The biphasic transmittance waveform: An early marker of sepsis in patients with neutropenia

Nazia Hussain, Dan Hodson, Robert Marcus, Trevor Baglin, Roger Luddington
Haematology Department, Addenbrooke’s Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, UK

Summary
Transmittance waveform (TW) analysis has been proposed as a method of both prediction and monitoring of non-overt and overt disseminated intravascular coagulation. This study assessed the use of the rapid TW of the activated partial thromboplastin time in the detection of sepsis in 49 consecutive neutropenic haematology patients. A slope 1 cut-off value of −0.050 was found to be optimum giving 85% sensitivity with 92% specificity and positive and negative predictive values of 62% and 98%, respectively. Furthermore a worsening slope 1 value at 24 hours was indicative of a 60% increase in mortality risk. Haematology patients have a significantly increased risk of developing sepsis during intensive chemotherapy, exacerbated by the resultant neutropenia. This sepsis may progress extremely rapidly and is associated with a high mortality. Early diagnosis is therefore critical and is currently made on a predominantly clinical basis with supporting microbiological evidence 2–3 days later. This study showed that TW offers an early marker, predictive of sepsis in neutropenic patients. It correlates with subsequent microbiological results and may identify patients at greater risk of clinical deterioration who may require more intensive early therapy or observation. It may also provide a useful marker to monitor the effects of treatment.

Keywords
Clot waveform analysis, sepsis, neutropenia

Introduction
Sepsis is a complex inflammatory response syndrome (SIRS). It develops following the initiation of an appropriate host reaction to an invading pathogen (1, 2). In 1992 the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) produced a definition of sepsis (3), which is still regarded as the gold standard (4). Haematology-oncology patients are at high risk of sepsis due to the intensive myelosuppressive chemotherapy used (5). The resultant neutropenia further increases the risk of developing sepsis and the speed of its progression as a result of the infection. Early indicators of potential sepsis are the non-specific markers of an increase in body temperature or elevated levels of C-reactive protein (CRP). Procalcitonin (PCT) has also been widely reported as a useful biochemical marker of sepsis; however, the literature is inconclusive as demonstrated by two recent systematic literature reviews with meta-analysis (6, 7). A clearer indication of sepsis can be obtained from the results of microbiological culture, but these are not immediately available to the clinician.

Downey et al. described biphasic transmittance waveform (bTW) (Fig. 1) in critically ill patients which was highly sensitive and specific for the development of disseminated intravascular coagulation (DIC) (8, 9). The optical changes seen in activated partial thromboplastin time performed using the MDA series coagulation analysers was found to be due to the formation of a calcium dependent complex between CRP and very-low-density lipoprotein (10). It has recently been shown that there are minimal differences of performance between the bTW, CRP or PCT for the diagnosis of severe sepsis (11).

Studies involving the bTW have centred on patients within intensive care units (ICU) (8–10,12–14). This study examines the use of the activated partial thromboplastin time derived transmittance waveform (TW) analysis in the detection of sepsis in neutropenic patients. In comparison to the ICU patients which often exhibit multifactorial coagulopathy this group show only minor alterations in standard coagulation screening tests. At the time of a bTW the mean coagulation screen results were; PT 14.4 seconds (s) (SD 2.6), APTT 31.6 s (SD 8.7), Fibrinogen 4.2 g/l (SD 1.9). Similarly the changes seen in the TW of neutropenic
septic patients in this study are also much less pronounced than those seen in the ICU setting (11).

Materials and methods

TW analysis was performed in 49 consecutive neutropenic hematological patients over a 10-month period. APTTs were performed daily as part of the routine monitoring of patients receiving chemotherapy on the haematology ward. Samples were collected into 0.105 M citrate anticoagulant (Sarstedt, Leicester, UK) and centrifuged for 10 minutes at 2,000 g prior to analysis. Analysis was completed within 4 hours (h) of sample collection. The APTTs were performed on the MDA II coagulometer (Trinity Biotech, Bray, Ireland) using the Platelin LS reagent (Trinity Biotech, Bray, Ireland).

Routine clinical data was captured on 50 consecutive patients with neutropenia. One was excluded from analysis because important data was missing.

Sepsis was defined by a rise in body temperature >37°C and positive microbiological blood cultures. The slope 1 values (Fig. 1) were recorded from the APTT TWs and a receiver operating characteristic curve (ROC) (Medcalc software Ltd, Mariakerke, Belgium) produced to determine the optimum cut-off value. Sensitivity and specificity values were then calculated (15, 16).

Results

Positive blood cultures were detected in 23/49 (47%) of the patients studied. The remaining 26 patients were used as a control group and showed no evidence of sepsis.

Using the slope 1 data a ROC was produced with sepsis as the positive outcome. From this data a slope 1 value of –0.050 was found to be optimum. Blood cultures cannot be seen as having 100% sensitivity for the detection of sepsis, and of the 23 positive cultures three were identified as gram-positive coagulase-negative Staphylococci which could have arisen as a skin contaminant. Therefore these three cases were removed from the analysis. The revised ROC is shown in Figure 2. A slope 1 value of –0.050 remained optimum giving 85% sensitivity with 92% specificity (area under curve = 0.925). The resultant positive and negative predictive fractions were 62% and 98%, respectively.

In the majority of cases a slope 1 of <0.050 showed improvement in the sample tested 24 h later. Five individuals showed a worsening slope 1 value at the 24-h sample. Of these five individuals, three died whilst neutropenic. These patients achieved a DIC score of 2/3 (pre DIC) using the JMHW scoring system applied to haematological malignancy (17), a D-dimer estimate was used in place of fibrin/fibrinogen degradation products (FDP) with a moderately raised D-dimer score as 1 and markedly raised D-dimer as 2. None of those individuals with an improving slope 1 at 24 h died during neutropenia despite one individual having a DIC score of 4.

Discussion

Currently clinical features including fever and microbiological cultures are used to identify and monitor sepsis. The assay of markers such as CRP or PCT can be used but are non-specific and often fluctuate during treatment. This study has shown that the detection of a bTW, as defined by a cut-off in the slope 1 value of –0.050, during routine APTT analysis offers an additional rapid marker for the presence of sepsis. The detection of a bTW in this group of patients indicated sepsis with a specificity of 92% and a sensitivity of 85%, positive and negative predictive values of 62% and 98%, respectively, and an area under the curve of 0.925 (Fig. 2). These figures compared favourably to the published specificity of 81% and sensitivity of 74% with positive and negative predictive values of 45% and 94% for bTW in the identification of DIC (14).

This study shows that the bTW provides a rapid, inexpensive marker of sepsis in neutropenic haematology-oncology patients. The results of the TW precede the blood culture results by up to three days. Concern has been raised regarding the widespread use of antibiotics in febrile neutropenic patients resulting in an emerging resistance to all commonly used antibiotics (18). However, due to the rapid onset of infection in these patients the current clinical practice of antibiotic treatment initiation at the first indication of potential sepsis is unlikely to change. The bTW can supplement this early diagnosis which is currently dependent upon rise in temperature alone.
Clinically the empirical treatment of neutropenic patients at the first signs of potential sepsis is imperative. However, the 60% mortality seen in patients with a worsening slope 1 value, 24 h after the −0.050 threshold is reached, may identify patients at greater risk of clinical deterioration. The change in PCT measurements at this time has also been suggested to correlate with outcome (19). In conclusion, although a presumptive diagnosis of sepsis resulting from a BTW is unlikely to change treatment strategies in these patients it is a very inexpensive addition to the panel of non-specific markers currently used.

References