A fatal case of post-transfusion sepsis caused by *Yersinia enterocolitica* after delivery

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Introduction

In recent years there has been a progressive strengthening of the safeguards that protect patients from unsuitable blood products. Blood donors are asked several questions concerning possible risk factors that may affect the safety of the donated blood and are deferred from donation if some of them are acknowledged. Moreover, blood donations are tested for numerous infectious agents, which has led to a significant reduction of viral infections after blood transfusion[1,2]. However, bacterial sepsis remains a significant hazard of transfusion. Among all blood components, red blood cell preparations are the most used and they are more frequently infected by Gram-negative bacteria, primarily members of the Enterobacteriaceae family[3-5]. *Yersinia enterocolitica* (*Y. enterocolitica*) is not inhibited in the range of 2-6 °C, which is the storage temperature of red cell concentrates. This, in addition to the pH of preparation of red blood cell units (7.3), supports bacterial growth[6].

Here we report a fatal case involving a woman, who had haemorrhagic shock in the early post-partum period. She required the transfusion of seven bags of red blood cells which, shortly after, led to the onset a *Y. enterocolitica* post-transfusion sepsis with a fatal outcome. In this case, the microbiological investigation performed on cadaveric blood supported the diagnosis of sepsis-related death. The presumably infected transfused red cell concentrate was identified by detection of high titres of antibodies against *Y. enterocolitica* in the donor's plasma.

The case

A 36-year old woman, gravida 2, para 1, at late term (gestational age 41 weeks +3) after induction of labour, had a vaginal delivery. She lost a total of 1,800 mL of blood during the delivery and required the transfusion of seven bags of red blood cells.

During the transfusion the woman's body temperature increased to 38 °C and she had some episodes of bilious vomiting and haematemesis, but a trans-abdominal ultrasound did not reveal any pathological signs. The patient also require mechanical ventilation because of severe respiratory failure. Antibiotic therapy with teicoplanin and subsequently with linezolid was administered and the patient was supported with dobutamine, adrenaline and noradrenaline.

During the 4 days after delivery, the woman's general condition worsened, with marked hypotension and refractory shock, associated with disseminated intravascular coagulation, acute renal failure with acute tubular necrosis, hepatic failure and an acute respiratory distress syndrome despite the mechanical ventilation. This pathological picture led to the death of the patient. An anaerobic blood culture from the patient was positive for *Y. enterocolitica*, but this result was obtained only after the patient's death.

A complete autopsy was performed 24 hours later. Histological investigations were performed on sections of organs taken during the autopsy and a microbiological analysis was carried out on post-mortem blood collected from the right and left heart cavities during the autopsy.

The autopsy revealed the presence of several subepicardial and subpleural petechiae, whereas the other organs did not show any specific alteration except for a severe vascular congestion and oedema. The histological examination of lung samples showed alveolar oedema, hyaline membranes lining the denuded alveolar walls, alveolar infiltrates of polymorphonuclear neutrophil leucocytes, alveolar haemorrhages and fibrin thrombi in the small arteries; in kidney samples there were copious fibrin thrombi in capillaries, extensive interstitial haemorrhages and acute tubular necrosis.

We used Seeplex Diarrhea-B2 ACE Detection (Seegene, Inc., Songpa-Gu, Seoul. Korea): this assay is composed of primer mixtures that are able to identify *Clostridium perfringens, Y. enterocolitica, Escherichia coli O157:H7,* and VTEC (Verocytotoxin-producing *Escherichia coli)*. Polymerase chain reaction (PCR) inhibitory effects were assessed by co-amplification of an internal control included in the primer mixtures. Multiplex PCR was performed according to the manufacturer's instructions. The detection limit declared by the manufacturer is 200 copies/reaction. PCR products

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were detected by the ScreenTape system (Lab901, Loanhead, UK), according to the manufacturer's instructions. The numerical value ascribed by the ScreenTape system to a positive signal in the detection step represents the intensity value relative to the marker. The manufacturer's instructions do not indicate a range or a breakpoint value to assign a positive result, but it is possible to do so by comparing the marker intensity value with the sample intensity value.

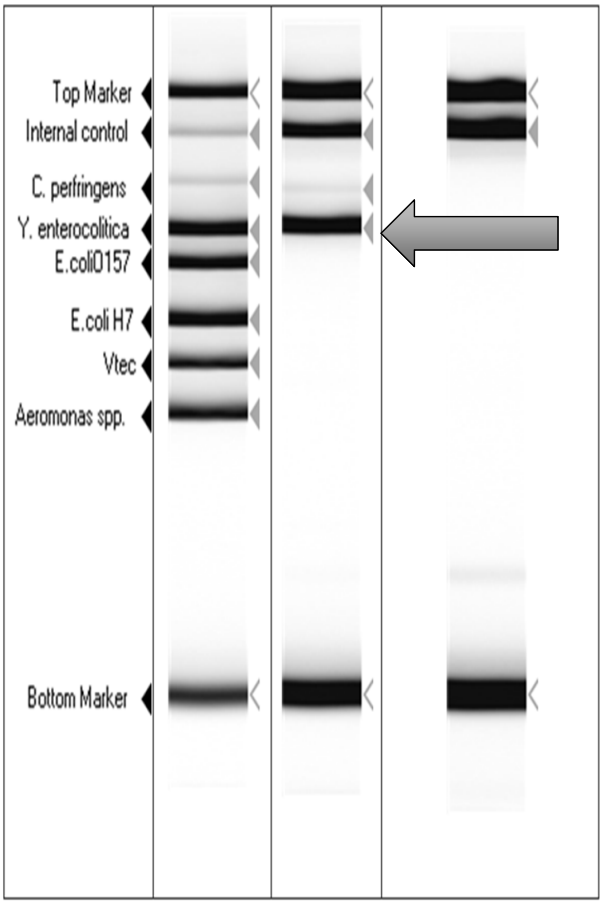
We identified the presence of *Y. enterocolitica* in a cadaveric blood sample as shown in Figure 1, and the contemporary presence of *C. perfringens* was also noted, although at a low concentration. *C. perfringens* is a spore-forming Gram-positive bacterium, involved in post-mortem processes. Anaerobic culture of blood taken before the patient's death was negative for *C. perfringens*.

After the identification of *Y. enterocolitica* in the post-mortem blood sample, we hypothesised the occurrence of post-transfusion sepsis and analysed the blood of all seven donors in order to identify possibly infected transfused red blood cells. We used the Widal reaction in human sera to establish the existence and to determine the quantity of specific agglutinating *Y. enterocolitica* antibodies. High titres of antibodies against *Y. enterocolitica*, serotype O:9, were detected in the plasma sample of one of the donors 1 month after blood donation (1/400, with laboratory standards of positivity of <1/200). The serotype O:9 is the most frequent serotype in Europe, along with O:3, and is conveyed by drinking and eating infected products, especially pork meat. The donor did not show any clinical signs or symptoms of intestinal infection at the time of donation.

The patient's death was attributed to multi-organ failure due to septic shock presumed to be caused by *Y. enterocolitica* post-transfusion sepsis.

Discussion

We describe an uncommon, fatal case of *Y. enterocolitica* post-transfusion sepsis associated with contaminated red blood cells. In this case septic



Lane	L7		L8		L9	
Sample ID	G1: pos control		H1: pz sample		A2: neg control	
Internal control	+	31	+	101	+	100
C. perfringens	+	21	+	12	-	
Y. enterocolitica	+	101	+	102	-	
E.coliO157	+	101	-		-	
E.coli H7	+	101	-		-	
Vtec	+	100	-		-	
Aeromonas spp.	+	101	-		-	
Unidentified	-		-		-	

Figure 1 - Microbiological polymerase chain reaction analysis on cadaveric blood taken from the woman: positive control (L7), cadaveric blood (L8) and negative control (L9).
VTEC (Verocytotoxin-producing *Escherichia coli*).

shock was due to the Gram-negative bacterial infection. A post-mortem microbiological analysis on blood samples collected during the autopsy allows us to diagnose the *Y. enterocolitica* post-transfusion sepsis. The presumably infected transfused red blood cell concentrate was identified by detection of high titres of antibodies against *Y. enterocolitica* in the donor's plasma. The donor did not have either clinical signs of intestinal infection at the time of donation or a recent history of febrile gastroenteritis.

A search of the literature from 1975 to June 2014 to estimate the number of cases of *Y. enterocolitica* post-transfusion sepsis and its associated mortality rate led to the identification of 51 cases, 26 of which were fatal, for a mortality rate of 51%. These data are concordant with those reported by Guinet *et al*.[5] in a review of 2011, in which the mortality rate was 54.5%.

In 79% of cases reported by Guinet *et al*.[5] symptoms had a rapid onset, during or within 3 hours after the transfusion. Typical symptoms were fever, rigors and hypotension, but digestive symptoms, cutaneous marbling and chest pain were also reported. The rapidity of the onset of symptoms was related to a worse prognosis. In the case reported here, the 36-year old woman became febrile during the transfusions and shortly after she developed marked hypotension. With regards to the diagnosis of post-transfusion sepsis and alternative possible diagnoses, such as complications of delivery or other transfusion hazards, alternative causes of death are not scientifically sound in this case. Anaerobic blood cultures from the patient were positive for *Y. enterocolitica*, but this result was obtained only after the patient's death. We also detected *Y. enterocolitica* in a cadaveric blood sample. Furthermore, high titres of antibodies (IgG) against *Y. enterocolitica*, serotype O:9, were detected in the donor's plasma sample 1 month after blood donation (1/400, with laboratory standards of positivity <1/200), strengthening the diagnosis of *Y. enterocolitica* post-transfusion sepsis associated with contaminated red blood cells. The contemporary presence of *C. perfringens* in a post-mortem blood culture was interpreted as post-mortem contamination by this spore-forming Gram-positive bacterium given its low concentration and the fact that anaerobic blood culture performed before the patient's death was negative for *C. perfringens*.

Among the 26 fatal cases found in the literature, only one involved a woman in the post-partum period; our patient is, therefore, the second case brought to the attention of the scientific community[7].

Y. enterocolitica is a pleomorphic Gram-negative coccobacillus belonging to the family Enterobacteriaceae. It typically causes mild disease, more frequently acute diarrhoea, terminal ileitis, mesenteric lymphadenitis, and pseudo-appendicitis. It predominantly affects young subjects, but whether this represents an increased susceptibility or a greater likelihood of developing symptomatic illness is unclear. Human yersiniosis is attributed to contaminated pork, milk, water, and tofu consumption[4,6,8]. Presently, accurate data regarding the incidence and geographic distribution of *Y. enterocolitica* post-transfusion sepsis are lacking, although in the last decade reports of fatal cases have become extremely rare.

In order to reduce blood transfusion reactions and side effects, a rigorous screening programme is implement in Italy. This programme includes a screening questionnaire to collect information regarding the state of health of the donor at the time of donation, testing for markers of viral infection and quality control of blood components[9]. The questionnaire does not include specific questions about gastrointestinal illness and/or diarrhoea, but only generic questions such as: are you in good health? Have you lost weight in an unjustified manner? Are you taking any medications?

Transfusion safety involves numerous actions aimed at ensuring that everyone has access to blood products that are as safe as possible, but it is a very complicated process and we agree with Sacchini *et al*.[10] in defining it as something that "goes beyond the intrinsic safety of the transfused therapeutic products, depending on a series of closely interconnected processes which start with the donor and finish with the recipient". Medical personnel must, therefore, always be alert to relevant symptoms appearing during or shortly after a transfusion.

The identification in the literature of 51 cases of *Y. enterocolitica* post-transfusion sepsis brought our attention to a question raised by Garraud and Lefrère[11]: are the risks of infection from transfusion currently "myth or reality"? It is our opinion that while systematic screening of blood donations for the presence of certain viruses has generated a significant decrease of viral infections[12,13], making them nearly a "myth", on the other hand, bacterial sepsis, which is the most frequent infectious complication of transfusion in developed countries[12,13], still represents a sad "reality".

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Authorship contributions

PF and VF conceived the study, participated in its design and coordination, and helped to draft the manuscript. MN, MADS, and FS carried out the histological and microbiological studies. FPB participated in the design of the study, drafted the manuscript and performed the bibliographic research. All Authors read and approved the final manuscript.

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The Authors declare that they have no conflicts of interest.

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