

Case Reports

Deep Vein Thrombosis and Pulmonary Embolism: An Almost Missed Diagnosis in a Chinese Boy – Case Report and Review

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Abstract

Deep vein thrombosis and pulmonary embolism are rare in children particularly in the Chinese population. We describe a 14-year-old previously healthy Chinese boy who developed deep vein thrombosis with pulmonary embolism after minor trauma. Because the index of clinical suspicion was low, the diagnosis of DVT was overlooked in the initial presentation. This case illustrates the importance of recognizing this seemingly rare condition in Chinese paediatric population. Furthermore, contrast enhanced spiral CT scan was found to be safe, efficient and accurate in making the diagnosis of pulmonary embolism.

Key words

Chinese children; Contrast-enhanced spiral CT angiography; Deep vein thrombosis (DVT); Pulmonary embolism (PE)

Introduction

Deep vein thrombosis (DVT) with pulmonary embolism (PE) is rare in paediatric population.¹⁻⁵ The majority of cases reported are associated with intravenous catheters, congenital heart diseases, major surgery, trauma, sepsis, prolong immobilization, neoplasms, drugs, congenital and acquired thrombophilia.^{1,3-7} Pulmonary embolism and DVT may often be missed in the Chinese paediatric population because of the low incidence and the low index of suspicion. We describe a 14-year-old previously healthy Chinese boy who presented with left lower limb pain and swelling. The diagnosis of DVT was overlooked in the initial presentation.

His subsequent clinical course and management are discussed. This case illustrates the importance of recognizing this seemingly rare condition in the Chinese paediatric population.

Case Report

A 14-year-old boy of Southern Chinese origin was admitted for investigation of fever and left limb pain. Apart from mild asthma, he was said to be previously well. Ten days prior to admission, he collided into a metal locker at school and sustained a mild left thigh contusion and laceration over his right shin. He developed pain over his left thigh and started to walk with a limp one week later. The pain was not relieved by non-steroidal anti-inflammatory medication. He visited a Chinese bonesetter and he was given some herbal tonic and topical herbal ointment for local massage. Subsequently, he developed low-grade fever, malaise with chills and rigors. He was immobilized for one day and then admitted to our hospital. On admission, he was afebrile but appeared lethargic. His blood pressure measured 92/43 mmHg and his pulse rate was 110 beats per minute. Cardiovascular and respiratory examinations were unremarkable. Mild hepatomegaly was detected. He had generalized muscle pain involving the neck

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muscles, intercostal muscles, abdominal muscles and both lower limbs. Both thighs were swollen, firm and tender. Tenderness was also noted in both calves especially the left. There was a mild effusion of the left knee with decreased range of movement.

Preliminary investigations showed normal peripheral blood white cell count but elevated erythrocyte sedimentation rate (ESR) 35 mm/hour. Transaminase was mildly elevated. Abnormal coagulation was found compatible with low grade disseminated intravascular coagulopathy (DIC). The activated partial thromboplastin time (APTT) was 41.1 seconds, prothrombin time (PT) 18.1 seconds, International Normalised Ratio (INR) 1.5 and platelet count $92 \times 10^{12}/L$. Plasma creatinine phosphate kinase was 888 unit/L (MB fraction 3%). Urine was negative for red cell and myoglobin.

He was hypotensive and tachycardiac. Echocardiogram revealed impaired cardiac contractility. He was started on inotropic support. Intravenous antibiotics including cloxacillin and gentamicin were given. Blood culture showed gram-positive cocci, which were later confirmed to be methicillin-sensitive staphylococcus aureus (MSSA). The differential diagnoses at that time were necrotizing fasciitis, osteomyelitis, pyomyositis, and septic arthritis.

From the second day of admission, he developed high swinging fever. Aspiration of left thigh muscle and left knee joint were done. The gram staining of both specimens were

negative. The patient had normal joint fluid microscopic, cytology and biochemistry findings. The subsequent cultures for bacteria were negative. X-rays of the lower limbs did not show any evidence of osteomyelitis. Later, conventional CT scan of his left thigh with contrast showed oedem of the whole muscle of vastus intermedius suggestive of infection or inflammation. A radiologist, 2 Paediatricians and 2 Orthopaedic surgeons had seen the CT films. None of them spotted the oedema around the left femoral vein vascular bundle which was subsequently identified to be a suspicious thrombus by another radiologist. Doppler ultrasound study of left lower limb confirmed venous thrombosis in the left superficial femoral vein extending from mid-thigh to the adductor canal. MRI of thigh (Figure 1) was also performed which showed irregular heterogeneous intensity inside the bone marrow at the metaphysis of the left lower femur with heterogeneous enhancement after contrast injection. No adjacent periosteal reaction was seen. The epiphyses and metaphyseal plate were not involved. The picture was compatible with osteomyelitis or bone infarct. Thrombus was seen inside the left superficial femoral vein.

Heparin was commenced with a loading dose of 3000 unit followed by a maintenance infusion 30-40 unit/kg/day. The APTT was kept at around 2-3 times that of normal control. Two days later, he developed increasing respiratory distress. Chest radiography (CXR) revealed bilateral pleural

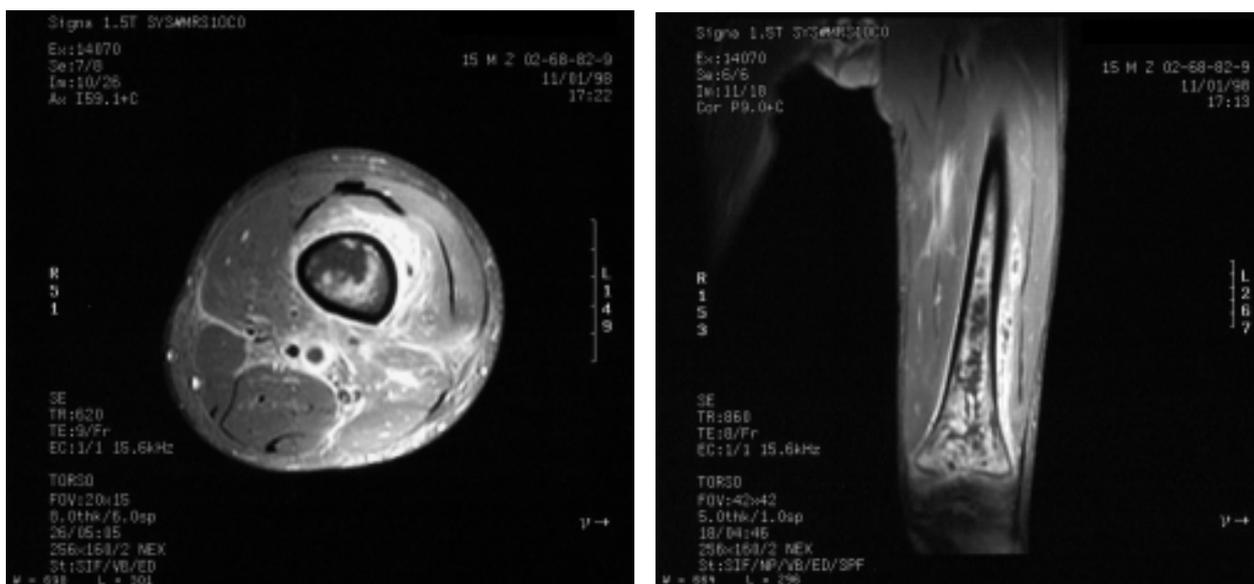


Figure 1 MRI of thigh showed irregular heterogeneous intensity inside the bone marrow at the metaphysis of the left lower femur with heterogeneous enhancement after contrast injection.

effusions and patchy opacities in both lungs mainly over peripheral the peripheral regions. Homogenous heavily blood stained pleural fluid was obtained following aspiration of the effusions but the cultures were negative. Lung ventilation/perfusion scan (VQS) showed multiple non-segmental matched V/Q defects in both lungs which were suggestive of parenchymal disease rather than PE. Spiral CT scan of thorax with contrast showed multiple small cavitating abscesses, which were compatible with multiple septic emboli to the lung. Follow up Doppler ultrasound study of left thigh one week after initial assessment showed proximal extension of the thrombus.

We considered Caval interruption by means of inserting an 'umbrella' filter into inferior vena cava to prevent major pulmonary embolism. This was not done because of the high surgical morbidity and mortality. Heparinization and antibiotic treatment were therefore continued. He remained febrile and his Erythrocyte Sedimentation Rate (ESR) and C-reactive protein level were persistently elevated (140 mm/hour and 31 mg/L respectively).

He developed sudden onset of chest pain and dyspnoea 2 weeks after admission. He was found to be cyanotic, tachycardiac and dyspnoeic. There was no evidence of pneumothorax on clinical examination and CXR. Electrocardiogram showed right ventricular strain pattern. An urgent spiral CT scan of the thorax with contrast enhancement was done, as we could not arrange an acute VQ scan. A hypodense lesion was noted within the right main pulmonary artery suggesting an intraluminal filling defect with 50% blockage of the lumen (Figure 2). A broad-base parenchymal consolidation measuring 2.2x1.8 cm in area was noted at the posterior basal segment of the right lower lobe. A thin layer of pleural effusion was present in the right pleural space. Similar areas of wedge-shaped appearance were also detected at the right upper lobe compatible with pulmonary infarcts.

One dose of recombinant Tissue Plasminogen Activator (r-tPA) at 0.7 mg/kg for 2 hours was given. Heparin therapy was continued aiming at APTT 3-4 times of normal control. His cardiac function was regularly monitored. No vegetation was detected by echocardiogram and right heart function was normal. Repeat spiral CT V/Q scan showed complete resolution of the pulmonary embolism. Doppler ultrasound study showed partial recanalization of the proximal portion of the superficial femoral vein.

His condition gradually improved. Intravenous heparin therapy was changed to oral warfarin by the end of the third weeks when he resumed a enteral diet. The warfarin

loading dose was 0.1 mg/kg and the maintenance dose 0.08 mg/kg/day. INR was kept around 1.5-2.5. Heparin therapy was stopped after 3 days. A six-week course of anti-staphylococcal treatment was given for the osteomyelitis.

Warfarin therapy was continued for 6 months. Follow-up Doppler ultrasound showed complete resolution of the thrombus. Screening for thrombophilia was performed three months after stopping warfarin. Serum Protein C, Protein S and anti-thrombin III levels were normal and no lupus anticoagulant was identified. Neutrophil function tests were also performed in view of the severity of the staphylococcal infection, which excluded Chronic Granulomatous Disease. There was no recurrence of thrombotic event or postthrombotic syndrome for 18 months follow up.

Discussion

Incidence of DVT/PE Among Chinese^{4,8-14}

The incidence of DVT/PE is estimated at 2.5% to 5% of the Western adult population.^{4,13} In contrast, the incidence was only 0.75% among Hong Kong Chinese adults based on autopsy findings.⁸ As for the paediatric population, it is reported to be between 0.07 per 10,000 to 5.3 per 10,000

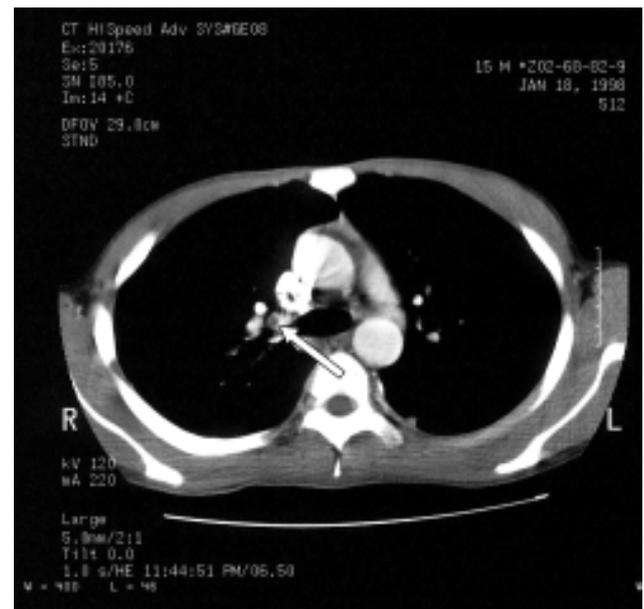


Figure 2 A hypodense lesion was noted within the right main pulmonary artery suggesting an intraluminal filling defect with 50% blockage of the lumen.

hospital admissions in a Canadian registry which is far lower than that of adult population.⁴ To our knowledge, this is the first reported case of PE in a Chinese paediatric patient with no prior history of cardiac catheterization or surgery. The recent discovery of racial differences in haemostasis and coagulation defects may explain the low incidence in the Chinese population. Activated protein C resistance was found in 40% of cases with thrombosis in a Swedish study.¹² However, there was complete lack of APC-resistance in 293 healthy Hong Kong Chinese blood donors.¹¹ Another local study demonstrated that the plasma level of protein C was increased significantly in the third stage of labour in normal pregnant Chinese women which may account for the almost negligible occurrence of thromboembolism in Chinese obstetric patients.¹⁰ Apart from these findings, some unknown factors may also exist in Oriental diet which alters gut flora and hence the level of plasminogen activators and resulting in increased fibrinolytic activity.⁹ A higher circulating level of anti-thrombin III was also postulated to be an important protective mechanism.⁹ However, there is a rising trend observed with a six-fold increase in incidence of thromboembolic events from 0.75% to 4.7% in our adult population.¹⁴ Growing elderly population, more aggressive approach by surgeons and westernization of Hong Kong Chinese in diet might all be important contributing factors.

Pathogenesis^{14-18, 27}

There are several unusual features in our case. Firstly, he was a previously healthy Chinese boy without thrombophilia or other significant predisposing condition. Secondly, the blunt trauma preceding the illness was quite mild. This is in contrast to many other case reports describing major orthopaedic trauma with limb fractures and prolonged immobilization or forceful events which produce direct or indirect injury to a vein.^{14,15} Thirdly, the site of formation of deep vein thrombus is unusual as in Chinese patients DVT usually occurs in the calf veins rather than in the more proximal deep veins.¹⁶ We therefore postulated that vigorous local massage by bonesetter may have aggravated the initial trauma leading to a partial tear in the endothelium of the superficial femoral vein. The use of herbs may have caused transient state of hypercoagulopathy as there were case reports show that some of the Chinese herbs can cause thrombotic events.^{17,18} However, we could not identify the exact nature of herbs used in our patient.

The association of DVT and acute disseminated staphylococcal disease (DSD) during childhood had

recently been reported.²⁷ Three children developed a triad of DVT, septic PE, and acute osteomyelitis with staphylococcus aureus cultured from blood and bone. One child succumbed, while 2 survived following prolonged, morbid hospitalizations. The rapid clinical deterioration observed in these patients might be caused by the aggressiveness of staphylococcal infection combined with an ongoing showering of septic emboli from the ileo-femoral DVT. It was suggested that infected DVT with septic PE had a pivotal role in the development of DSD in these children. The presence of this triad should prompt aggressive treatment with the appropriate antibiotics, anticoagulation, surgical drainage, and assisted ventilation when indicated. However, it is unclear which comes first. Is the staphylococcal infection predisposing DVT and PE or vice versa?

Standard Heparinization^{5,13,19-21}

Heparin is the most widely used anticoagulant in paediatric patients. The current recommendation for the treatment of venous thromboembolism is an initial bolus of 75 to 100 units/kg of standard heparin over 10 minutes followed by maintenance of 20 units/kg/hour for children over 1 year of age or 28 units/kg/hour for younger infants.^{5,19} Initial heparinization of our patient was suboptimal with proximal extension of the thrombus and occurrence of P/E despite high maintenance dose of 30-40 unit/kg/hour. The acute-phase reactants including ESR and C-RP were grossly elevated in our patient which could contribute to heparin resistance by competing with heparin to binding of antithrombin III.^{13,21} Thus, monitoring the APTT level alone may be inadequate. In fact, APTT values accurately reflect standard heparin concentrations in children in only 70% of measurements. It is recommended that the APTT should be calibrated to reflect a heparin concentration of 0.30 to 0.70 U/ml by anti-Factor Xa assay or 0.2 to 0.4 U/ml by protamine sulphate assay.^{13,19,21} Standard heparin should be administered for a minimum of 5 days, with many children requiring 7-14 days particularly for those with extensive DVT or PE. We continued heparin therapy for 3 weeks in our case as oral feeding was frequently interrupted by his unstable condition.

Oral Anticoagulant^{13,19-22}

Children on warfarin therapy for venous thromboembolism should be monitored with a target INR range between 2 and 3.^{13,19,21} In our patient, we employed low dose therapy of warfarin with an INR 1.5-2.5 based on

extrapolation from local experiences in Hong Kong Chinese children with congenital heart disease.²² There is no consensus with regard to the duration of warfarin therapy. Some studies showed patients with identifiable reversible factors responded well to a 6-week to 3-month course of therapy whereas patients without risk factors had high incidence of recurrence. Thus, it is recommended that a short course of anticoagulant therapy can be considered in the former group and to continue treatment for up to 6 months in the latter group of patients.^{13,21} We decided to treat this patient with warfarin for 6 months as he had a life-threatening thrombotic event in the absence of strong predisposing factors.

Thrombolytic Therapy^{13,19-22}

The thrombolytic agents used in paediatric patients are streptokinase, urokinase and tissue plasminogen activator (tPA). The actions of these agents are mediated by converting endogenous plasminogen to plasmin. Children may not respond well to these thrombolytic agents because of physiological or pathological decreased plasma concentrations of plasminogen.²⁰ One of the major complication of thrombolytic therapy is bleeding and the risk benefit ratio in children is not known. Therefore, thrombolytic agents are only considered in children for the treatment of significant PE, for PE not responding to heparin and for acute large DVTs.^{13,19,21} We chose tPA in our patient as he had history of asthma and there was an increased risk of anaphylaxis with streptokinase.^{21,23}

Cava Interruption^{13,21}

The common indications for caval interruption in adult patients are anticoagulant induced bleeding, anticipated haemorrhagic complications in patient with predisposed lesions and failure of anticoagulation provided that the anticoagulant effect has been within the prescribed therapeutic range.¹³ However, its role in the management of DVT/PE in the paediatric population is less well defined.²¹ Also, the septic thrombus may block up the filter quickly and repeated revision of filter is likely required. It may be even detrimental if a septic complex sets up in the veno-caval system.

Diagnosis of PE with Spiral CT Thorax^{13,24-26}

The diagnosis of acute PE is difficult to establish clinically. Pulmonary angiography is regarded as the gold standard for imaging PE but carries certain risks (mortality 0.5% and morbidity 1-2%).²⁴ VQS is the most frequently

used imaging technique for PE. Combined with clinical assessment, it helps to establish or exclude the diagnosis of PE in less than 50% of patients.¹³ Recently, spiral computed tomographic pulmonary angiography (SCTA) has emerged as a means of imaging for PE. It is a non-invasive technique which can demonstrate the pulmonary embolus directly. The sensitivity of detecting PE in central pulmonary arteries by SCTA is over 80% compared to 45% with VQS²⁴ although there may be some difficulties detecting emboli to subsegmental vessels alone. It is suggested that SCTA should replace VQS as the initial investigation for PE where logistically feasible.^{24,25} In addition, ancillary signs of wedge shaped pleural based consolidation, linear bands and dilated central or peripheral pulmonary arteries were shown to be significantly associated with PE, thereby increasing the accuracy in making the diagnosis.²⁶ The imaging of the lungs, mediastinum and pleura may also reveal non embolic lesions presenting with symptoms identical to PE which are likely to produce non-diagnostic VQS. Our case lends support the technique is safe, efficient and accurate in making the diagnosis of PE even in patients of younger age. The short duration of the procedure may offer further advantage to small children where sedation is normally required.

Prophylaxis^{2,7,13,21}

Prophylaxis of DVT/PE is generally not required in paediatrics patients because of its low incidence. It may be considered in children identified to be at high risk for example those with previous or congenital thromboembolic diseases in high risk situations such as immobility, significant surgery or trauma.^{2,7,21} The options include low dose heparin, intermittent pneumatic compression of the legs, oral anticoagulants, graduated compression stockings and low molecular weight heparin. These approaches are of proven value in adult patients.¹³ The common practice of infusion small amounts of heparin solution into indwelling arterial lines, or heparin added to alimentation solutions in many paediatric and neonatal intensive care units may perhaps offer prophylactic effect to patients who are at high risk of developing DVT/PE.²¹

Conclusion

Paediatricians managing Chinese children should not overlook the possibility of DVT/PE because it is a disease

entity that does occur at times especially in those who are approaching young adulthood. Herb consumption is common practice in our culture and population, which may disturb the delicate equilibrium of the coagulation system. The most important prerequisite for the diagnosis of DVT/PE is a clinical suspicion. The difficulty of correctly diagnosing making the correct diagnosis of PE in the Asian population is compounded by a deep-rooted belief in clinicians that Asians are rarely affected by DVT and hence PE. A prompt diagnosis and appropriate management are important in order increase the chances of a favourable outcome. Using the non-invasive technique Spiral CT for the diagnosis of PE is promising. A low dose warfarin regimen to maintain a target INR of 1.5-2.5 probably provide adequate protection in Chinese children against thromboembolism whilst allowing safe outpatient monitoring of the anticoagulation status.

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References

- Rosendaal FR. Thrombosis in the young: epidemiology and risk factors. A focus on venous thrombosis. *Thromb Haemost* 1997; 78:1-6.
- Rohrer MJ, Cutler BS, MacDougall E, et al. A prospective study of the incidence of deep venous thrombosis in hospitalised children. *J Vasc Surg* 1996;24:46-9, discussion 50.
- Nuss R, Hays T, Manco-Johnson M. Childhood thrombosis. *Pediatrics* 1995;96(2pt1):291-4.
- Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian registry of VTE. *Blood* 1994; 83:1251-7.
- David M, Andrew M. Venous thromboembolic complications in children. *J Pediatr* 1993;123:337-46.
- Nguyen LT, Laberge JM, Guttman FM, Albert D. Spontaneous deep vein thrombosis in childhood and adolescence. *J Pediatr Surg* 1986;21:640-3.
- Buck JR, Connors RH, Coon WW, Weintraub WH, Wesley JR, Coran AG. Pulmonary embolism in children. *J Pediatr Surg* 1981; 16:385-91.
- Chan CW, Hoaglund FT. Pulmonary thromboembolism and venous thrombosis in the Chinese. *Clin Orthop* 1980;150:253-60.
- Chau KY, Yuen ST, Ng HK, Ng WF. An autopsy study of pulmonary thromboembolism in Hong Kong Chinese. *Pathology* 1991;23:181-4.
- Lao TT, Yuen PM, Yin JA. Protein S and Protein C levels in Chinese women during pregnancy, delivery and the puerperium. *Br J Obstet Gynaecol* 1989;96:167-70.
- Chan LC, Bourke C, Lam CK, et al. Lack of activated protein C resistance in healthy Hong Kong Chinese blood donors: correlation with absence of Arg506-Gln mutation of Factor V Gene. *Thromb Haemost* 1996;75:522-3
- Dahlback B. Inherited resistance to activated protein C, a major cause of venous thrombosis, is due to a mutation in the Factor V Gene. *Haemostasis* 1994;24:139-51.
- Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism. A statement for healthcare professionals. Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. *Circulation* 1996;93:2212-45.
- Zionts LE, McCampbell EJ, Szentfulopi T, Goodman RM, Harvey JP Jr. Deep-vein thrombosis in children following trauma. A report of two cases. *J Bone Joint Surg Am* 1983;65-A:839-40.
- Horwitz J, Shenker IR. Spontaneous deep vein thrombosis in adolescence: clinical observations with 10 patients. *Clin Pediatr (Phila)* 1977;16:787-90.
- Chau KY, Yuen ST, Wong MP. Clinicopathological pattern of pulmonary thromboembolism in Chinese autopsy patients: comparison with Caucasian series. *Pathology* 1997;29:263-6.
- Gorey JD, Wahlqvist ML, Boyce NW. Adverse reaction to a Chinese herbal remedy. *Med J Aust* 1992;157:484-6.
- Ni L, Zhu Y. Clinical application of the tonification method in orthopedics and traumatology. *J Tradit Chin Med* 1998;18:115-7.
- David M, Manco-Johnson M, Andrew M. Diagnosis and treatment of venous thromboembolism in children and adolescents. On behalf of the Subcommittee on Perinatal Haemostasis of the Scientific and Standardization Committee of the ISTH. *Thromb Haemost* 1995;74:791-2.
- Streif W, Mitchell LG, Andrew M. Antithrombotic therapy in children. *Curr Opin Pediatr* 1999;11:56-64.
- Streif W, Andrew M. Venous thromboembolic events in pediatric patients. *Diagnosis and Management. Hematol Oncol Clin North Am* 1998;12:1283-312.
- Cheung YF, Leung MP. Low dose oral anticoagulation therapy in Chinese children with congenital heart disease. *J Paediatr Child Health* 1998;34:563-7.
- Evans DA, Wilmott RW. Pulmonary embolism in children. *Pediatr Clin North Am* 1994;41:569-84.
- Cross JJ, Kemp PM, Walsh CG, Flower CD, Dixon AK. A randomized trial of spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism. *Clin Radiol* 1998;53:177-82.
- Garg K, Welsh CH, Feyerabend AJ, et al. Pulmonary embolism: diagnosis with spiral CT and ventilation-perfusion scanning: correlation with pulmonary angiographic results or clinical outcome. *Radiology* 1998;208:201-8.
- Coche EE, Muller NL, Kim KI, Wiggs BR, Mayo JR. Acute pulmonary embolism: ancillary findings at spiral CT. *Radiology* 1998;207:753-8.
- Gorenstein A, Gross E, Houris S, Gewirts G, Katz S. The pivotal role of deep vein thrombophlebitis in the development of acute disseminated staphylococcal disease in children. *Pediatrics* 2000; 106:E87.