at Rome Fiumicino or Milan Malpensa airports where they are screened by the Maritime and Aerial Border Health Office. If they do not present any symptoms, are allowed to go back to their hometowns. The Ministry of Health continues to track their movements and alerts the authorities at the place of arrival. Two hospitals are designated as national reference laboratories and centers: Lazzaro Spallanzani Institute in Rome and Luigi Sacco Hospital in Milan. National and international agreements as well as trained and selected teams and equipped dedicated rooms have to be in working order to face any emergency.

Sardinia is an island in the Mediterranean Sea, and a proper interconnection is not well established. Many regional operational protocols have been effective since 2003, the year in which developed countries were threatened by severe acute respiratory syndrome (SARS). On 29 October 2014, a new protocol was approved for the management on the island of suspected or confirmed cases of EVD, based on the WHO and Italian Ministry of Health’s guidelines. This document identified a regional crisis unit (RCU), comprising the General Director of Health, representatives of the Public Health Office, emergency responders, infectious disease unit, medical laboratory, and the Maritime and Aerial Border Health Office. RCU representatives supervise, in each field of application, two local crisis units (LCU), comprising representatives of the operating unit who are designated to manage the emergency; one is located in northern Sardinia, Sassari, and one is in the south, Cagliari. The protocol includes an assignment of a color code to differentiate risk levels, contact control measures, management and transport of suspected cases in the territory, LCU equipment and training, directives about isolation, waste disposal, and decontamination. Though many of these issues were raised in the protocols, there were no clear answers in practice; as a result, finding a solution during the emergency for preventable problems provoked a delay in management [11,12] (Figure 2).

**Case management prior to admission**

On 8 May 2015, the Director of Health in Sardinia received two documents approved by the Ministry. The first document provided general information about the

![Figure 2. Color code for suspected Ebola virus disease case management.](image-url)
person who had come back from an endemic area and the NGO he had been working for; the second document was issued by the Maritime and Aerial Border health Office and confirmed that the healthcare worker was not in a febrile state when he landed. The worker then spent 24 hours in Rome, and on the following day, 9 May 2015, he returned to his hometown, arriving at Alghero airport (Sassari). First, a code green was assigned since he had had contacts with confirmed cases of EVD, even though he declared that he had always used the PPE and he was in good health. He went to his family's house. His body temperature was daily checked in the morning by the Public Health Office. Symptoms started on 10 May 2015 in the evening, but only on 11 May did he declare a febrile state up to 39°C. Immediately, he turned from code red to code green, as a suspected case of EVD. After he isolated his family members in separate rooms, a dedicated ambulance went to pick him up. He was safely transported to the infectious disease unit by trained and PPE-equipped personnel. Based on operational protocols, suspected cases without massive bleeding but only fever do not need biobags.

Once the patient’s positive test was confirmed on 13 May, his relatives were reclassified from code green to code pink, leading to a movement from their apartment to an isolated country house. They were not allowed to go out, and the Public Health Office monitored their body temperatures twice daily and reported them through an officially registered call. Sixteen health workers were monitored once daily as well. They were identified as code green and consequently had a lower risk of exposure due to the use of PPE. They were only recommended to avoid crowded public places, including their work locations. None of these staff members or the patient’s family members subsequently presented any symptoms [12,13].

Conclusions

The first EVD case diagnosed and confirmed in Italy is reported here. On 9 June 2015, the patient resulted EVD negative. On 20 July, Italy was declared Ebola-free.

The implementation of operational protocols, provided by the WHO and the Italian Ministry of Health, ensured the safe management of the emergency. Isolated rooms and availability of PPE and trained personnel were essential. These efforts prevented the spread of the infection [11,14-16].

Early diagnosis was crucial for a good prognosis. Based on cases reported in the United States, the timely administration of hydration therapy might have played a key role, as proposed by Lyon et al. [17].

EVD is a serious but preventable disease whose prognosis is variable. In countries economically disadvantaged where an isolation ward, early diagnosis, and access to intensive care are not available, the management of the emergency would not have been possible [17,18].

It is not easy to prevent what could happen in an emergency, but timing, training, and available equipment reduce the discrepancy between protocols and the practice of the operating unit. To face the lack of closed-loop instruments, the infectious disease unit was provided with point-of-care testing to perform laboratory analysis safely. Overall, in the unit, a selection of the personnel based on stress resistance management and physical performance is compulsory. Furthermore, a remarkable delay occurred due to Sassari being located on an island.

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