Fatal transfusion reaction due to *Serratia marcescens*

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**Synopsis**  A fatal blood transfusion reaction due to contamination of the blood by *Serratia marcescens* is described. The diagnosis and treatment of such cases is described briefly. The importance of teamwork in all concerned with blood transfusion is stressed.

Massive contamination of blood is a fortunately rare complication of blood transfusion but cases continue to be reported from time to time, emphasizing the need for constant vigilance and awareness of this hazard on the part of all concerned. We report a fatal transfusion reaction involving *Serratia marcescens*, an organism previously thought to be a harmless saprophyte (Burket and Burn, 1937; McEntegart, and Porterfield, 1949) but one which has, in recent years, become increasingly incriminated as a human pathogen (Wheat, Zuckerman, and Rantz, 1951; Hawe and Hughes, 1944; Robinson and Woolley, 1957; Papapanagiotou and Aligizakis, 1959; Graber, Tumbusch, Rudnicki, and Vogel, 1960; Haiby, McFarland, and Moore, 1961; Taylor and Keane, 1962; Graber, Higgins, and Davis, 1965).

**Case Report**

The patient was a 21-year-old primigravida. She had been well during the pregnancy and was admitted early in labour. On admission it was found that her haemoglobin was 11·1 g./100 ml. and that her blood group was O, Rhesus-negative. No irregular antibodies were detected.

The following day a forces delivery was performed on account of delay in the second stage of labour. After delivery she remained clinically well, but two days later her Hb level was found to be 6·6 g./100 ml. and it was decided to transfuse with 2 units of blood. These were crossmatched with the patient's serum by saline, papain, and indirect antiglobulin techniques, and found compatible. Transfusion was begun the following day at approximately 7.30 p.m. and after the first unit (540 ml.) of blood had been given uneventfully the second unit was set up at 12.30 a.m. next morning. At 2.15 a.m., after the patient had received about 100 ml., she had a rigor and complained of pain in the chest, and the transfusion was immediately stopped. She became flushed, with a pulse rate of 140/min., blood pressure 85/60 mm. Hg and temperature 103·2°F (39·5°C.) and shortly after this was incontinent of faeces and passed a loose stool. There was no backache and no evidence of pulmonary oedema. The reaction was thought to be of allergic type and Phenergan 50 mg. was given. The patient then became more comfortable but the pulse remained rapid and the temperature rose to 105°F (40·6°C.) and at 5 a.m. she was again incontinent of faeces and vomited some bloodstained material. She was given Largactil 50 mg. and remained more comfortable until 8.30 a.m. when she suddenly became dyspnoeic. The pulse rate was 146/min., weak and thready: systolic blood pressure 80 mm. Hg, diastolic unrecordable; temperature 102·6°F (39·2°C.). Moist sounds were present throughout the chest and diagnosis of left ventricular failure was made. She was given oxygen and intravenous digoxin and Frusemide but deteriorated steadily and died at 9.20 a.m.

**Investigation of Reaction**

The transfusion bottles were returned to the laboratory and, on examining them, it was noted that the residue of blood in the first bottle which had been used appeared normal. The blood remaining in the second bottle, however, was of a permanganate colour suggesting lysis and this was confirmed by centrifugation. Using strict aseptic precautions, a specimen was taken for bacteriological examination and preliminary examination of a Gram-stained film showed numerous small Gram-negative bacilli. The pilot bottle was sterile. Meanwhile the grouping and cross-matching tests were repeated and found to be in order. Investigations to determine the sequence of events before transfusion were instigated, and it was ascertained that the blood, on being removed from the blood bank refrigerator, had been taken directly to the theatre refrigerator in the maternity block where it was held before use. It was discovered that the offending bottle had previously been removed.

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from the blood bank, the top punctured, and the bottle left lying at room temperature for several hours before being returned to the blood bank and replaced in the blood bank refrigerator. These events occurred outside laboratory hours and were not reported to the laboratory staff.

The health of the blood donor and the history of the bottle from the donor session onwards were checked and no other irregularity was found.

**Necropsy Findings**

Post-mortem examination revealed gross pulmonary oedema and bilateral adrenal haemorrhages. The kidneys showed cortical adrenal haemorrhages. Apart from evidence of recent parturition, there were no other significant findings.

**Bacteriological Findings**

**Necropsy** Bacteriological examination of specimens of spleen and liver grew only intestinal contaminants.

**Blood** A Gram-stained film made from an uncentrifuged sample of the blood which had been used in the transfusion revealed the presence of numerous small Gram-negative bacilli. A hanging-drop preparation demonstrated active motility.

When attempts were made to culture the organism it was found that it grew very poorly at 37°C on nutrient agar, blood agar, or MacConkey's media even after 30 days. Good growth was, however, obtained on all three media in 24 hours at room temperature (22°C) and was of maximum colonial size after 48 hours. At 4°C there was no growth at 48 hours but by 72 hours there was growth on all three media equivalent to that obtained by 24 hours at room temperature; maximal growth at 4°C was obtained after six days.

The antibiotic sensitivity of the organism was tested at 22°C. using paper discs supplied by Mast Laboratories. It was found to be sensitive to tetracycline 25 mcg.; streptomycin 10 mcg.; ampicillin 25 mcg.; chloramphenicol 25 mcg.; kanamycin 30 mcg.; neomycin 10 mcg.; nalidixic acid 30 mcg.; and resistant to cephaloridine 25 mcg.; penicillin 1 i.u.; colistin 200 mcg.; erythromycin 5 mcg. It will be seen that the organism exhibited sensitivity to most of the antibiotics which were generally used in treating infection with a Gram-negative bacillus.

The organism was able to utilize Koser's citrate and grow in KCN; it liquified Loeffler's serum slightly in 48 hours and liquefied gelatin in less than 48 hours. It was gluconate, Voges-Proskauer, and catalase positive and was able to reduce nitrates to nitrites; it fermented glucose anaerobically. Most of the other common sugars were fermented with the production of acid: generally speaking, the reaction was anaerogenic but, if gas was produced, the volume was always small; it acidified litmus milk, producing clotting after seven days and digestion of the clot after another three days.

It failed to produce indole, hydrolyse urea, or produce H₂S on lead acetate agar; it was oxidase, malonate, and methyl red negative.

All the biochemical reactions were performed at 22°C and for 30 days. Positive and negative controls were used in every case.

From the above results, it was concluded that the organism belonged to the Enterobacteriaceae and, in that family, conformed most closely to the typical picture of *Serratia marcescens*. It was tested for 30 days for pigment production on the following media with negative results: potato slope, Hartley's digest agar (Cruickshank, 1965), mannitol yeast-extract agar (Cowan and Steel, 1965), and King, Ward, and Raney's medium A (Cowan and Steel, 1965). Ewing, Johnson, and Davies (1962) however, have pointed out that only 26.6% of strains produce pigment and it has been reaffirmed by Edwards and Ewing (1962) that pigment production can no longer be considered a cardinal feature of the group.

**Discussion**

Although there are many previous reports of transfusion fatalities due to psychrophilic Gram-negative bacilli (Borden and Hall, 1951; Pittman, 1953; Braude, Williams, Siemieniski, and Murphy, 1953; McEntegart, 1956) this case is, as far as we can determine, the first occasion on which *Serratia marcescens* has been implicated as the offending organism. It is, however, only recently that nonchromogenic strains of *Serratia marcescens* have begun to be described in the literature as pathogens (Bövre and Tönjun, 1963; Elston, 1965; Elston and Magnuson, 1965) and it may well be that some of the bacteria described earlier as 'paracolobactrum', etc., could, in fact, have been *Serratia marcescens*. This lack of a standard classification of the Gram-negative bacilli has been commented upon by various authors and in particular by Pittman (1953).

In any case the isolates described in the majority of previous reports appear to share the following characteristics: they are Gram-negative bacilli capable of proliferating at room temperature and in some cases at 4°C; they produce powerful endotoxins; they are capable of utilizing citrate; they are ubiquitous organisms with a widespread distribution in nature and play only a minor role as parasites or pathogens of man (Borden and Hall, 1951; Braude,
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Sanford, Bartlett, and Mallery, 1952; Braude et al., 1953; Pittman, 1953; Geller and Jawetz, 1954; McEntegart, 1956; Braude, 1958). It is generally agreed that although Gram-positive organisms, and Gram-positive cocci in particular, are more common than Gram-negative bacilli as contaminants of stored blood, they are only of minor importance statistically as a cause of serious transfusion reactions (Braude et al., 1952). This may be accounted for by the fact they do not produce powerful endotoxins and that their optimum growth temperature is 37°C.

Even when the best possible precautions are taken during blood donor sessions, it has been observed (Braude et al., 1952) that approximately 2% of bottles will be contaminated by bacteria at the time of collection. There is general agreement that the most important factors at this stage are the size of the initial inoculum and the type of organism (Braude et al., 1952; Geller and Jawetz, 1954); if the inoculum is small then the organism will be destroyed by the antibacterial substances present in whole blood; if the inoculum is larger then this delicate balance will be upset and some organisms may survive. It follows that if the bacteria are of a cold-growing type then they may be present in enormous numbers when the blood comes to be used for transfusion, particularly if the blood has been left for any length of time at room temperature. In spite of these observations, statistics show that bank blood properly handled and stored is remarkably safe. Some authors have suggested the addition of small amounts of antibiotics to stored blood (Braude, Carey, and Siemieniak, 1955) but such a practice has not come into general use.

The risk of contamination following the withdrawal of plasma from bottles is so great that this practice is forbidden by the minimum requirements for citrated blood of the United States National Institutes of Health. Gibson, Pond, and McManus (1960) have pointed out the advantages of using plastic bags in place of bottles in this respect, and it would appear that these bags might obviate the risk of an accident such as that described.

Although it has been observed by Mollison (1943) that haemolysis may not be obvious in banked blood due to the haemolysed cells being held beneath the white cell layer, if the possibility that the transfusion reaction may be due to contaminated blood is borne in mind, the diagnosis may rapidly be reached by examination of a Gram-stained film and by centrifugation of an aliquot to show lysis.

As regards treatment, the problem is essentially one of septic shock, and Litwin, Walter, Ejarque, and Reynolds (1965) have shown that the action of endotoxins is potentiuated by free haemoglobin, due to blockade of the reticulo-endothelial system. Antibiotics and hydrocortisone should be given, and further transfusions of plasma or blood if required. The latter should be as fresh as possible to avoid the introduction of more free haemoglobin into the circulation. Treatment with vasco-active drugs should be aimed at maintaining adequate tissue perfusion rather than simply raising the blood pressure (National Academy of Sciences Workshop on Septic Shock, 1965). Isoprenaline a β-adrenergic receptor stimulant, which increases cardiac output and causes peripheral dilatation, has recently been used successfully in septic shock (Du Toit, Du Plessis, Dommisse, Ronke, Therom, and De Villiers, 1966). Phenoxylbenzamine (Dibenzyline), an alpha receptor blocking agent, has also been used to improve peripheral flow (Nicksen, 1963).

In spite of all emergency therapeutic measures the mortality rate in bacteraemic shock is still extremely high and in view of this prevention of such accidents should be given priority.

We have reported this case in some detail as it illustrates some potential hazards of blood transfusion. Transfusion therapy involves many persons and grades of staff, each of whom should be made aware in differing degrees of the hazards and their avoidance. In particular the need to consider all reactions as serious and to report them at once should be stressed.

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REFERENCES


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