Clinical Reports

Sonoclot coagulation analysis and plasma exchange in a case of meningococcal septicaemia

Ulf Schött MD PhD, Elisabeth Björsell-Östling MD

On the basis of a patient with fulminant meningococcaemia and severe disseminated intravascular coagulation (DIC) syndrome, the diagnostic potential of a clot impedance test – Sonoclot coagulation analysis – was used to evaluate plasma exchange. A 17-yr-old girl was treated for a fulminant infection with Neisseria meningitidis in our intensive care unit. She developed severe DIC. Whereas platelet administration caused immediate arterial oxygen desaturation necessitating ventilatory support, plasma exchange improved pulmonary and mental function. Three separate exchanges all improved haemostasis. Sonoclot analysis was used together with routine coagulation analyses to evaluate this DIC treatment. Sonoclot signs, such as lack of the shoulder and peak, prolonged shoulder-peak interval and peak time predicted clinical bleeding manifestations (haematuria, haemoptysis, epistaxis) and were improved by platelet transfusion and plasma exchange. Plasma exchange was successful even at a very low platelet count of $<23 \times 10^9 \cdot L^{-1}$. *Sonoclot coagulation analyses were normalised several days before routine coagulation analyses. The Sonoclot gave additional information to routine coagulation studies, correctly indicated insufficient haemostasis and predicted a positive outcome. Also, plasma exchanges and platelet transfusions could be controlled in the management of DIC.*

Key words
BLOOD: coagulation, DIC;
COMPLICATIONS: meningitis;
MONITORING: coagulation; Sonoclot, TEG.

From the Department of Anesthesia and Intensive Care and Regional Blood Center, Örebro Medical Center Hospital, Örebro, Sweden.

Address correspondence to: Dr. Ulf S. Schött, Department of Anesthesiology and Intensive Care, Örebro Medical Center Hospital, S-701 85 Örebro, Sweden.

Accepted for publication 26th August, 1994.

A l'occasion d'une méningococcémie fulminante (syndrome de Waterhouse-Friderichsen) compliquée d'une coagulation intravasculaire disséminée grave (CIVD), le potentiel diagnostic du test d'impédance du caillot, l'analyse de coagulation Sonoclot, est utilisé pour évaluer la plasmaphérèse. Une jeune fille de 17 ans déjà sous traitement pour une méningite fulminante neissérienne dans notre unité de soins intensifs développe une CIVD grave. Comme l'administration de plaquettes produit une désaturation artérielle subite nécessitant une assistance ventilatoire, on a recours à la plasmaphérèse qui amélior l'activité mentale et pulmonaire. Trois échanges consécutifs restaurent l'hémostase. L'analyse au Sonoclot est utilisée en même temps que les tests de coagulation habituels pour évaluer le traitement de la CIVD. Les indications du Sonoclot, comme l'absence d'épaule et de pointe, la prolongation de l'intervalle épaule-pointe et l'instant du pic prédisent les manifestations cliniques du saignement (hématurie, hémoptysie, epistaxis) qui sont améliorés par la plasmaphérèse. La plasmaphérèse est efficace même lorsque le décompte des plaquettes est inférieur à $23 \times 10^9 \cdot L^{-1}$. *Les analyses du Sonoclot sont redevenues à la normale plusieurs jours avant les tests de coagulations habituels. Le Sonoclot a donné des renseignements supplémentaires sur les épreuves de coagulation habaituels en décelant l'insuffisance de l'hémostase et en prédisant l'évolution favorable. La plasmaphérèse et les transfusions de plaquettes ont pu être contrôlées pendant le traitement de la CIVD.*

Fulminant infection with N. meningitidis, or Waterhouse-Friedrichsen syndrome, is a major challenge to any ICU. In the fulminant form of the disease there is rapid deterioration in the general condition of the patient, with disseminated intravascular coagulation (DIC), adrenal haemorrhage, and multi-organ failure (MOF). Death may occur within hours.[1,2].

It is important not to avoid delay in the treatment of the fulminant infection.[2] Blood culture is essential

before starting antibiotic therapy. If, however, the patient has to be transported to hospital, antibiotics without previous culture should perhaps be considered.[2,3] Lumbar puncture should also be carried out, but unless samples can be obtained at the first attempt, treatment should be started immediately. The antibiotic spectrum should be broad and a combination of benzyl penicillin and a cephalosporin or chloramphenicol is common. Once meningococcal infection is confirmed, chloramphenicol may be withdrawn.[2] Usually the diagnosis is first confirmed by Gram stain CSF, though meningococci may not be seen if antibiotics have been given, then immunological methods may verify the diagnosis. Blood cultures may be negative and it may take up to a week to verify N. meningitides.[2] Mapping of antibiotic resistance will confirm the sensitivity of N. meningitidis to penicillin. Treatment should take place in an ICU where close monitoring can be undertaken and treatment of systemic failure is routine. Hydrocortisone is given if adrenal haemorrhage is suspected. Even with prompt treatment, the prognosis is poor in fulminant forms.[1,2,4,5]

Plasmapheresis and leucopheresis or blood exchange has been used in cases of meningococcaemia with DIC in which conventional treatment has been insufficient.[4-8] In addition to removing circulating endotoxin, activated complement, activated clotting factors, lysozymes from activated granulocytes, activated and aggregated granulocytes, which excrete superoxide, activated monocytes exposing thromboplastin and activated platelets with endotoxin attached, the plasma exchange can replenish protein C, S, AT III, deficient complement components and other plasma factors.[4] Also, restoration of the phagocytic function of the reticuloendothelial system due to clearing of immune complexes has been described.[9]

In the following report, a patient with fulminant infection with N. meningitidis who was treated with plasma exchange in a critical stage will be described. The use of bedside clot impedance test/viscoelastometry – Sonoclot coagulation analysis (Sienco Inc, Morrison, CO) – to evaluate treatment with plasma exchange and plasma products in the management of DIC will be highlighted.

Thromboelastography and Sonoclot coagulation analyses have been criticised as being unspecific and for poor correlation with routine coagulation tests. However, these tests have the potential to provide additional information on the haemostatic process, due to measurement of interactions of various components of the clotting process in whole blood.[10] Most routine coagulation analyses end with the formation of the first fibrin strands and are performed on isolated blood fractions.

Sonoclot coagulation analysis requires only 0.4 ml whole blood. The Sonoclot measures the viscoelastic drag (impedance) that fibrin and platelets impose upon the oscillating Sono-probe, and a time-based printer produces a graph that reflects plasma coagulation factor activity, fibrin production, platelet-fibrin interaction and finally clot retraction.[11-13] The graph is called the Sonoclot signature (Figure 1).

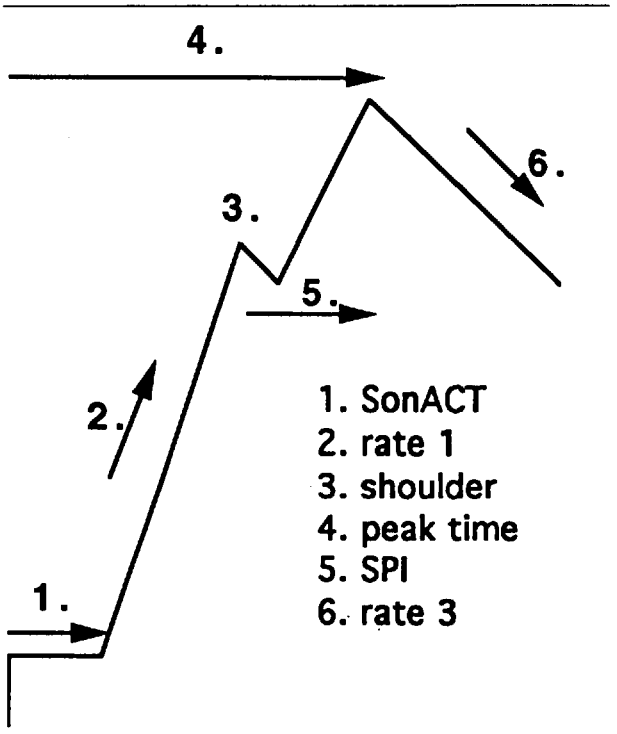

FIGURE 1 The Sonoclot signature. (1) SonACT (activated coagulation time) is the time for the first fibrin to form (normal range 1.5–2.5 minutes (min)). (2) Rate 1 (R1) (15–30% · min^{-1}) is the rate of increase in clot impedance to the Shoulder (3). Peak time (4), (6–10 min). (5) shoulder-peak interval (SPI) (2–4 min). (6) Rate 3 (R3) (2–8% · min^{-1}) indicate clot contraction events.

Saleem *et al.*[12] have studied the different parts of the Sonoclot signature with electronmicroscopy. They studied platelet-poor plasma and the effects of different platelet counts on the Sonoclot signature. Appearance of both a shoulder point and a sharp peak were signs of improved platelet counts. The shoulder peak-interval was stressed as the most sensitive variable and this has been confirmed by Blifeld *et al.*[14]

Case report

A 17-yr-old girl was admitted to the intensive care unit with signs of fulminant meningococcaemia (Waterhouse-Friedrichsen syndrome). She had a three-day history of coryza and during the last 12 hr had had nausea, vomiting, chills, spiking fever up to 39°C, widespread petechiae, large ecchymoses, scleral bleeding and increasing somnolence. On admission (12 noon) to the ICU, she

showed clinical signs of shock, with a systolic blood pressure of 60 mmHg, heart rate 120 · min^{-1}, peripheral vasoconstriction and tachypnoea, with a respiratory rate of 21 · min^{-1}. She had signs of meningitis, with neck stiffness and a positive Lasègue's test. She was comatose but had normal averting reactions to painful stimuli.

Lumbar puncture was performed and CSF analysis was normal. Blood and urine samples and airway swabs were obtained for culture, gram stain (verifying meningococcemia) and *iv* therapy was started with benzyl penicillin 3 g q.i.d. Methylprednisolone 2 g *iv* was injected. The initial routine laboratory analyses showed signs of DIC with a platelet count of 89 × $10^9 \cdot L^{-1}$ (normal 180–350 × $10^9 \cdot L^{-1}$). AT III of 71%; (normal 80–120%); prothrombin complex of 41%; (normal 70–130%), activated partial thromboplastin time of 41 sec (normal 25–35 sec) and fibrin degradation products >200 mg · L^{-1} (normal <10 mg · L^{-1}). Serum was 3.3 g · L^{-1} (normal value 2–4 g · L^{-1}). Serum creatinine was increased to 188 μmol · L^{-1}. Leucocyte count was low, 2 × $10^9 \cdot L^{-1}$.

A central venous catheter was introduced through the external jugular vein (central venous pressure (CVP) was −2 mmHg) and the bladder was catheterized. Two litres of oxygen was administered via a nasal catheter and arterial blood gas analysis showed a PaO_2 of 28 kPa and a PCO_2 of 4 kPa. Haemoglobin (Hb)-oxyhaemoglobin saturation was 99%. Base excess was −6 mmol · L^{-1} and pH 7.39.

The patient was resuscitated with two litres Ringers' acetate, one litre 5% albumin, one litre buffer – Tribonat® (Kabi Pharmacia, Sweden) and eight units (two litres) fresh-frozen plasma. She also received inotropic support with dobutamine up to 18 μg · kg^{-1} · min^{-1} and dopamine 3 μg · kg^{-1} · min^{-1}. Blood pressure improved to 115/70 mmHg, CVP from −2 to +8 mmHg, and diuresis started after three hours.

At 5 p.m. the patient had macroscopic haematuria and haemoptysis. Laboratory analysis indicated dilutional and/or consumptive coagulopathy with a decrease in B-Hb to 82 g · L^{-1}, in platelet count to 52 × $10^9 \cdot L^{-1}$ and in NPT to 34%, and an increase in APTT to 46 sec. Administration of six units leucocyte-depleted platelet concentrate improved the platelet count to 82 × $10^9 \cdot L^{-1}$. However, O_2 saturation decreased from 91% to 67%, PaO_2 from 9.0 kPa to 6.6 kPa and PCO_2 from 4.5 to 3.7 kPa (0.4 FiO_2). Pulmonary auscultation indicated pulmonary oedema. After oral tracheal intubation mechanical ventilation with 10 L · min^{-1}, using 0.8 FiO_2 and 10 cm positive end-expiratory pressure (PEEP) the O_2 saturation gradually increased to 94% and PaO_2 to 12 kPa. Chest *x*-ray immediately after intubation revealed both interstitial and alveolar oedema.

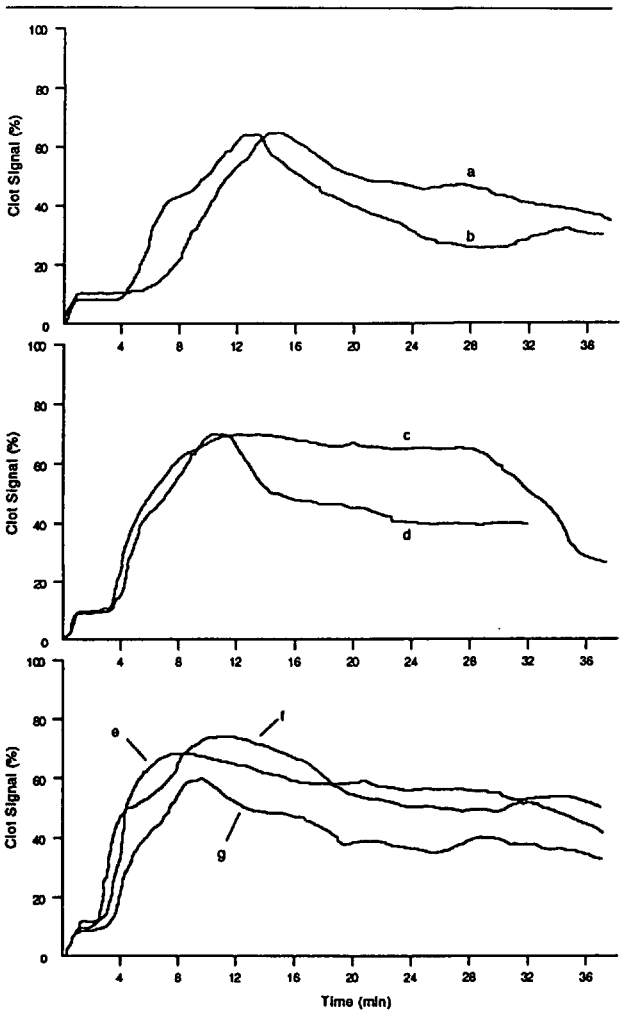

FIGURE 2 The Sonoclot signature before and after the first (a,b), second (c,d) and third (e,f) plasma exchanges. The effect of platelet transfusion after the last exchange is marked (g).

At 9 p.m. the patient again started to bleed from the trachea, gingiva and urinary tract. The platelet count was 74 × $10^9 \cdot L^{-1}$ and the temperataure increased to >41°C. The patient received a discontinuous plasma exchange with an exchange volume of 2.6 L (calculated plasma volume was 2.3 L) using one litre 4% albumin and 0.5 L 5% albumin initially followed by seven units (2 L) leucocyte-depleted plasma. Bleeding from the airways and the urinary tract ceased at the end of the plasma exchange.

The FiO_2 of 0.8 prior to plasma exchange (PaO_2 9.5 kPa) and could be lowered to 0.4 at the end (PaO_2 11.5 kPa). The B-Hb had increased from 83 g · L^{-1} prepheresis to 96 g · L^{-1} post-pheresis. No shoulder point could be detected on the prepheresis Sonoclot signature (Figure 2a). SonACT was prolonged to six minutes and

peaktime was prolonged to 14 min. In the postpheresis Sonoclot signature (Figure 2b), a shoulder point could be discerned with SPI of four minutes and SonACT was reduced to 3.3 min. The routine coagulation data still indicated a consumptive/dilutional defect with APTT 49 sec: NPT 41%, FDP >200 $mg \cdot L^{-1}$, platelet count $73 \times 10^9 \cdot L^{-1}$, AT III 47%, and S-fibrinogen was 2.7 $g \cdot L^{-1}$.

A very high calculated APACHE II score of 35 was calculated for the first 24 hr of treatment. The patient again had macroscopic haematuria and slow diffuse nasal bleeding on the morning of day 2 which stopped after a second plasma exchange. Prior to plasma exchange the Sonoclot signature showed no peak or shoulder and only a completed clot retraction after 36 min (Figure 2c); The Sonoclot signature was improved after the exchange with a shoulder point (SPI four minutes) and peak (peak time nine minutes) (Figure 2d). However, routine laboratory measurement indicated a deterioration after the plasma exchange with a decrease in platelet count from 61 to $32 \times 10^9 \cdot L^{-1}$ after the exchange. Only NPT improved from 32 to 45%. The patient received no sedation and opened her eyes spontaneously at the end of the plasma exchange.

The next morning (day 3), the trachea was extubated. Macroscopic haematuria and airway bleeding again occurred during the day and the platelet count decreased to $25 \times 10^9 \cdot L^{-1}$. Because of a lack of resources for plasma exchange, five units of leucocyte-depleted platelet concentrates were transfused. Bleeding stopped but hypoxia again developed, necessitating reintubation. Chest *x*-ray showed reappearance of pulmonary oedema. The SPI decreased from seven to three minutes, peak time from 14 to 9 min, and rate 3 increased from $0{,}5\% \cdot min^{-1}$ to $6\% \cdot min^{-1}$. In the evening two units of erythrocyte concentrate increased B-Hb from 77 to 103 $g \cdot L^{-1}$ and increased the CVP from 4 to 7 mmHg.

On day 5 the macroscopic haematuria and slow diffuse nasal bleeding reappeared and the platelet count decreased to $23 \times 10^9 \cdot L^{-1}$. A third plasma exchange (3.4 L) was performed. The Sonoclot showed no clear peak or shoulder prior to pheresis (Figure 2e). Post pheresis the Sonoclot signature (Figure 2f) showed a shoulder point, but a broad-based peak and long shoulder-peak interval (SPI 8 min). Six platelet concentrates increased the platelet count to $71 \times 10^9 \cdot L^{-1}$ and reduced SPI to four minutes (Figure 2g). This time there was no impairment of lung function and bleeding stopped. The trachea was extubated four hours later. Heparin was then started for thromboprophylaxis and the dosage was adjusted to maintain a normal Sonoclot signature. At day 11 FDP, NPT, AT III and S-creatinine had returned to normal.

Discussion

Our patient suffered from undesirable transfusion reactions to platelet concentrates, which increased the pulmonary leakage and desaturation. Her DIC and sepsis progressed and plasma exchange was decided upon in addition to conventional treatment. Plasma exchange was repeated on several occasions as an alternative to platelet transfusion when clinical findings indicated insufficient platelet activity.

The improvement in arterial oxygen tension after all three plasma exchanges has been described previously by Bjorvatn *et al.*[4] who also noted improvement of peripheral circulation, mental status and urinary output.

Tesoro *et al.*[15] suggested that the presence of altered mental status, particularly coma, shock, low peripheral leucocyte count and nonblanching rash was a "red flag" predicting a poor prognosis. Mental status was dramatically improved after the second plasma exchange in the morning of day 2. The B-Hb and haemodynamic state were stable throughout this plasma exchange.

The Sonoclot variables of insufficient platelet function, i.e., lack of shoulder point/prolonged shoulder-peak interval and lack of peak/prolonged peak time or a slow clot contraction rate (rate 3) were all improved by plasma exchange. The most probable mechanism of the beneficial effects of plasma exchange were the removal of platelet-inhibiting substances such as endotoxins,[4,7] activated platelets with endotoxin attached, and a replacement of plasma coagulation factors and restoration of natural inhibitors such as AT III, protein C and S.[11,16] However, there is a risk that the plasma exchange/pheresis procedure itself will lower the platelet count,[4] as was illustrated after the second exchange. Even then, plasma exchange stopped the bleeding and corresponded with improved platelet function in the Sonoclot coagulation analysis.

The Sonoclot signature was normal after day 6, whereas routine coagulation data such as prothrombin complex (NPT), FDP and antithrombin III were first normalised on day 11. Thus the Sonoclot predicted a positive outcome in this patient earlier than the routine tests.

In conclusion, plasma exchange in a 17-yr-old girl with fulminant meningococcaemia improved the clinical signs of haemostasis and the assessment of platelet function by Sonoclot coagulation analysis. However, routine coagulation analyses failed to indicate an improvement after plasma exchange and the Sonoclot predicted a normalising trend and a positive outcome earlier than routine coagulation analysis.

References

1 *Fox B.* Disseminated intravascular coagulation and the

Waterhouse-Friderichsen syndrome. Arch Dis Child 1971; 46: 680–5.

2 *Raman GV.* Meningococcal septicaemia and meningitis: a rising tide (Editorial). BMJ 1988; 296: 1141–2.

3 Anonymous: Fever with purpura (Editorial). The Lancet 1990; 335: 889.

4 *Bjorvatn B, Bjertnaes L, Fadnes HO, et al.* Meningococcal septicaemia treated with combined plasmapheresis and leucapheresis or with blood exchange. BMJ 1984; 288: 439–41.

5 *Scharfman WB, Tillotson JR, Taft EG, Wright E.* Plasmapheresis for meningococcemia with disseminated intravascular coagulation (Letter). N Engl J Med 1979; 300: 1277–8.

6 *Drapkin MS, Wisch JS, Gelfand JA, Cannon JG, Dinarello CA.* Plasmapheresis for fulminant meningococcemia. Pediatr Infect Dis J 1989; 8: 399–400.

7 *van Deuren M, Santman FW, van Dalen R, Sauerwein RW, Span LFR, van der Meer JWM.* Plasma and whole blood exchange in meningococcal sepsis. Clin Infect Dis 1992; 15: 424–30.

8 *McClelland P, Williams PS, Yaqoob M, Mosafa SM, Bone JM.* Multiple organ failure – a role for plasma exchange? Intensive Care Med 1990; 3: 100–3.

9 *Gurland HJ, Lysaght MJ, Samtleben W.* Immunomodulation: clinical aspects. Artif Organs 1986; 10: 122–7.

10 *Zuckerman L, Cohen E, Vagher JP, Woodward E, Caprini JA.* Comparison of thrombelastography with common coagulation tests. Thromb Haemost 1981; 46: 752–6.

11 *von Kaulla KN, Ostendorf P, von Kaulla E.* The impedance machine: a new bedside coagulation recording device. J Med 1975; 6: 73–88.

12 *Saleem A, Blifeld C, Saleh SA, et al.* Viscoelastic measurement of clot formation: a new test of platelet function. Ann Clin Lab Sci 1983; 13: 115–24.

13 *Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD.* Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass. Anesth Analg 1989; 69: 69–75.

14 *Blifeld C, Courtney JT, Gross JR.* Assessment of neonatal platelet function using a viscoelastic technique. Ann Clin Lab Sci 1986; 16: 373–81.

15 *Tesoro LJ, Selbst SM.* Factors affecting outcome in meningococcal infections. American Journal of Diseases of Children 1991; 145: 218–20.

16 *Nilsson I, Schött U.* Sonoclot coagulation analysis and antithrombin treatment (Abstract) Thromb Haemost 1991; 65: 909.