Chapter

Management of Pulmonary Thromboembolism

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Abstract

Pulmonary thrombo-embolism (PTE) is a major cause of cardiovascular morbidity and mortality. Incidence of PTE and its associated mortality is affected by the Prescence of associated risk factors, comorbid conditions and advancement in the treatment options. Clinical probability, D-Dimer, echocardiography and CT pulmonary angiography are used in the diagnosis. Management starts with stratification, with high-risk category being benefited from the thrombolytic therapy. Catheter directed therapy may be used in ineligible or failed cases with surgical embolectomy being used as final salvage therapy. Patients with persistent hemodynamic stability can be started on anticoagulation alone. Supportive therapy with fluid expansion and inhalational Nitric oxide may provide benefit in few. Patients with PTE should receive secondary preventive anticoagulation to prevent recurrences. High risk patients with sub-segmental PTE may benefit from anticoagulation. For early detection of long-term complications of PTE a patient cantered follow-up is needed. Chronic thrombo-embolic pulmonary hypertension (CTEPH) is a dreaded complication with pulmonary end-arterectomy being a gold standard management option in eligible patients with non-surgical therapy (balloon pulmonary angioplasty and pulmonary vasodilators) also being used in many cases.

Keywords: Pulmonary thrombo-embolism, Thrombolysis, Anti-coagulation, CTEPH, Sub-segmental PTE, Covid-19

1. Introduction

Pulmonary thrombo-embolism (PTE) is a most dangerous form of venous thrombo-embolism (VTE), and undiagnosed or untreated can be fatal. Furthermore individuals who survive PTE can develop post-PTE syndrome that is characterized by chronic thrombotic remains in pulmonary arteries, causing persistent right ventricular dysfunction, decreased quality of life and/or chronic functional limitations.

Clinical probability, assessed by validated prediction rule and age adjusted D-dimer testing is the basis for all diagnostic strategies. Computer tomographic pulmonary angiography (CTPA) is the definitive diagnostic investigation.

Acute PTE presents with varying degrees of clinical stability & thus a careful clinical assessment is needed. Patients should be evaluated in the context of various available treatment options including medical, catheter-based, and surgical interventions. Several improvements are made in therapeutic management of acute PTE in recent years.

A crisp review of the best available literature on which, multiple societal guidelines on PTE management where based, is made. Also, an evidence-based suggestions on the debatable and poorly studied PTE management topics like follow-up, sub-segmental PTE, catheter directed thrombolysis, CTEPH and covid-associated PTE were made. Areas where further need for clinical research were also highlighted.

2. Management of acute pulmonary thromboembolism

2.1 Supportive therapy

The initial approach to patients with PTE should focus on the supportive measures. It includes oxygen therapy, mechanical ventilatory support, volume expansion therapy and antibiotics (e.g., in lung infarction).

2.1.1 Volume expansion therapy

a. Expanding intra-vascular volume in patients with acute PTE is both a challenging and complicated issue.

b. In patients with moderate to severe right ventricular (RV) dysfunction; the aggressive fluid administration may lead to further increased end diastolic pressure (RVEDP) and thus leading to decreased RV coronary perfusion pressure, ultimately resulting in RV ischemia and further deterioration in RV function.

c. On the other hand, volume expansion in patients with collapsible IVC/ patients with intravascular depletion can improve cardiac output (CO). However, Identification of these 'volume responsive patients' in many times is challenging and cannot be determined with certainty.

So, in patients with no (or probably mild) RV dysfunction & when central venous pressure (CVP) is not high (< 12-15 mm Hg), then fluid therapy may be considered in hypotensive patients. However, in any case, monitoring of the RV function on a regular basis during volume expansion is recommended [1, 2].

2.1.2 Oxygen and ventilatory support

a. Patients with oxygen saturation of less than 95% in pulse oximetry must be treated with supplemental oxygen (had shown to lower RV afterload in PE). Hypoxemia can usually be controlled by oxygen inhalation.

b. In patients requiring mechanical ventilation, it is advisable to use small tidal volumes (TV) with low inspiratory pressures and low positive end expiratory pressure (PEEP) because of its adverse effect on RV function [3, 4].

2.1.3 Circulatory support

a. The ideal pharmacological agent should enhance RV function through positive inotropic effects and increase mean arterial pressure (MAP) through peripheral vasoconstriction without significantly increasing pulmonary vascular resistance (PVR).

b. The hypotensive patient with decreased cardiac output (CO) should be first started on vasopressors, and inotropes can be added later if cardiac output remains low. In contrast, inotropes can be started first in normotensive patients with evidence of decreased cardiac output, and vasopressors can be added if a hypotensive response to inotropes develops.

c. Norepinephrine can be considered a more preferable vasopressor agent for the following reasons. First, α-mediated vasoconstriction leads to increase in MAP which in turn increases right coronary perfusion pressure. Second, β1-mediated inotropic effect may improve RV function. Third, it has minimal effect on PVR.

d. Dobutamine in medium doses of up to 10 μg/kg/min can be considered as inotrope of choice. However, it should be kept in mind that, dobutamine administrated at improper high doses, increases perfusion of nonventilated regions of the lungs and may worsen respiratory insufficiency secondary to increased ventilation-perfusion (V/P) mismatch [5–7].

e. Pulmonary vasodilators like epoprostenol and inhaled nitric oxide (iNO) are shown to decrease PVR and increase CO. iNO (10–20 ppm) may be considered as a temporizing agent in patients with life-threatening PE, until therapeutic, mechanical, or spontaneous thrombolysis can be achieved and hemodynamics have improved.

Though epoprostenol causes pulmonary vasodilatation, a major concern about its use is the possible risk of worsening V/P mismatch or increasing PCWP in patients with concurrent LV dysfunction. On contrary, iNO appears to improve the V/P mismatch by increasing perfusion only to areas that are well-ventilated.

f. Based on minimal clinical data it may be suggested that if CO remains low despite vasopressors and inotropes, a pulmonary vasodilator trial with iNO may be beneficial when pulmonary hypertension is present [5–8].

Whenever possible, vasopressors and inotropic agents be used with caution, only if absolutely necessary, at the lowest possible doses.

g. Mechanical circulatory support (VA-ECMO) is sometimes may be used to provide temporary cardiopulmonary support to patients with acute cardio-pulmonary failure. In the latest ESC recommendations, ECMO was classified as "may be considered".

The Impella RP®™ (axial flow pump) and TandemHeart Protek®™ (Centrifugal pump) are RV assist devices to augment the antegrade flow; There are limited single centre reports describing the use of these devices in high-risk PTE cases [9].

To summarize the issue of supportive therapy, it can be concluded that, while used empirically based on clinical and theoretical data, there are no robust guidance emerging from the evidence-based medicine and hence needs further studies.

2.2 Medical therapy

The medical management [10–22] of acute PTE consists of anticoagulation and systemic thrombolysis.

2.2.1 Anticoagulation

a. When acute PTE is considered likely, anticoagulation should be begun while pursuing the diagnostic workup. In a hemodynamically unstable patient, it is reasonable to start anticoagulation immediately and preferably with short-acting, intravenously administered unfractionated heparin (UFH).

The rapid reversibility of IV UFH is important for these patients who may require thrombolysis or surgical embolectomy. Short-acting, intravenously administered UFH should be initiated with a bolus of 80 U/kg followed by a continuous infusion of 18 U/kg per hour.

For stable patients with PTE, low-molecular-weight heparin (LMWH) or fondaparinux are preferred to UFH due to lesser incidence of inducing major bleeding, thrombocytopenia and are associated with equal or probably superior efficacy. These agents should be continued for at least 5 days and until the INR is >2.0 for at least 24 h followed by long-term coagulation with vitamin K antagonist, VKA (the dose of warfarin should be adjusted to maintain an INR of: 2.0-3.0) or DOACs, Dabigatran and edoxaban (preferred over VKA) administered after an initial treatment of 5-10 days with LMWH.

b. As per new guidelines, haemodynamically stable patients not necessitating any thrombolytic, surgical or interventional treatment, anticoagulation can now also be started via the oral route, using one of the DOACs, apixaban or rivaroxaban (Higher doses should be used for 1 week and 3 weeks respectively).

c. Long-term anticoagulation therapy for acute PTE can be considered as 2 phasic treatments. Primary phase is for the treatment of index episode and following completion of primary treatment for the initial VTE, providers must decide whether to discontinue anticoagulant therapy or continue with long-term anticoagulation (secondary phase) with an intent to prevent VTE recurrence (secondary prevention).

d. Clinical data suggests that, all patients with PTE should receive three or more months of anticoagulant and extended oral anticoagulant reduces the risk of recurrent VTE, but the risk of bleeding partially offsets this benefit. In addition, Unprovoked PTE have a higher risk of recurrence compared to patients who had a provoked PTE (Patients with persistent risk factors are at higher risk of recurrence than those with transient risk factors).

e. Available evidence can be summarized as follows:

1. Optimal duration of anticoagulation remains uncertain and has to be considered on a case-to-case basis. In patients with provoked (identifiable risk factor) PTE, a minimum of 3 months is usually recommended, but a 6-month therapy may be considered if the patient with minor transient risk factor has low bleeding risk. Clinical data suggests against thrombophilia testing to decide the duration of anticoagulation.

2. Indefinite anticoagulation is probably appropriate for majority of the patients with unprovoked PTE (except in patients with high bleeding risk where 6 months therapy is recommended).

In certain circumstances, such as when balance between risks and benefits is uncertain, use of prognostic scores (HERDOO2, Vienna, DASH), D-dimer testing (6 month after the start of initial anticoagulation), or ultrasound assessment for residual thrombosis (after completing 6 months of anticoagulation) from an initial DVT episode may aid in reaching a final decision.

3. In cancer associated PTE, cancer is a major persistent risk factor and the need for extended anticoagulation therapy beyond 6 months is suggested for patients with an active cancer (metastatic disease) or receiving chemotherapy, provided their bleeding risk remains acceptable (low or moderate bleeding risk).

f. There is no interaction between the specific agent used and the risk of mortality, PTE. Factors such as once vs. twice-daily dosing, out-of-pocket cost, renal function, concomitant medications and the presence of cancer, may impact DOAC choice. It should be noted though there are no head-to-head trials, low quality evidence from indirect comparisons indicated that apixaban is safest DOAC.

For patients with breakthrough PTE during therapeutic VKA treatment, LMWH is preferred over DOAC therapy. For patients with concomitant stable CVD who initiate anticoagulation and were previously taking aspirin for cardiovascular risk modification, suspending aspirin over continuing it for the duration of anticoagulation therapy is recommended (not apply to patients with a recent acute coronary event or intervention).

2.2.2 Thrombolytic therapy

a. Sautter and colleagues were the among the first, who described the first successful cohort of PE patients treated with thrombolysis in 1967, demonstrating excellent clinical response with noted radiographic and hemodynamic response to therapy.

b. Thrombolytic drugs are agents that actively dissolve the thrombus & are associated with early normalization of both hemodynamic parameters and right ventricular function, but at the cost of increased risk of bleeding.

In has to be noted that even, intrinsic thrombolysis is also potent and several studies suggest that 1 week after anticoagulant therapy, the degree of vascular obstruction and right ventricular dysfunction are similar between thrombolysis-treated and anticoagulation-treated patients.

c. In clinical practice, the net benefit of thrombolysis for PTE likely exists on a continuum, highly dependent on the severity of the clinical presentation, patient's comorbidities and bleeding risk, as well as the availability of alternative therapies.

Different societal guidelines and consensus statements convey differing approaches to risk stratification, largely based on echocardiographic features and cardiac biomarkers (troponin and BNP). Systematic review data suggest that of the 17 different pulmonary embolism risk prediction scores Pulmonary Embolism Severity Index (PESI) and the simplified-PESI (sPESI) had the most robust evidence and validation for clinical risk assessment of patients with PTE.

d. Data from randomized trials and systematic literature reviews suggest that:

   1. Presence of hemodynamic instability (defined as systolic blood pressure < 90 mm Hg for 15 minutes or more) is the most important determinant of short-term mortality and represents a high-risk cohort. So, these patients should receive immediate systemic thrombolytic therapy (TT) though the evidence on the mortality benefit is of only low quality.

   2. In hemodynamically stable PTE patients presenting with both RV dysfunction and elevation of myocardial injury markers (troponins and BNP) are classified as intermediate-high–risk PE. Early thrombolysis in this group prevents hemodynamic decompensation which was offset by the higher bleeding events and the net effect on mortality is controversial.

   In light of this evidence, full-dose systemic TT is routinely recommended for intermediate-high risk PTE and should be only be reserved as rescue therapy for those presenting with clinical deterioration after initial anticoagulation.

   Because the bleeding risk associated with TT is dose dependent, lower doses of thrombolytic drugs may provide a more favorable safety profile with comparable efficacy. In fact, in a systematic review, low-dose tPA was associated with lower risk of major bleeding than full-dose tPA, with no difference in recurrent PTE.

   Thus, in low bleeding risk patients (ex. young, < 65 kg) with intermediate high-risk PTE, low-dose systemic thrombolysis (with tPA) at presentation may result in the net favorable outcomes & should be considered (PEITHO-III [NCT04430569] is an ongoing placebo-controlled RCT evaluating the mortality benefit of this approach).

   3. TT is effective if applied within the first 48 hours of symptom onset. Its efficacy decreases significantly after 7 days, but it may be beneficial up to 14 days from symptom onset.

   4. Data on the use of systemic TT in patients with PTE-related cardiopulmonary arrest, patients at high risk for decompensation due to concomitant cardio-pulmonary disease and free thrombus in the right ventricle or atrium are limited, and probably a case-based approach is recommended.

e. Three different thrombolytics have FDA approval for PTE: urokinase as a 4400-IU/kg intravenous (IV) bolus, followed by a 4400-IU/kg/h infusion over 12 to 24 hours; streptokinase via a 250,000-IU IV loading dose over 30 minutes, followed by 100,000 IU/h over 12 to 24 hours.

Alteplase is the most commonly administered thrombolytic agent. Although the FDA-approved dose of 100 mg of alteplase over 2 hours is most commonly used, European and Canadian guidance supports the option of alteplase 0.6 mg/kg administered over 15 minutes.

Though not approved many studies had shown the efficiency of reteplase (2 bolus doses of 10 U each, 30 min apart) and tenecteplase (single bolus dose of 0.5 mg/Kg) in treating pulmonary embolism.

Only few comparison trials of available thrombolytic agents have been conducted. Available data suggest a clinical superiority of tenecteplase over streptokinase, alteplase over urokinase and streptokinase. Further studies are needed to truly identify the choice of thrombolytic agent and regimen in PTE.

2.3 Catheter directed therapies

a. Catheter-directed therapy provides an alternative reperfusion approach that allows localized drug delivery and can be combined with mechanical thrombus removal that may result in better clinical outcomes.

   Catheter-based therapies include MT, mechanical thrombectomy (thrombus fragmentation, aspiration, rheolytic thrombectomy), Pharmacologic catheter directed thrombolysis (CDT, via thrombolytic infusion catheter or ultrasound-facilitated CDT), or a combination of both.

b. Different techniques of MT include [23, 24]

   1. Thrombus maceration (Using a pigtail catheter or guidewire). However, distal embolization may be an inadvertent risk.

   2. Rheolytic thrombectomy using AngioJet®™ device uses rapid-speed saline that facilitate thrombus fragmentation. The catheter can also be used to deliver low-dose thrombolytic agent into the thrombus to aid clot removal.

   3. Aspiration thrombectomy using FlowTriever®™ device is the first MT procedure approved by FDA. The Indigo Thrombectomy CAT 8 system®™ and AngioVac®™ catheter are other systems used for this purpose.

c. Endovascular thrombolysis is done by placement of a multi-hole catheter within the pulmonary artery (PA) and infusing a thrombolytic agent (most commonly used is tPA, at a rate of 0.5–1 mg/h per catheter when 2 catheters are used, or 0.5–2 mg/h when only 1 catheter is used) for 12-24 hours.

   1. To improve the efficacy and speed of clot clearance, fibrinolysis can be combined with low-intensity ultrasound waves (EkoSonic Endovascular System®™) in an approach called ultrasound-assisted thrombolysis [25]. However, there is no clear evidence demonstrating the benefit of ultrasound-enhanced thrombolysis over standard CDT. On the contrary, the procedure times are significantly longer than for standard CDT [26–28].

   2. The major advantage of CDT over systemic thrombolysis is lower bleeding risk [25]. In fact, in a meta-analysis of outcomes of CDT, the rates of major bleeding were significantly lower were compared to systemic thrombolysis in patients with high- and intermediate-risk patients. However, current evidence supporting the use of CDT in acute PTE is limited to a small RCTs or single-arm studies focusing on short-term surrogate outcomes rather than long-term clinical outcomes.

   3. Due to lack of strong RCT evidence regarding the short- and long-term clinical benefits, based on the critical review of meta-analytic and clinical studies it may be suggested that [26–32]:

In patients with high-risk PTE, CDT is recommended when systemic thrombolysis is contraindicated or has failed or as alternative in high bleeding risk patients (e.g., coagulopathy).

Though in Intermediate-risk PTE, CDT is associated with lower mortality with equivalent rates of major bleeding compared to systemic anti-coagulation alone, quality of evidence is not robust. CDT may thus be reserved for these patients who develop signs of hemodynamic instability despite adequate anticoagulation as an alternative to systemic thrombolysis in case-to-case basis.

Additional studies with larger sample sizes are required to elucidate the optimal use of CDT in sub-massive PTE.

2.4 Surgical pulmonary embolectomy

a. Surgical pulmonary embolectomy was associated poor outcome as it is performed only as a lifesaving therapy. Systematic review data suggest that in-hospital mortality rate in patients undergoing the procedure was around 25% with a better value of about 15% from recent studies.

b. It is useful to treat patients with massive PTE when other methods are contraindicated or fail and when the patient presents a relatively low surgical risk. It may be also used when there is a large proximal or intracardiac thrombi with a risk of paradoxical embolism via a patent foramen ovale, in expert surgical centres [33, 34].

2.5 Follow-up

a. Care for patients with acute PTE after discharge includes attention aimed at prevention of major bleeding, identification of underlying disease, and monitoring for long-term complications. Timing of follow-up is based on the patient's characteristics and the ideal time for the initial visit must be individualized, and generally ranges from 2 weeks to 3 months.

b. There are no guidelines for post-PTE imaging due to lack of clinical trials. But available small-scale data suggests that:

   1. Though the gold standard technique for assessing the pulmonary arterial hypertension (PAH) is right heart catheterization (RHC). TTE (transthoracic echocardiography) should always be performed at discharge to evaluate PAH. TTE at follow-up (at 3 months) should be considered only for those patients with RV–RA gradient >45 mmHg or in the presence of both dyspnoea and a RV–RA gradient ranging between 32 and 45 mmHg at discharge.

   2. Lung perfusion scan must be performed 3 months after the acute event in those patients with persisting symptoms and/or in the presence of right ventricular dysfunction or pulmonary artery hypertension.

   3. Computed tomography of pulmonary vasculature and pulmonary vascular MRI are not useful to define therapeutic strategies during the follow-up and are thus not recommended.

c. Thrombophilia testing in its current form does not significantly impact clinical management or improve outcomes for most VTE patients. Data strongly

suggest against testing in provoked PTE, where as in unprovoked PTE there is only limited data to suggest the benefit of testing and is usually not recommended except in those patients with a positive familiar history of VTE or recurrent thrombosis or suspecting APLA syndrome.

Though ESC guidelines recommend against the use of DOAC in APLA syndrome, recent systematic review suggests that rate of VTE recurrence and bleeding events were both low and comparable in patients with various thrombophilia receiving VKA or DOAC suggesting that DOAC are appropriate treatment option even in this population.

d. Extensive screening for occult cancer in every patient with unprovoked VTE is not recommended, however guidelines suggest a limited screening strategy though clinically significant benefit of this approach is unknown.

"Limited screening strategy" includes medical history, physical examination and laboratory analyses with blood cell count, renal and liver function parameters and calcium levels as well as a simple chest x-ray. In addition, according to national recommendations, specific screening based on sex and age (colon, breast, cervical and prostate) should be performed [35–41].

However, some patients with high-risk features (RIETE score of >3 may benefit from extensive cancer screening with CT imaging. Prospective validation of this approach is still being tested (SOME RIETE, NCT03937583 & MVTEP2-SOME2, NCT04304651 trails).

3. Prophylaxis

3.1 Medical prophylaxis

a. Many meta-analysis that includes both observational and intervention studies suggest a beneficial effect of statin use for prevention (primary and secondary) of VTE. In intervention studies, therapy with rosuvastatin significantly reduced VTE (including PTE) compared with other statins.

But scientific committees feel it is still too early to make any guideline recommendations based on the current evidence [42, 43].

b. Guidelines suggest that hospitalized patients who have an active malignancy should receive pharmacologic thromboprophylaxis (combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy) in the absence of contraindications. However, routine thromboprophylaxis generally not be offered to patients admitted for minor procedures or chemotherapy infusion [44].

c. Risk of VTE is high in patients undergoing major orthopedic surgeries like a knee or hip surgeries. At least 10-14 days, preferably 35 days from the day of surgery, pharmacological thromboprophylaxis is recommended in the absence of risk factors for bleeding.

For assessing VTE risk is patients undergoing non-orthopedic surgery, modified Caprini risk assessment score is used. Based on this assessment score, patients with moderate to high-risk should receive pharmacological prophylaxis (+/− mechanical methods).

d. Although data comparing pharmacologic prophylaxis to placebo is of low quality, major clinical practice guidelines still recommend pharmacologic VTE prophylaxis for almost all acute medical critically illness.

Commonly used pharmacological agents for prophylaxis are: UFH, LMWH & Fondaparinux (later two are usually preferred over UFH) [45].

Duration of DVT prophylaxis is typically until the patients can ambulate or discharge from the hospital. In patients undergoing abdominal or pelvic surgery for cancer and with a low risk of bleeding, pharmacological prophylaxis is extended to a total duration of 4 weeks [45].

3.2 IVC filters

a. Because majority of emboli to pulmonary circulation arise from deep veins of legs, use of IVC filter (retrievable or non-retrievable) was emerged as a therapy for preventing PTE.

b. In clinical practice, clinicians use them in diverse VTE population, like patients with poor compliance to anticoagulant use, limited cardio-pulmonary reserve, large free-floating proximal DVT and also in patients with high risk of VTE prophylactically [46].

   In-fact, meta-analytic data suggest that the IVC filters were associated with reduction of recurrent PE but causes increased risk of DVT, and albeit no significant effect on PTE-related or overall mortality [47, 48].

c. In should be noted that majority of the evidence for the use of IVC filters in people with VTE was of very low quality, which is majorly insufficient to make any strong recommendations.

Expert consensus based on all the available evidence recommend not to offer IVC filters to people with DVT or PTE unless it is part of a clinical trial or was covered by their other recommendations for people in whom anticoagulation is contraindicated or who have PTE taking appropriate anticoagulation treatment.

Systematic review [49] suggests that IVC filters with cylindrical or umbrella elements have highest reported risk of IVC thrombosis compared to conical filters, clinical relevance of this is yet to be studied.

4. Hot topics in PTE

4.1 Isolated sub-segmental pulmonary embolism

ISSPE is defined as a contrast defect in a sub-segmental artery, that is, the 1st arterial branch of any segmental artery independent of artery diameter.

a. With the advent of improved technology in CTPA, there is a better visualization of peripheral vessels, thereby increasing the detection rate if subsegmental pulmonary embolism (SSPE) and it accounts for 15% of all PE diagnosis recently.

b. Data suggest that ISSPE is not usually associated with adverse clinical outcomes and mortality, leading to an ongoing debate on the need for anticoagulation in these patients. In a systematic review, comparison of the pooled clinical data from

uncontrolled outcome studies shows no increase in VTE recurrence for patients who were not anticoagulated compared to patients who received anticoagulation.

c. However, some patients may be at higher risk of recurrent events. A clinical expert panel favors anticoagulation treatment in case of prior VTE, APLAS - antiphospholipid syndrome, active cancer and proximal DVT [50–54].

4.2 Covid associated PTE

a. A major concern in patients with severe COVID-19 pneumonia is concomitant prothrombotic state known as COVID-19-associated coagulopathy (CAC) and its pathophysiology centres around the bidirectional model of thrombosis and inflammation (thrombo-inflammation). Systematic review data suggest that:

   1. The frequency of PTE in patients with COVID-19 is highest in the ICU (25-50%), followed by general wards (15-25%). PTE in COVID-19 is more commonly located in peripheral than in central pulmonary arteries, which suggests local thrombosis to play a major role. Increasing age & body mass index was associated with an increasing prevalence of PTE.

   2. Patients with PTE had significantly higher D-dimer levels and a D-dimer assessment may help to select patients with COVID-19 for CTPA, using D-dimer cut-off levels of at least 1000 μg/L (cut-off levels which have been used to identify patients with PE varied between 1000 and 4800 μg/L in different studies). The odds of mortality are significantly higher among patients who developed PTE compared to those who did not.

b. Data from low-quality studies, show that in adult hospitalized patients AC, anticoagulation is associated with improved pulmonary oxygenation, decreased coagulopathy markers and decreased mortality.

Though Anticoagulation dosing varied throughout the studies and may be classified as standard VTE prophylaxis, intermediate dosing, or full dose AC. Limited data also suggests that therapeutic doses might be associated with better survival compared to prophylactic doses.

However, at present, no randomized data is available to support one approach over another. Based on the available clinical evidence it may be suggested that

1. Routine thrombo-prophylaxis with SC heparin (UFH or LMWH) may be recommended in all adult hospitalized (in particular ICU) patients with standard VTE prophylactic dose provided there are no contraindications. LMWH can be preferred over UFH (to limit exposure) and DOACs (to limit drug interactions).

2. Considering a 50% increase in the dose in obese patients (>120 kg or BMI > 40 kg/m^2) and using therapeutic dose in patients on mechanically ventilation or proven VTE event (present or past).

Though little data suggested D-dimer driven escalated thrombo-prophylaxis - i.e. Using therapeutic anticoagulation in patients with very high D-Dimer levels (ex. > 3.0 μg/ml) or significantly rising D-dimer levels (ex. > 0.5 μg/ml per day) even after prophylactic dosing; may improve clinical outcomes, large scale studies are needed and presently daily monitoring of d-dimer for the purpose of guiding anticoagulant therapy is not recommended (but, worsening clinical

status in conjunction with rising D-dimer, may necessitate the escalation of anticoagulation therapy). In should be noted that a French guidance document recommends full-therapeutic dose anticoagulation for patient with increase in fibrinogen to >8 g/l or D-dimer of >3.0 μg/ml.

3. Due to the absence of the clinical studies, use of antiplatelet agents for VTE prevention should not be used based on data from non-covid-19 patients. Addition of mechanical thrombo-prophylaxis to pharmacological agents may be considered in critically ill patients.

4. Physical activity and ambulation should be recommended to all discharged patients when appropriate. Extended VTE prophylaxis should be considered in patients with documented VTE event. In others though elevated d-dimer levels (greater than twice the upper limit of normal), in addition to comorbidities such as cancer and immobility, may help to risk stratify there is no clinical guidance in whom VTE prophylaxis be given and may be only considered on case-to-case basis (up to 6 weeks); because, cumulative incidence of a VTE episode in the post-acute COVID-19 setting is <5% at 30-45 days follow-up.

   COVID-19 patients who are at low bleeding risk (VTE-Bleed score < 2 or Orbit score < 3) and were admitted to the ICU, intubated, sedated, and possibly paralyzed for multiple days may get benefited from out-of-hospital prophylaxis.

c. So, at this point of time, full role of therapeutic-dose anticoagulation must be further elucidated in the settings of larger RCT. Furthermore, whether heparin-based anticoagulants are superior to DOAC or VKA in terms of clinical outcome in patients with COVID-19 requires further study. Agent of choice (DOACs vs. enoxaprin), indications and duration of post-covid thromboprophylaxis need to be further evaluated. Role of antiplatelet agents such as aspirin as an alternative (or in conjunction with anticoagulation agents) for thromboprophylaxis in COVID-19 has not yet been defined.

d. In critically ill COVID-19 hemodynamically stable patients (systolic blood pressure, SBP >90 mmHg) with documented PE, parenteral AC might be preferred to oral anticoagulant therapy (LMWH may be preferred over UFH except in patients with severe renal dysfunction and/or with high bleeding risk) due to frequent association of drug interactions, GI and kidney dysfunction. Challenges for thrombolytic therapy in hemodynamically unstable (SBP <90 mmHg for >15 minutes) covid-19 patients:

   1. Coagulopathy associated with covid changes from supressed-fibrinolytic (elevated D-dimer, normal fibrinogen) to enhanced-fibrinolytic type (elevated D-dimer, decreased fibrinogen) during the disease progression and thrombolytic therapy (TT) may be dangerous in the later type.

   2. Due to critically ill nature of disease, cause for hemodynamic instability cannot ascertained to PTE with certainty in all.

   3. Associated comorbid condition (GI and kidney dysfunction) may increase attendant bleeding risk with TT.

Though there is a scare data on the efficiency of inhalation therapy with fibrinolytic substances in PTE in general, they should be used only in clinical trial settings and in all other situations TT (systemic thrombolysis using a peripheral vein over CDT) should be considered in high-risk PTE patients when other causes of instability are reasonably excluded [55–65].

5. Management of CTEPH

CTEPH is major cause of chronic pulmonary hypertension leading to right heart failure and death. Lung ventilation/perfusion scintigraphy is the screening test of choice; a normal scan rules out CTEPH. In the case of an abnormal perfusion scan, a high-quality pulmonary angiogram is necessary to confirm and define the pulmonary vascular involvement and prior to making a treatment decision. Its management principles are [66–73]:

a. After the diagnosis of CTEPH was made patients should receive diuresis for volume overload and supplemental oxygen for hypoxemia if indicated.

b. Pulmonary end-arterectomy (PEA) is considered as a gold-standard treatment in eligible patients. CTEPH operability has to be assessed by experienced CTEPH multidisciplinary teams.

   Systematic review data suggest that only 60% of CTEPH cases are operable and in 25% of operated patients, pulmonary hypertension persists; for whom non-surgical alternative therapies (BPA and Pulmonary vasodilator therapy) must be considered, because they were shown to improve pulmonary hemodynamics and 6-minute walk distance (6MWD). However, their impact on mortality is yet to be proven.

c. Pulmonary vasodilators: Endothelin receptor antagonists (ERA: Oral Bosentan & macitentan), Soluble guanylate cyclase stimulators (Riociguat), Prostanoids (Epoprostonil IV, trepostinil SC), PDE5i (sildenafil) are used. Only Riociguat (Soluble guanylate cyclase stimulator) remains the only approved medical therapy for CTEPH patients deemed inoperable or with persistent PH after PEA [34].

d. Balloon pulmonary angioplasty (BPA) is an interventional angiographic procedure in which stenotic segmental and subsegmental pulmonary arteries are dilated using a standard balloon angioplasty technique.

   Though, preliminary encouraging data suggests that BPA might have higher survival rate with fewer complication rate compared with PEA [74], at this point of time CTEPH still remains the standard therapy for operable CTEPH cases and guidelines state that BPA may be considered for patients who are technically inoperable or who carry an unfavorable risk/benefit ratio for PEA.

e. Anticoagulation: Lifelong anticoagulation is routinely recommended and used in CTEPH to prevent recurrent venous thromboembolism. The ideal choice of anticoagulation agent has not been established.

Multi-centre data suggested that the use of DOAC therapy resulted in a higher incidence of PTE recurrence compared with VKA without any survival difference.

Although, there are an emerging positive data regarding the efficacy of DOAC therapy in this setting, standard practice is to use VKA (target INR of 2-3).

6. Important relevant latest guidelines

See references [75–82].

7. Conclusion

a. Management of acute PTE starts with risk stratification based on (s)PESI scoring and the patients with hemodynamic instability should receive systemic thrombolysis (ST). Patients with intermediate-high risk PTE may be thrombolysed if they deteriorate after initial anticoagulation or upfront low dose ST may be considered particularly if the patient has no high bleeding risk.

   However, choice of thrombolytic agent and evidence-based indications to stop ST in indicated patients is largely unknown.

b. Both catheter-based therapies (CBT) and surgical pulmonary embolectomy (SPE) are well accepted second line therapies in patients who have failed ST. However, comparative effectiveness of these approaches is difficult to study with systematic review data suggesting significantly higher absolute mortality with SPE compared to CBT.

   Based on the available evidence catheter directed thrombolysis (CDT) may be considered as 2nd line therapy in appropriate patients, if ST fails. Use of CDT in sub-massive PE need further evidence to define its appropriate role.

c. DOACs should be preferred to VKA for the long-term management of PTE with available evidence suggesting similar efficiency of all 4 DOACs and relatively lower bleeding risk with apixaban. There is no routine role of thrombophilia testing in PTE and in almost all do not alter our choice of preferring DOACs over VKA.

d. Management of sub-segmental PE is ongoing hot-debate with limited RCT data. Expert opinion is not to anticoagulate the patient until the patient has high risk features like proximal lower limb DVT.

   Further studies are in need of the hour to identify the significance of subsegmental PE and appropriate candidates for systemic anticoagulation.

e. Appropriate follow-up of PTE patients is clinically very important for early recognition of CTEPH, which is managed with surgical end-arterectomy is eligible patients and in others, non-surgical therapies like balloon pulmonary angioplasty or pulmonary vasodilator therapy with available evidence suggesting a clinical superiority of former therapy.

f. Statins may be considered for secondary prophylaxis in PTE patients. Primary prophylaxis with heparin (UFH or LMWH) should be considered in appropriate patients with acute medical illness, active cancer and high-risk surgeries.

Use of IVC filters is based on low quality evidence and at present may be inserted in only a subset of PE patients (ex. contra-indication for anticoagulation) as secondary prophylaxis.

g. Covid associated PTE is related to thrombo-inflammation and routine prophylaxis with standard dose of LMWH is recommended in all hospitalized patients and role of therapeutic dose of LWWH as prophylaxis in yet to be properly defined. Extended VTE prophylaxis in patients with no documented in-hospital VTE episode should be considered on case-to-case basis.

Ongoing clinical trials will shed more light on the role of aspirin for VTE prophylaxis, dose and duration of AC for VTE prophylaxis in hospitalized and non-hospitalized patients.

Conflict of interest

None to declare.

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