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Mini Review

Venous Thromboembolism in 2022

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Venous thromboembolism encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Other venous thrombotic occlusion like superficial vein thrombosis, thrombophlebitis, cortical vein thrombosis, hepatic nonocclusive disease, portal vein thrombosis, mesenteric venous thrombosis, splenic vein thrombosis, upper extremity venous thrombosis, are not included in the same category by international societies including American college of chest physician, American college of physician, European society of cardiology, European respiratory society, European society of Haematology, due to the significant mortality and morbidity caused by pulmonary embolism and lower extremity deep vein thrombosis [2-6]. All international societies updated the guidelines and pathways for these two serious diseases, changes in the guidelines included clinical diagnosis, stratification the risk of thrombosis, recurrence, complications, risk of bleeding is seriously considered when initiating anticoagulation. Age adjusted D-dimer rather than cut off of 500 is a significant factor to predict the duration of treatment after the first event specially for patients older than 60 years [7,8]. Clot burden is another factor into consideration for duration of treatment [9].

Direct oral anticoagulants played a major part for medical society to spot patients who can receive treatment at home, with no admission to medical ward [10]. Another areas which had been updated in the new guidelines included choice of anticoagulation for cancer associated PE, indication of thrombolysis in high risk PE, alternative to failure of thrombolysis, treatment of incidental found symptomatic PE, when to treat subsegmental PE, indication and contraindication of inferior vena cava filter, detailed assessment of provoking PE, classifying the provoking factor into transient or permanent, minor or major, benign or malignant, duration of treatment for cancer associated PE [11]. Recently literatures devoted great attention to comorbidities of PE including thromboembolic pulmonary hypertension and chronic post PE syndrome, utility of cardiac biomarkers (pro-BNP, and troponin) in risk stratification of PE, assessment of right ventricular function by computerized tomography (CT) or echocardiogram for every patient with PE including low risk PE.

In this review we are going to discuss the new guidelines for diagnosing, stratifying and treatment of PE and lower extremity PE.

Pulmonary Embolism

It is not uncommon disease which can be fatal and cause significant comorbidity. Symptoms of PE can be very nonspecific, symptoms can vary from no symptoms at all to severe decompensation, hypotension, shock and death, patients with low cardiopulmonary reserve can be symptomatic even with subsegmental PE, or very minor transient non-malignant provoking factor [12]. Patient with no comorbidity can develop minor symptoms even with high clot burden PE [12]. Failure to diagnose PE in timely manner can result in death. Few studies found there is no correlation of clot burden and symptoms [13,14].

Pulmonary embolism is one of the diseases where diagnosis embedded in the history and not in the examination. More than 50% of patients with confirmed proximal lower extremity venous thrombosis developed pulmonary embolism [15,16]. Common nonspecific symptoms of PE are pleuritic chest pain, shortness of breath at rest, dry cough, calf pain, haemoptysis, dizziness, syncope, and palpitation. Syncope in PE indicates saddle thrombus, high burden clot, impending hypotension, obstructive shock, right ventricular involvement, and ventricular arrhythmias [17,18].

Right bundle branch block is an ominous sign of impending shock in one of our patients who was pregnant and developed PE before delivery [19]. We found that tachycardia and inverted T in V1, V2, V3 is very specific for pulmonary embolism with involvement of the right ventricle [20]. Sinus tachycardia in patients with no comorbidity and with even minor provoking factor has specificity in my cohort of patients with confirmed diagnosis of PE. A double blinded multicentre study to look at the specificity of sinus tachycardia in patients with unprovoked PE and no comorbidities would be very valuable, S1Q3T3 is not sensitive but more specific for diagnosis of PE [21].

In the updated guidelines from American College of chest physicians, American society of hematology and European society of cardiology, patients diagnosed with pulmonary Embolism are stratified as hemodynamic unstable or high risk or hemodynamic stable [22].

Hemodynamic unstable patients

Hemodynamic unstable are patients with systolic blood pressure <90 mmHg, decrease of blood pressure by 40mmHg more than 15 minutes or any form of hypotension which needs

of stabilization with inotropes, vasopressors, other forms of instability included organ hypoperfusion like oliguria, other causes of instability which included sepsis, arrythemias, myocardial infarction, aortic dissection. Internal bleeding should be ruled out. The term massive PE is not used any more. Diagnosis of saddle PE does not predict instability of all patients as it could be clot in transient [23]. Unstable patients might not be able to have a CTPA, initial resuscitation should take the precedence in the form of oxygen to keep oxygen saturation above 92%, fluids, inotropes, endotracheal intubation and mechanical ventilation. A bedside transthoracic echocardiogram is acceptable alternative to CTPA as it could rule out aortic dissection, myocardial infarction, and confirm the diagnosis of pulmonary embolism. In addition to signs of right ventricle compromise like abnormal free wall motion of the right ventricle in the form of dyskinesia or hypokinesia with including the infundibular right ventricle normal with normal contraction of the right ventricular apex (McConnel sign), bulging of the interventricular septum to the right ventricle, tricuspid incompetence, right ventricular dilation, right ventricle/left ventricle end diastolic volume >1 , tricuspid annular plan annular systolic excursion<15mm, right ventricle/right atrium gradient >30mm [3]. Other abnormal blood tests including D-Dimer, Troponin and Pro-BNP support the diagnosis of pulmonary embolism. Unstable patients with high probability PE should not denied lifesaving systemic thrombolysis pending confirmation of the diagnosis if the bleeding risk is acceptable. Unstable patient with high probability of PE with unacceptable bleed risk should receive catheter directed thrombolysis with or without mechanical clot removal, methods of mechanical clot removal included ultrasound-assisted catheter directed thrombolysis, percutaneous mechanical disruption and removal of the clot [22]. Rhyolitic thrombectomy using high pressure jet saline at the tip of the catheter which creates lower pressure zone behind the jet, the high pressure jets disturb the clot and allows its aspiration in the lower pressure zone. Other method included aspiration thrombectomy through a flexible catheter tip, mechanical thrombectomy can be done by a catheter with large-bore device. Other option is surgical thrombectomy as a last resort if other if other options could not be done. Retrieval inferior vena caval filter should be deployed during clot removal in order to prevent systemic embolization. When resuscitation unstable patients with pulmonary embolism, anaesthetist with subspeciality in cardiology should be involved as unstable patients with right ventricular failure needs special care like careful fluid resuscitation as right ventricle could overstretch with excess fluid causing decrease in pre-load. Hypoxaemia can be treated better with extracorporeal membrane oxygenation, tracheal intubation. Positive pressure ventilation can precipitate hypotension and positive plateau pressure therefore should not be applied. Borderline and dobutamine are the stander of care as borderline does not cause tachycardia and dobutamine improves cardiac contractility without tachycardia if high dose is applied and this wallows to stop noradrenaline. Successful thrombolysis should be followed with systemic anticoagulation if the bleeding risk is under control.

Invasive treatment for PE should depend on the expertise and the volume of the procedures in the centre. Recently pulmonary embolism response team (PERT) started to develop the experience on how to make a balanced decision for treatment with systemic thrombolysis. Few unstable patients who have mild hypotension and conscious with low oxygen requirements can improve with anticoagulation only and avoid thrombolysis. Pulmonary Embolism response team (PERT) is a recent model of care and not available in all large centres [24]. Unacceptable high risk of bleed like recent surgery, brain metastasis, homorganic stroke, active bleed are absolute contraindications to thrombolysis and to even anticoagulation, Ceiling of management for patient with those conditions is supportive care and infer vena cava filter.

Haemodynamic stable patients

The recommendation in this article on the recent approach and management for pulmonary embolism stable patients were based on the revised guidelines by the American college of Chest Physicians, American Society of Hematology and European Society of cardiology. The recent changes in guidelines concentrate on stratification of stable patients with confirmed diagnosis of pulmonary embolism into intermediate risk and low risk, more update on the term of provoked pulmonary embolism and the impact on medical therapy, choice of anticoagulation, duration of treatment and

Home treatment for low-risk PE

Age adjusted D-dimer: D-dimer is a factor for decision making when to stop anticoagulation, the utilisation of serum biomarker (PNB, Pro-PNB, troponin) in making decision for PE treatment, indication when to treat subsegmental PE, follow up pulmonary embolism patients in outpatient clinic, essential inpatient investigation, indication of inferior vena caval filter. In updated guidelines the cut of 500 for patient younger than 50 stay the same. As D-dimer increases with age, patients older than 50, D-dimer will be calculated as the age multiplied by 10 [8]. Diagnosis of pulmonary hypertension is not always easy as symptoms are vague and nonspecific. Diagnosis of pulmonary embolism is of paramount important and should be made in a timely fashion. Failure to diagnose PE in a timely manner could result in death in the first seven days specially if the patient had comorbidities and decreased cardiopulmonary reserve [25]. Clinical probability and D-dimer is important for assessment, diagnosis and stratification the severity of PE. The most common scores are Wells score, and Simplified Pulmonary Embolism Severity Index. Wells score higher then 4 signifies high probability of PE, while less then 2 deems probability [26].

Pulmonary Embolism Rule-out Criteria (PERC) [27]:

patient <50 years

Oxygen saturation >95

Heart rate<100

No history of DVT or PE

No leg swelling

No recent surgery or recent hospitalisation

No Haemoptysis

No pleuritic chest pain

No history of oestrogen use

Patient with low probability PE - Wells score < 2: Patient with low Wells score and a negative PERC negative should have a D-dimer testing. If D-dimer is negative, patient can be discharged home and no need to proceed with imaging. Patients with positive D-dimer should proceed for imaging (e.g. CTPA). If CTPA proved positive and no signs of right ventricle compromise or positive cardiac markers, patient is identified as low risk PE. Patient should also have a secured access to medications, care and home circumstances in order to be discharged home safely with Non-Vitamin K antagonist oral anticoagulants (NOAC) for three months, presuming patient had no kidney or liver failure [3]. Patient should be assessed in outpatient clinic after three months.

Patient with high probability PE - Wells score > 4: These patients should go for CTPA or V/Q scan if there is contraindication to contrast or estimated GFR<30. Alternatively, compression U/S can be considered if V/Q unavailable. If investigation is going to take more than 4 hours, practitioner should start treatment empirically with low molecular heparin. Patients with hypoxaemia, dyspnoea, systolic blood pressure around 100, have comorbidities or decreased cardiopulmonary reserve should start to receive treatment immediately and empirically on anticoagulation if the bleeding risk is acceptable (<3). Other important investigations, e.g. Pro-PNB, PNB, troponin, transthoracic echocardiogram are part of the standard of care in 2022. Patient with positive cardiac biomarkers or has right ventricular compromise been classified as intermediate risk.

Patient with intermediate risk

These patients should be monitored in the hospital and not discharged home as patient can decompensate any time in the form of hypotension, hypoxia, sever tachycardia, impaired organ perfusion in the form of oliguria, anuria, mental confusion, raising of transaminases due to shocked liver. Patients should be started on anticoagulation. Clinicians should have low threshold to start patients on systemic thrombolytics if they decompensate, taking the bleeding risk into account. Inferior vena caval filter should be deployed if patients have contraindication to anticoagulants or thrombolytics if indicated. Patients with low cardiopulmonary reserve might be eligible for inferior ven cava during anticoagulation.

Duration of treatment

All societies included American College of Physician, American Academy of Hematology and European Society of Cardiology recommend indefinite treatment for unprovoked pulmonary embolism presuming that the risk of PE outweigh that of the bleeding. Reduced dose of apixaban or rivaroxaban after the first six months is recommended by American College of Physicians and American Society of Hematology but not by European Society of cardiology.

Provoked pulmonary embolism

Provoking factor can be minor or major, benign or malignant, transient (reversable) or permanent [3]. Patients with major transient factors like surgery with general anaesthesia more than 30 minutes, immobilisation in the hospital over three days, major trauma, or fracture should receive anticoagulation for three months, only except if the patients have high clot burden, dysfunction of the right ventricle or positive cardiac biomarkers, in those condition anticoagulation can be extend to six months [9]. Patients with persistent risk factors like antiphospholipid (positive lupus anticoagulant, positive anticardiolipin and positive anti-beta2-glycoprotein) who had PE or DVT should stay on vitamin K antagonist indefinite. Patients with active cancer should receive 3-6 months of direct oral antagonist followed by low intensity apixaban or rivaroxaban taking into consideration the bleeding risk [22]. Patient with gastric cancer should not take direct oral anticoagulants and take low molecular weight heparin instead [28]. PE provoked by minor reversable factor, for instance, short flight, minor surgery, less than 30 minutes anaesthesia, can consider indefinite treatment with anticoagulation being changed to low intensity after six months. Patients on long-term anticoagulation should be assessed regularly for risk of bleeding. Patients with recurrence of PE or DVT with no provoking major factors should stay on indefinite treatment.

Inherited thrombophilia

Five percent of the population tested positive for inherited thrombophilia and does not increase the risk of thrombosis in heterozygous patients, therefore testing thrombophilia for asymptomatic patients are not required [29]. The most common types of inherited thrombophilia are Factor V Leiden and Factor II Prothrombin Bene Mutation, both can increase the risk of DVT more than PE in homozygous patient with family history of venous clot. The contribution to a second clot by inherited thrombophilia is not supported in the literatures. It is not clear if protein C and S deficiency can cause any clotting with a significant provoking factor.

Sub segmental PE

Single subsegmental PE with no lobar or segmental involvement in the absence of cancer does not need treatment, surveillance is acceptable. Patients with cancer can be treated for three months if there is no high risk of bleed, while those with low cardiopulmonary reserve can be treated for three months in the absence of high bleeding risk.

Deep vein thrombosis (DVT)

Proximal DVT: It referred to thrombus in popliteal, iliac or femoral veins. More than 50% of patients with proximal DVT may have PE [16]. Compression U/S confirm the diagnosis of DVT. All patients with proximal DVT whether being symptomatic or not, should receive anticoagulation for three months assuming that bleeding risk is low. Extending treatment beyond three moths depend on the risk of recurrence, risk of bleed and whether the thrombus is provoked or not.

Patients who are considered having high bleeding risk or other contraindications to anticoagulation should have inferior vena cava filter and regular surveillance. Patients with high clot burden in the iliofemoral veins and at risk of phlegm Asia cerulean doles, and at risk of venous gangrene and compartment syndrome should be assessed for urgent catheter directed thrombolysis and/or thrombectomy and fasciectomy. Patient

diagnosed with DVT due to heparin induced thrombocytopenia should not be treated with any form of heparin and should start on non-heparin anticoagulation (e.g. danaparoid or fondaparinux) in combination with warfarin.

Distal deep vein thrombosis

Distal vein thrombosis is commonly located in the posterior tibial and peroneal veins with sparing of the popliteal vein. Diagnosis can be confirmed by whole leg compression U/S. Asymptomatic patients do not need any anticoagulation, unless the patients are considered at high risk for extension to proximal veins, which include high D-dimer, unprovoked DVT, thrombosis close to proximal veins or if they diagnosed with Covid 19. This group of high risk patients need surveillance with serial ultra sound to diagnose extension of the thrombus to proximal veins.

Upper extremity Deep vein thrombosis

It is common in the young athletic population related to trauma and strong physical exercise. It also relates to peripherally inserted central catheter (PICC line) insertion for people on chemotherapy, haemodialysis arteiovenousgraft dysfunction. Axillary and subclavian veins are commonly affected. Upper extremity DVT due to central venous catheter is not an indication to remove catheter, and can be used to administer medication. Provoked DVT does not need long-term anticoagulation. CT angiogram or MRI angiogram is mandatory to exclude thoracic outlet syndrome. Vascular surgical service should be involved to treat thoracic outlet and compartment syndrome to prevent catastrophic complications like upper limb gangrene. Prolonged intravenous anticoagulation is advised for patients with persistent thoracic outlet syndrome, severe post thrombotic syndrome and indwelling venous catheter.

Vignette 1

23-year-old lady presented with recurrent left upper extremity symptoms consistent with DVT. She noticed that swelling involved the whole left leg with pigmentation. Leg pain increased with exercise and relieved by either rest or elevation of the left leg. No family history of venous or arterial thrombosis were aware. She is not on oestrogen medication, as she denied any provoking factors like recent surgery, immobilisation flying. Compression ultrasound showed the left ilio-caval veins were poorly compressible with small size thrombus. Patient improved every time with 6 weeks anticoagulation. A vascular physician arranged a vasculitis screen, antiphospholipid study and inherited thrombophilia screen which all came negative. Transthoracic and transesophageal echocardiogram with agitated saline did not show patent foramen ovale (PFO). How would you like to proceed with investigation and management?

Vignette 2

40-year-old patient brought to ED with pleuritic chest pain and shortness of breath after a long flight from London to Sydney. The past medical history was unremarkable, especially no family history of clots and he is not on any regular medication. On examination his heart rate was 110 bpm, regular, blood pressure was 110/85, and oxygen saturation was 93% on three litres of oxygen. Urgent CTPA showed bilateral lobar and segmental pulmonary embolism with high clot burden. Pro-PNB and troponin were just above normal. Bedside echocardiogram showed dilated right ventricle, dilation of the inferior vena cava with failure to collapse, protrusion of the interventricular septum to the left, tricuspid regurgitation velocity more than 3m/second, right ventricular acceleration time < 80 mins, right ventricular wall motion abnormality with preservation of the right ventricular apex, right ventricular end diastolic volume/left ventricular end diastolic volume was >1, moderate degree of tricuspid regulation. Patient was diagnosed with an intermediate risk of pulmonary embolism, admitted to intensive care unit for monitoring and started on unfractionated heparin. Patient improved with the treatment and the tachycardia and hypoxia were settled. The unfractionated heparin changed to low molecular weight heparin. He was moved to normal medical ward and assessed for discharge on Apxipan 5mg twice daily for three months, arranged assessment in thrombosis clinic in three months with repeat echocardiogram and D-dimer. Before discharge, patient developed slurry speech and right sided hemiparesis, urgent non-contrast CT brain was normal. How are you going to approach the new developments in patient clinical picture?

Vaginette1

The first patient had recurrent DVT with no provocation, and no family history of thrombosis.

Despite that the patient had above knee DVT, whole leg was swollen, compression ultrasound poorly compressible left iliac vein, size of thrombus was small, patient demonstrated signs of venous insufficiency in the form of pigmentation and venous claudication in the form that pain settled with rest and elevation of the left leg. Despite that all the above mentioned medical facts does not rule out unprovoked DVT, more investigations were required to rule out alternative diagnosis given that vasculitis, antiphospholipid syndrome and inherited thrombophilia had been ruled out. Other non-invasive investigation like MRI/MRV is required to rule out rare alternative diagnosis like abnormal anatomic lesion, lymphedema, malignancy causing compression on the left iliac vein and thrombosis.

May-Thurner Syndrome

MRI revealed left iliac vein compression by the right common iliac artery, intravascular ultrasound confirmed the diagnosis of May-Thurner Syndrome. Patient was treated by catheter directed thrombolysis followed by angioplasty and stenting with resolution of all symptoms.

Patient in vignette 2

Patient presented with provoked intermediate risk of pulmonary embolism with positive myocardial biomarkers and had echocardiographic findings of right ventricular compromise and early signs of thromboembolic pulmonary hypertension. This patient was treated with unfractionated heparin with resolution of all symptoms and stabilisation of all vital signs including heart rate, oxygenation. Patient was close to discharge before he developed right sided stroke, non-contrasted CT brain ruled out haemorrhagic stroke, prolonged telemetry ruled out atrial fibrillation. Diffusion-weighted magnetic resonance imaging

diagnosed respective defect in the distribution of M3 segment of left middle cerebral artery, rest of circle of Willis was intact. Repeat transthoracic echocardiogram showed improvement of right ventricular size and function with early signs of pulmonary hypertension. Transoesophageal echocardiogram with contrast confirmed haemodynamic patent foremen oval with increased pressure in the right side of the heart leading to paradoxical thrombus causing a stroke. Patient was treated with anticoagulants. After recovery, patent foramen oval was closed, patient continued on anticoagulant and was refereed to pulmonary hypertension clinic for ongoing care.

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