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Septic deep venous thrombophlebitis and distant emboli in injecting drug users – treatment experience and outcome

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ABSTRACT Injecting drug use is a world-wide problem responsible for numerous minor and major complications which are well recognised. After years of injecting drug use, superficial and peripheral veins may become obliterated and the committed drug user attempts to inject drugs into proximal and more central veins. Besides the potential for mechanical and toxic complications such as vascular injury, intra-arterial drug injection, pneumothoraces, mycotic aneurysms and deep abscess formation, use of large proximal veins may result in life threatening septic deep vein thrombophlebitis.[1,2,5]

Aseptic and septic thrombophlebitis of peripheral veins is a well recognised complication of intravenous catheters and usually responds to removal of the intravascular device. Catheter related septic thrombophlebitis of proximal large veins and great central veins are also widely reported. However septic or suppurative thrombophlebitis of deep veins in IDUs characterised by micro abscess formation within the thrombotic veins and repeated bacterial embolisation into the circulation, is a severe systemic disease which has received little attention in the literature.[1,3]

We recently observed ten IDUs (11 episodes) with septic DVT admitted to the infectious diseases unit in Fife, Scotland within a period of 28 months. This report summarises our experience in the diagnosis, treatment and follow-up of these patients.

KEYWORDS Emboli, injecting drug user, sepsis, thrombophlebitis

LIST OF ABBREVIATIONS C-reactive protein (CRP), computed tomography (CT), deep venous thrombosis (DVT), injecting drug user (IDU), intravenous (IV), low molecular weight heparin (LMWH), methicillin-resistant-*S.aureus* (MRSA), Scottish Drugs Misuse Database (SDMD), white cell count (WCC)

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METHODS

Case notes of all patients with septic thrombophlebitis admitted to our unit over a period of 28 months (November 2002–March 2005) were reviewed retrospectively. Deep venous thrombosis was diagnosed using Doppler ultrasonography and/or contrast enhanced CT. Routine laboratory results, including WCC, CRP, blood cultures and wound swab results, were collected using case notes and computer records. Patient details, site of thrombosis/emboli, diagnostic imaging, concominent diseases, antibiotic therapy used, duration/dose, time for clinical improvement and details about length of hospital stay were reviewed in detail. Follow-up was ascertained using hospital computer records or telephone conversation with the patient's general practitioner.

RESULTS

We identified 10 patients with 11 episodes of septic thrombophlebitis over a period of 28 months. Clinical data and evolution of septic thrombophlebitis of these 10 patients are summarised in Table 1. All patients had a history of IDU lasting a few years. Mean age was 34·4 years (range 24–50 years). Male to female ratio was 8:2. All patients had ileofemoral segment DVT. Eight patients had right sided, one patient left sided and one bilateral DVT. A single patient had two admissions in six months; initially she was admitted with septic DVT and was admitted six months later with septic thrombophlebitis, septic pulmonary emboli and posterior mitral valve leaflet endocarditis. Reviewing these episodes showed four episodes involved pure septic DVT whilst the other seven episodes were complicated by distant emboli mainly involving the lungs. One patient had embolic infarcts

involving mid brain whilst another had splenic infarcts. Two patients also had left sided endoarditis.

Median CRP on admission was 225 (range 31·2–347). Median WCC was 10·9x10^9 /L (range 5·6–23·8x10^9/L). At presentation, nine of eleven episodes were treated for injection related infectious complication, but in two cases an infective element was only diagnosed five and nine days after admission. Multiple blood cultures showed an isolation of gram-positive organisms in ten of eleven episodes. Five episodes showed an isolation of *Staphylococcus aureus* from blood cultures whilst Streptococci were isolated on four occasions. This included group A, B, F and G Streptococci. Multiple organisms were isolated on four occasions. *Candida albicans* was isolated from blood cultures on a patient with a central line after a few days of hospital stay.

Choice of antibiotic depended on the patient's clinical condition. All patients who were clinically stable at presentation received IV Benzyl penicillin and β-lactamase resistant penicillin such as flucloxacillin. Patients who were unstable and had signs of severe sepsis or septic shock received a combination of IV clindamycin, a third generation cephalosporin and metronidazole until they clinically improved and the culture results were available. The regime was then simplified according to culture results. Intravenous teicoplanin followed by oral linezolid was given to one patient when MRSA was suspected. Duration of antibiotic was guided by CRP results and clinical improvement. All patients received antibiotics until normalisation of CRP (duration 2–6 weeks).

All patients received IV antibiotics at the onset of the illness. Central venous access was frequently necessary not only for IV antibiotics but also for fluid resuscitation in acutely septic patients. Five of eleven episodes required central venous access within three days of admission, but if this proved difficult, and if the patient had improved clinically, oral ciprofloxacin and clindamycin was used.

Duration of IV antibiotics varied from 5–42 days. Patients with septic thrombophlebitis with no evidence of distant emboli received IV antibiotics for a shorter duration (5–10 days). Patients with distant emboli received IV antibiotics for at least two weeks. One patient with *S.aureus* sepsis and pulmonary embolism self discharged after five days. Therefore antibiotics were changed to oral flucloxacillin. Mean time for resolution of fever was 10·3 days (range 1–41 days). Mean length of hospital stay was 28 days (range 5–124 days).

All patients were started on therapeutic subcutaneous LMWH on admission. The dose was weight dependent. Patients with DVT received three months of LMWH whilst those with distant emboli received six months of LMWH. The injections were monitored by general practice or district nurses. All patients completed treatment and there were no reported side effects. Warfarin therapy was not used in our patients.

DISCUSSION

Injecting drug use is a major public health issue in Scotland with an increasing number of patients seeking medical help for secondary complications from the NHS. Opiates continue to be the most common drug type used illicitly by those reported to the SDMD on entering drug treatment services. The most common opiate used illicitly was heroin. Although most NHS boards across Scotland have shown a slight fall in the percentage who report injecting in the month prior to seeking treatment over the last five years, there have been exceptions in certain areas. NHS Fife covers such an area where the percentage increased during our study period (36% in 2001/2002 to 47% in 2004/2005).[4] This was reflected by the number of admissions with drug related infections to the infectious diseases unit.

Although there are many complications of IDUs, our study only concentrated on septic deep venous thrombophlebitis. The repeated trauma of venepuncture, local infections and irritant qualities of the drugs and adulterants, are the main cause of superficial and DVT in IDUs.[15–18] Combination of factors favours a deep venous thrombus to become septic. When illicit narcotics sold on the street, such as heroin or cocaine, reach the consumer, they have been diluted ('cut') several times by 50–99%.[19,22] The list of substances used to dilute the drug is long and may include quinine, lactose, caffeine, dextrose, sucrose, starch, magnesium silicate (talc) and other substances. The drug, usually in the form of a powder, may also contain soil, dust and pathogens introduced during manufacturing or storage.[21,22,23] When the narcotic is prepared for injection, it is mixed with water, lemon juice or other liquid, increasing the potential for contamination. Also, the ritual surrounding the injection may include the use of unsterile supplies, the sharing of equipment and lack of skin antisepsis.[24] Some IDUs lick needles, use saliva to clean the skin or dilute the drug. Pathogens from oral flora in addition to skin can contribute to sepsis in these cases.

Diagnosis of septic thrombophlebitis was established by the history of IV drug use, local signs of thrombosis such as swelling and pain, laboratory results pointing to systemic bacterial infection and radiological confirmation of DVT and distant emboli.

Imaging studies are useful to rule out thrombosis of deep system vessels, but they cannot distinguish between septic and nonseptic thrombophlebitis.[13] Our observation showed the use of dopplar ultrasonography or contrast enhanced CT scan to diagnose DVT. Ultrasound technique was found to be inexpensive, non invasive, non-ionizing and accurate in the diagnosis of DVT. However, contrast enhanced CT scanning was able to more readily

visualise anatomical structures located in the pelvis or other areas. Furthermore, CT may readily delineate pathologies of structures adjacent to the vein such as perivenous fluid, soft tissue abscesses or haematomas.[1]

Recurrent and persistent bacterial seeding can also lead to endocarditis and distant septic emboli. Although right sided endocarditis has characteristically been associated with IV drug use, our observation showed left sided endocarditis in two of eleven episodes. If clinical suspicion exists or if temperature remains high, all patients should be investigated with transthoracic followed by transoesophageal echocardiogram to exclude endocarditis.

Septic pulmonary emboli are commonly seen in this group of patients and may show characteristic radiological features which may permit early correct diagnosis. The emboli may present as small, scattered areas of consolidation simulating bronchopneumonia, or as round wedge shaped peripheral opacities on chest X-rays. These excavate and often produce thin-walled cavities simulating pneumatocoeles. Coalescence of necrotic infarcts may result in formation of large lung abscesses. Lesions may extend to involve the pleura, causing empyema, bronchopleural fistula and pneumothorax.[6] However, chest radiograph at presentation could be non-specific and CT pulmonary angiogram could be more helpful and accurate in diagnosing pulmonary emboli in patients with clinical suspicion.[7] Embolisation can also involve other organs including spleen and brain secondary to persistent bacterial seeding or endocarditis.

Blood cultures are usually positive in suppurative septic thrombophlebitis. Although the source of pathogens is variable most originate from flora of the skin and oropharynx. The most common organisms isolated in our cases were gram positive, namely *S.aureus* and Streptococci. This was consistent with other reported cases. Four of eleven episodes showed more than one organism isolated from blood cultures. Although our study did not show any anaerobic isolation from blood cultures, groin swabs and abscess fluid showed anaerobic isolation in two of eleven episodes. Use of contaminated heroin can also lead to the introduction of spore-forming bacteria. From 2000 to May 2004 a marked increase in illness resulting from spore-forming bacteria in injecting drug users has been reported in the UK.[8] Cases of necrotising fascitis due to a variety of Clostridia species, wound botulism due to *Clostridium botulinum* and tetanus due to *Clostridium tetani* have been reported in IV drug users.[9] The reasons for the increase in illness was unclear but the major risk factor was thought to be injecting contaminated heroin subcutaneously or intramuscularly (skin or muscle popping). This practice can create an anaerobic environment in the resultant devitalised tissue conducive to Clostridial toxin formation.[10, 11] Epidemic spread of MRSA among IDUs has occurred in Europe and North America.[14] We did not observe any MRSA isolation in our group of patients. However, one should have a high index of suspicion and consider these possibilities in managing this group of patients. Nosocomial infections are also frequently encountered and are a significant problem, mainly related to repeated attempts at trying to gain IV access, IV catheter devices and long periods of hospital treatment. If patients fail to improve with treatment, this possibility should be considered. The management of this group of patients can therefore be difficult due to the possibility of rare infections such as botulism, tetanus and nosocomial infections in addition to the original illness.

Choice of initial antibiotics should be based upon the gram stain results whenever possible. However this is not always practical. Initial empiric antibiotic therapy should therefore cover commonly encountered organisms such as S. *aureus* and streptococci. Based on our observations, we recommend benzylpenicillin and flucloxacillin intravenously. However, if patients have signs of severe sepsis or septic shock the regime should also cover gram negatives and anaerobes. We used a combination of clindamycin, a third generation cephalosporin and metronidazole successfully. A quinolone such as ciprofloxacin could be used as an alternative to cephalosporin. If MRSA infection was suspected, a suitable antibiotic should be added to the regime. This regime can be simplified after clinical improvement and the availability of culture results. There is no reliable data on whether aminoglycosides should be added in the initial regime in this group of patients. Aminoglycosides were not used in our group of patients, however it should be considered if *S.aureus* and streptococcal endocarditis are suspected.

Fibrin is an integral part of intravascular thrombi and may provide a protective environment for micro-organisms. As penetration of antibiotics into fibrin is limited, therapy of conditions such as septic thrombophlebitis is often ineffective or necessitates long term therapy.[28] Clinical studies on humans are indeed difficult, because septic thrombophlebitis is an infrequent and heterogeneous disease. However *in vitro* and *in vivo* experimental fibrin clot models of endocarditis have suggested that the pharmacokinetics and pharmacodynamics of diffusion into fibrin may govern the efficacies and optimal dosage regimens of antibiotics. Autoradiographic distribution patterns of labelled compounds have been used to describe three different diffusion patterns. Antibiotics such as 14C-teicoplanin, was shown to remain concentrated at the periphery of the vegetation and not diffuse into the core of the vegetation.[24, 25] This was considered one explanation for the failures observed with teicoplanin in the therapy of human staphylococcal endocarditis. The second pattern was observed with 14C-ceftriaxone[25, 26] which progressively diffused into the vegetation, but a high concentration gradient persisted between the periphery and the core. To a lesser degree this concentration gradient was observed with 14C-

Age/Sex	Thrombosis/Emboli	Microorganisms	Material with bacterial growth	Concominent disease	CRP(mg/l) WCC(10/l) Neutrophils	Diagnostic imaging	Therapy (days=d)	Time to deferve-scence (days)	Length of hospital stay	Follow-up
27 M	Common femoral vein thrombus, multiple septic pulmonary emboli	Bacteroides species	Groin swabs		334 9·4 7·38	Doppler ultrasound CTPA Echo	clindamycin 450 mg IV 6h x 14d + ceftazadime 2 g IV 8h x 7d + metronidazole 500 mg IV 8h x 7d. followed by clindamycin 450 mg po 6h + ciprofloxacin 500 mg po 12h x 14d	18	27	Readmitted after 6 months for ipsilateral DVT due to IV drug use.
38 M	Common femoral and iliac vein thrombus, multiple septic pulmonary emboli, splenic infarcts	Coag -ve Staphylococci (2 strains)	Blood cultures x 4	Hep C	205 23·5 22·10	Contrast CT chest/ abdomen and pelvis Echo/TOE	flucloxacillin 1 g IV 6h x 3d + benzylpenicillin 1·2 g IV 6hx 3d then teicoplanin 400 mg IV 24h x 21d + ceftazadime 2 g IV 8h x 21d + metranidazole 500 mg IV 8h x 10d followed by ciproxin 500 mg po 12h + linezolid 600 mg po 12h x 21d	16	30	Readmitted to surgical ward with contralateral cellulites after 4 months. Relapsed into IV drug use.
40 M	Common femoral vein thrombus, septic pulmonary emboli with multiple lung abscesses	Group F Streptococcus	Blood cultures x 2		120 14·9	Doppler ultrasound CTPA Echo	benzylpenicillin 1·2g IV 6h x 18d + flucloxacillin 1 g IV 6h x 18d, followed by flucloxacillin 500 mg po 6h x 28d + Fucidin 500 mg po 8h x 28d	3	21	Lost to follow-up.
31 M	Femoral vein thrombus, pulmonary emboli	*Staphylococcus aureus*	Blood cultures x 2		184 9·5 6·48	Doppler ultrasound CTPA	flucloxacillin 1 g IV 6h x 5 d + benzylpenicillin 1·2 g IV 6h x 5d followed by flucloxacillin 500 mg po 6h x 14d	3	5	Self discharged and lost to follow-up.
24 F	Common femoral vein thrombus	*Staphylococcus aureus*	Blood cultures x 2 Groin swabs		245 10·5 7·09	Doppler ultrasound	flucloxacillin 2 g IV 4h x 5d + gentamicin 80 mg IV 12h x 5d followed by flucloxacillin 500 mg po 6h 10d	1	5	Self discharged after 5 days readmitted after 7 months with *staphylococcus aureus* septic DVT, pulmonary emboli and mitral valve endocarditis.
38 M	Femoral vein thrombus	*Streptococcus oralis* *Streptococcus agalactiae*	Blood cultures x2		152 23·8 22·20	Doppler ultrasound Echo	benzylpenicillin 1·2 g IV 6h 10d + flucloxacillin 1 g IV 6h 10d, followed by flucloxacillin 500 mg po 6h x 21d + amoxycillin 500 mg 8h x 7 d	3	17	Lost to follow-up.

TABLE 1 Synopsis of 10 patients with septic thrombophlebitis and emboli after injecting drug use.

Age/Sex	Thrombosis/Emboli	Microorganisms	Material with bacterial growth	Conco-minent disease	CRP(mg/l) WCC(10/l) Neutrophils	Diagnostic imaging	Therapy (days=d)	Time to deferve-scence (days)	Length of hospital stay	Follow-up
50 M	Femoral vein thrombus Septic pulmonary emboli with cavitation	Group G Streptococcus	Blood cultures x 2		312 10·6	Doppler ultrasound CT scan chest/ abdomen, pelvis Echo	clindamycin 300 mg IV 6h + cefotaxime 2 g IV 8h + metranidazole 500 mg IV 8h 1d then clindamycin 300 mg po 6h x 35d + metronidazole 400 mg po 8h x 10d + benzylpenicillin 2·4 g IV 4h x 7d followed by ciprofloxacin 500 mg po 12h 28d	8	25	Readmitted to hospital after 2 months with COPD exacerbation. Stopped IV drug use.
24 F	Bilateral femoral vein thrombus	*Streptococcus pyogenes* *Staphylococcus aureus* Enterococcus Bacteroides Coliforms	Blood cultures x 2 Groin swabs Groin abscess swab	Hepatitis C	290 17·3 13·50	Doppler ultrasound CT chest	flucloxacillin 1 g IV 6h + benzylpenicillin 1·2 g IV 6h 5d, followed by flucloxacillin 500 mg po 6h + metranidazole 500 mg po 8h x 27d (Groin abscess surgically drained)	1	26	Stopped IV drug use at 1 year follow up.
34 M	Femoral and popliteal vein thrombus	*Staphylococcus aureus*	Blood cultures x 4	HIV Hepatitis C	31·2 5·6	Doppler ultrasound	flucloxacillin 500 mg IV 6h 5d, followed by flucloxacillin 500 mg 6h po 14d	11	19	Readmitted after 5 months with cellulites, rabdomyolysis and renal failure due to IV drug use.
38 M	Femoral vein thrombus. Endocarditis with posterior mitral valve leaflet perforation. Embolic infarcts mid-brain	*Staphylococcus aureus* *Candida albicans*	Blood cultures, wound swabs Blood cultures, CVP line tip cultures	Hepatitis C	347 11·3	Doppler ultrasound Echo/TOE CT Chest Ultrasound abdomen CT/MRI head	clindamycin 450 mg IV 6h + ceftazadime 2 g IV 8h + metranidazole 500 mg IV for 2d (Surgical drainage of groin abscess.) Then flucloxacillin 2 g IV 6h 12d + benzylpenicillin 1·2 g IV 4h 10d + metranidazole 500 mg IV 8h 12d followed by flucloxacillin 2 g IV 4h 35d + voricanazole 200 mg IV 12h 3d and po 21d	33	123	Lost to follow up.

TABLE 1 Cont. Synopsis of 10 patients with septic thrombophlebitis and emboli after injecting drug use.

penicillin.[24] The third most frequent pattern was described with antibiotics such as tobramycin, and daptomycin, where a homogeneous diffusion throughout the whole lesion was observed.[25, 27] However other factors such as the killing rate of the antibiotic, the possible inactivation of the antibiotic by local physiochemical conditions, and the metabolic state of the bacteria in fibrin clots could also play a role in the effectiveness of antibiotics in treating this condition.[25]

There are few empirical data on optimal duration of antibiotic therapy and when therapy can safely be switched from IV to an oral regime. By analogy with recommendations in patients with infective endocarditis, it is common practice to use IV treatment for at least four weeks in this group of patients. Our report on eleven episodes showed that duration of IV antibiotics varied from 5–42 days. We observed that patients with pure septic DVT generally required shorter duration of IV antibiotics (5–10 days) when compared to patients with distant emboli (2–6 weeks). However, if prolonged IV treatment is not feasible, oral clindamycin and ciprofloxacin may be valuable alternatives if the patient clinically improves. Duration of antibiotics was mainly dependant on clinical progress and improvement in inflammatory markers (CRP).

Low molecular weight heparin has largely replaced IV unfractionated heparin for the initial management of DVT. Low molecular weight heparin has been shown to be as effective as conventional heparin and it is also easy to administer without the need for therapeutic monitoring. It is therefore convenient for long-term outpatient usage. Low molecular weight heparin may cause thrombocytopenia although it is less likely to do so than unfractionated heparin. It is advisable to monitor platelet count for the first ten days of treatment.[12] Risk of osteoporosis is less than with conventional unfractionated heparin. We used LMWH (daltaparin) for 3–6 months. This proved easy to manage with supervision of district or practice nurses. No side-effects were reported during this period. Oral anticoagulation with warfarin is extremely difficult in this group of patients mainly due to the difficulty in monitoring international normalised ratio, poor compliance, chaotic life style and risk of haemorrhage with over anticoagulation.

In patients with catheter-related septic DVT, resection or ligation of the involved veins, or thrombectomy with removal of the involved clots, has been reported to be helpful after unsuccessful conservative therapy. However, none of our patients required surgical intervention. Our experience supports the view that medical therapy alone is usually sufficient for this group of patients. For concominent problems such as soft tissue abscesses, surgery may still be necessary. Harm reduction programs, including needle exchange programs, safer injecting facilities and injection opiate substitution programs can also reduce the incidence of infections in addicted IDUs.[14] All our patients were referred to the community drug team and were enrolled in a methadone programme prior to discharge.

In conclusion, septic DVT in IV drug users is a potentially life threatening disorder. Blood cultures are mandatory in every IV drug user with DVT and fever. Chest X-rays may be helpful but non specific in diagnosing pulmonary emboli. Computed Tomography Pulmonary Angiogram may however be useful in confirming pulmonary emboli. Empirical antibiotic therapy should cover *S.aureus* and Streptococci. If patients are systemically unwell, suitable antibiotics should be considered to cover gram positive, gram negative and anaerobic organisms, until culture results are available. Community acquired MRSA infection should also be considered in relevant areas. Low molecular weight heparin is easy to use in this group of patients as it does not require monitoring blood levels. Clinical vigilance is necessary and surgeons should be involved early in the management if drainage and debridement is needed.

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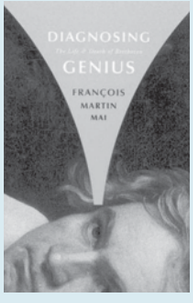
DIAGNOSING GENIUS: THE LIFE AND DEATH OF BEETHOVEN

By Francois Martine Mai (McGill-Queens University Press, 270 pp, £15.99)



Professor Mai has added yet another very interesting volume to the already extensive literature on Ludwig van Beethoven. However, his title is misleading. Readers who have been led to expect a discussion of the characteristics by which genius may be recognised will be disappointed. His subtitle is much nearer the mark; a little over half the book is devoted to an account of Beethoven's life and times.

But this adds little to what is already well known. The essence of the book is in Professor Mai's discussion of the ailments suffered by Beethoven during his lifetime and his inquest into the cause of Beethoven's death.

Professor Mai makes excellent use of the best secondary sources. He also finds relevant information in letters written by Beethoven and letters to him written by his friends. The *Conversation Books*, the writing pads that Beethoven's friends and visitors used to communicate with him after his deafness became complete, all survive and these too have been examined for clues. The Heiligenstadt Testament, the document in which Beethoven reflected on his life while suffering a period of severe depression, is quoted in full.

The reader is also provided with the available medical testimony. This has been extracted from physicians' reports, from autopsy reports and from the toxicological analysis of a lock of Beethoven's hair carried out in 1996.

Having considered all the evidence, Professor Mai does not seek to impose a definitive judgement. Nevertheless, he steers the reader towards the conclusion that Beethoven suffered irritable bowel syndrome for most of his life; that his deafness was due to otosclerosis, that he died of liver failure; that this resulted from many years of alcohol dependence; that the wine he drank was adulterated with lead, causing lead poisoning late in his life. However, all the evidence is fairly and clearly presented and the reader may reach his own conclusion.

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