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KSTH PROPOSED GUIDELINES ON DIAGNOSIS AND MANAGEMENT OF THROMBOSIS & COAGULOPATHY IN COVID-19 IN KENYA
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KSTH PROPOSED GUIDELINES ON DIAGNOSIS AND MANAGEMENT OF THROMBOSIS & COAGULOPATHY IN COVID-19 IN KENYA

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ABSTRACT

Thrombosis and coagulopathy are emerging as the most lethal, yet silent killer complications associated with COVID-19. The evidence for the complications from clinical, imaging, and laboratory test results is overwhelming. Both clinical experiences in Kenya and publications from afflicted countries indicate that anticoagulation is associated with decreased mortality. Despite the evidence, anticoagulation in COVID-19 patients is neither universally practiced in Kenya nor incorporated in the Country guidelines for the disease management at the moment. The Kenya Society on Thrombosis and Haemostasis (KSTH) has reviewed the evidence from original sources and consensus statements of other professional societies regarding the issue and found there is a strong case for adoption. In response, a guideline for diagnosis and management of thrombosis and coagulopathy is herein recommended for adoption.

INTRODUCTION

The commonest clinical presentation of COVID-19 is cough, dyspnea and low body oxygen levels, usually regarded as being of respiratory origin. However, these symptoms could also be secondary to pulmonary thrombosis or embolism (1). There is now overwhelming evidence of non-respiratory and extra-pulmonary involvement in COVID-19 disease (1–3). Indeed, emerging evidence from autopsy and imaging studies indicates that a majority of the patients suffer from or die from thrombosis related complications (2). These clinical findings have been corroborated by laboratory evidence of coagulopathy that can be used to stratify mortality (4–6).

Published literature emanating from many countries afflicted by serious COVID-19 such as China, Italy, Netherlands, France and UK indicates that mortality rates are lower in patients who received some form

of anticoagulation compared to those that did not(7,8). As a result of these observations, many nations and professional societies have taken cognizance of this and adjusted their treatment protocols to reflect the emerging reality (9–11). Some of the professional societies and countries that have released these new guidelines include but are not limited to, the European Society of Cardiology (ESC) (12) International Society of Thrombosis and Hemostasis (ISTH) (3,11) and the National Health Service (NHS) of the UK (5,10). It is noteworthy that the clinical experience from centers in Kenya handling COVID-19 patients strongly confirms observations from centers overseas. It is with the foregoing discussion in mind that the Kenya Society on Thrombosis and Haemostasis KSTH) which is the Kenyan affiliate of ISTH has prepared these management guidelines for use by Kenyan and African healthcare practitioners in the management of thrombotic complications of COVID-19.

There is a need for local disease management guidelines due to the presence of differences in disease presentation between various regions. A review of literature shows that there are variations in guidelines and recommendations depending on the country/territory and institutions. Consensus statement from International Society on Thrombosis and Haemostasis (ISTH) and discussions with African experts highly recommend individual country guidelines taking into account unique perspectives (See attached consensus statement). In addition, there is need to customize recommendations according to local conditions as well drug product availability.

Rationale and justification of this guideline: Critical care Society of Kenya (CCSK) convened a meeting in April 2020 involving Kenya Society of Anaesthesiologists (KSA), Kenya Association of Physicians (KAP) as well as Kenya Society on Thrombosis and Haemostasis (KSTH) to discuss in country experiences in clinical presentation and management of emerging COVID-19 in the Kenyan context. Thereafter, a series of virtual meetings were held and KSTH were tasked with the purpose to summarize the literature and develop draft guidelines for discussion and ratification. In the meantime, there were consultations between KSTH and International Society on Thrombosis and haemostasis (ISTH) consensus statement that was endorsed by member countries for onward transmission to WHO for adoption and incorporation in case management guidelines. KSTH was among the over 70 country professional societies that signed and endorsed the document. The current document has been prepared to take into account the local disease presentations, drug availability and clinicians experiences borrowing on best practices elsewhere.

Pathophysiological Mechanisms of COVID Associated Coagulopathy and Thrombosis: It is estimated that 20-55% of COVID-19 patients admitted to hospital have laboratory evidence of coagulopathy (6) with the incidence of thrombosis in critically ill COVID-19 patients estimated to be 31% (13) which is higher than in the general ICU population. The sites of thrombosis include the limbs (ischaemic gangrene) (14,15), aorta (16), pulmonary circulation (thrombosis/embolism) (17) lower limb (deep venous thrombosis -DVT) (18), cerebral circulation (ischaemic stroke) and kidneys(19). COVID Associated Coagulopathy (CAC) is associated with the following unique features: elevated D-dimers, elevated fibrinogen, minimally altered prothrombin time (PT) and activated partial thrombin time (APTT) and platelet count despite disease severity (10). These features are in contrast to bacterial sepsis induced coagulopathy (SIC) or disseminated intravascular coagulopathy (20). Accordingly, the coagulopathy in COVID-19 patients do not meet the International

Society on Thrombosis and Haemostasis (ISTH) criteria of DIC since there is little evidence of consumption.

The multi-organ thrombosis seen in COVID-19 is postulated to arise from endothelial injury leading to the derangements in the activation of coagulation pathways (21). The SARS-Cov-2 virus enters the body by attaching to its cognate ACE-2 receptors that are abundantly distributed on the respiratory tract and endothelial surfaces (22, 23). The virus-ACE-2 complex that is recognized by macrophages which release various cytokines such as IL-1, IL-2, IL-6, IL-8, and TNFα (24,25) which manifests as the "cytokine storm"(26). The cytokines induce tissue factor expression on monocytes surfaces (27) leading to the detachment of membrane bound TF microparticles (MP-TF). The combined effect of monocyte TF and MP-TF leads to the initiation of the extrinsic coagulation cascade (28).

Cytokines also induce NETosis in neutrophils i.e. the formation of nuclear extracellular traps (NETs)(29,30). NETs which contain Neutrophil elastase (NE), Myeloperoxidase (MPO), cell free DNA (cfDNA), and citrullinated histones (Cit4Hist) (29–31) as well as circulating endothelial cells (32) form web-like scaffolds that trap and activate platelets as well as provide negatively charged surfaces for contact activation of the coagulation pathways. In addition, cytokines and NETs (specifically human neutrophil elastase) synergistically destroy endothelial membrane linings (33). NETs exacerbate thrombosis by causing fibrinolytic shutdown by degrading plasminogen and plasmin (3,34)

Finally complement system proteins are activated by COVID-19 and form complexes that destroy endothelial tissues causing endothelioitis and microthrombi formation (35). Findings of neutrophilia, tissue neutrophil infiltration and NETs in association with organ microthrombi in autopsy studies validate the mechanistic postulations described above (36)The plasma of COVID-19 patients often contains abundant procoagulant Microparticles (MP) increased surface expression of negatively charged phosphatidylserine (PS) and tissue factor decryption catalyzing coagulation reactions (37)

In addition, a high neutrophil to lymphocyte ratio is a cardinal feature of COVID-19 severity. These facts have been known outside COVID-19 under the concept of "two path unifying theory" (23). The ensuing activation of coagulation and formation of microthrombi in the lungs has been referred to as "pulmonary intravascular coagulopathy" (PIC)(33) that is strongly believed to present as ARDS like picture.

In conclusion, the linkage of intense immune response and causation of coagulopathy probably explains the observations that convalescent plasma exchange, use of steroids or immunosuppressants decrease coagulopathy.

Evaluation of Thrombosis risk factors: Elderly patients with chronic concurrent non-communicable conditions are highly susceptible to severe COVID-19 disease. These conditions are also known to predispose patients to thromboembolism. Further the isolation, quarantine, hospitalization and the effects of the virus on the vascular system are additional risks. The following patient factors should therefore be sought and documented:

- Hypertension, coronary heart disease,
- Previous Venous Thromboembolism (VTE), Deep Venous Thromboembolism (DVT), stroke,
- Diabetes mellitus, endocrinopathies
- Chronic kidney disease, malignancy, structural pulmonary disease, immunosuppression

- Acquired or hereditary bleeding disorders, peptic ulcer, liver cirrhosis, haemorrhoids
- Concurrent medications such as antiplatelet, anticoagulants

Imaging: While it is recognized that there are different levels of care available in Kenya and therefore on the availability of imaging services, it is recommended that:

- Bedside ultrasound be performed to screen for DVT routinely in these patients.
- The logistics and nature of disease may not allow for Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI), but strongly encouraged when available for the severe cases to rule out overt thromboembolism.

Laboratory evaluation

While there are no definite laboratory biomarkers for thrombosis, tests are performed to assist in staging and prognosis of the illness. The deranged levels have been associated with increased mortality.

Mandatory: Blood count, especially platelet count, routine coagulation tests such as Prothrombin Time (PT), Activated partial Thrombin Time (APTT), Thrombin Time (TT) and International Normalized Ratio (INR); D-dimers, fibrinogen.

Preferable: Immune assay markers such are C-reactive protein (CRP), plasma ferritin, procalcitonin

*Optiona*l (depending on level availability): Fibrin degradation products (FDP), Antithrobin III (AT III) &FVIII levels, vWF (von Willebrand Factor) & ADAMTS 13 (a disintegrin and Metalloproteinase with a thrombospondin type 1 mortif, member 13), fibrinolytic assays (t-PA, PAI-1, PAP), viscoelastographic assays (VHA) such as Thromboelastography (TEG) or thromboelastometry (ROTEM). These tests are useful to define the extent of hypercoagulability/ hypocoagulability and fibrinolysis but are not necessary for routine investigation and management of COVID-19.

It is recommended that abnormal results require no correction if there is no associated bleeding.

Staging of COVID Associated Haemostatic Abnormalities (CAHA) Coagulopathy

According to Thachil (11) this is useful in profiling and decision on level of anticoagulation.

Stage 1 CAHA: Asymptomatic patient at home, or with mild symptoms of dyspnea, cough and desaturation inpatient in hospital ward. D-dimers elevated 2-3 times normal; normal routine coagulation tests: PT (sec), APTT (sec), platelets (count above 150 X $10^3/\mu L$) and fibrinogen (mg/dL). Imaging shows no evidence of thrombosis since microthrombi may be limited to lungs not detectable.

Stage 2 CAHA: Symptomatic patient requiring specialized care in HDU. Patients have markedly elevated D-dimers (three to six times above normal), mild reduction in platelet counts (100-150), minor prolongation of PT and APTT whether or, not on prophylaxis. There are associated imaging evidence of asymptomatic DVT by ultrasound or filling defects on CT chest or pulmonary thrombi or emboli. Other extra pulmonary manifestations of COVID-19 are beginning to show organ failure such as acute kidney injury, skin gangrene, bowel or cerebral.

Stage 3 CAHA: The clinical picture has worsened with multiple organ failure requiring higher level critical support in ICU such as mechanical ventilation, inotropic support, dialysis, extracorporeal membrane oxygenation. There are overt features, both on imaging (CT chest and ultrasound) of thrombosis or VTE, ischaemia of skin (gangrene), limbs, gut or cerebral (stroke). Laboratory features are elevated D-dimers (more than sixfold above normal), low platelets (<100 count), decreased fibrinogen, markedly prolonged PT and APTT (>1 ½ to

2 times normal). Features of frank DIC can be observed

Terminal stages of CAHA: multiple organ failure, very hemodynamically unstable which may be unsalvageable. These stages are illustrated in figure 1.

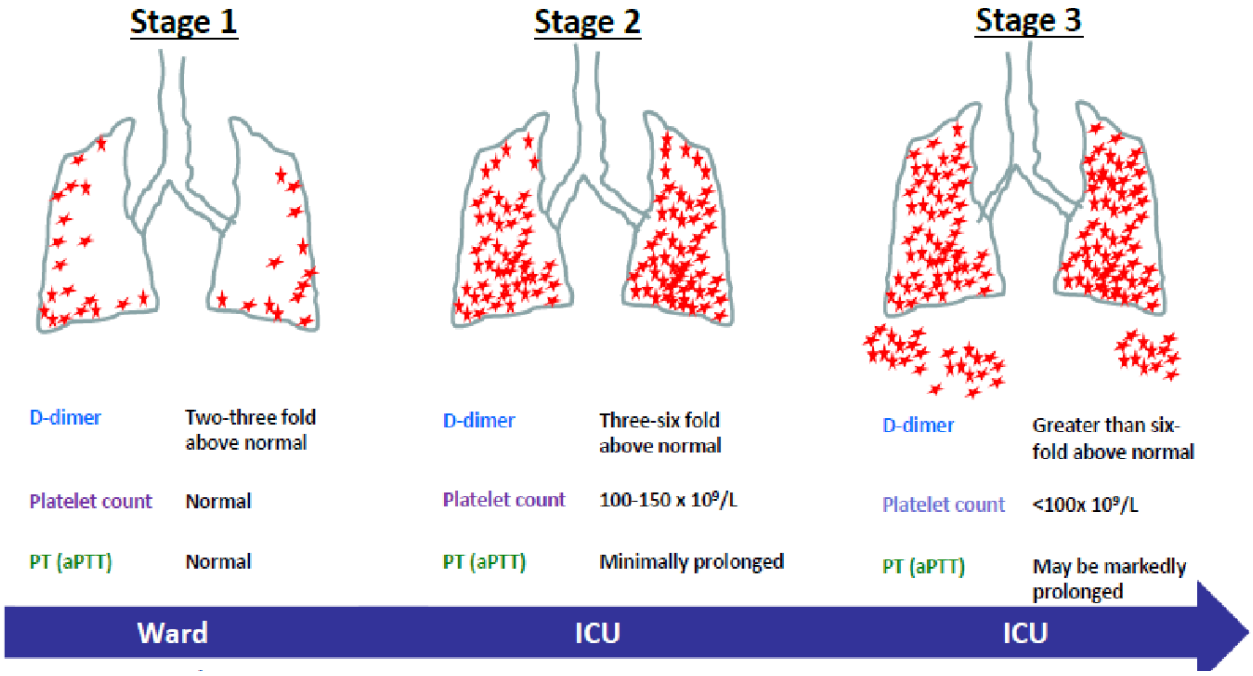

Figure 1: Three stages of COVID Associated Haemostatic Abnormalities (CAHA). Stage 1-regions of microthrombi in peripheral parenchyma; Stage 2-extension to most lung fields; Stage 3-coagulation activation becomes systemic thrombi. Adapted from Thachil (11)

Anticoagulation

Due to the high prevalence of thrombosis in COVID-19 than in non-COVID-19 patients, it is recommended that anticoagulation should start early to avert disease progression or prevent severe forms. The preferred anticoagulants of choice are the heparins which, apart from being antithrombotic, have additional anti-inflammatory and anti-viral effects. Although unfractionated heparins (UFH) may be effective, they are less preferred due to the associated requirements of repeated administration that may expose staff to infection. Therefore, on this basis low molecular weight heparins (LMWH) are to be preferred.

It is to be noted that in developing this guideline, considerations were drug availability as well as long period of familiarity/clinical experience in Kenya. Drugs such as Nadroparin, Apixaban, Fondaparinux and Rivaroxaban though available in Kenya, are limited to a few centers and relatively expensive as well as not many clinicians are NOT experienced in their prescription. Furthermore, not much literature in COVID-19 referring to them. Nevertheless, they are listed to avoid biases despite the aforementioned.

It is recommended that anticoagulation dosage be calculated on weight basis rather than fixed dosages. The following recommendations are made:

- Patients in stage 1 should receive prophylactic anticoagulation, unless contraindicated, irrespective whether they have risk factors for thrombosis or not.

- Stage 2 patients should be given therapeutic treatment
- Stage 3 patients should be given optimized, escalated therapeutic anticoagulation in combination with other classes of anticoagulant such as antiplatelet agents.
- In the very critically ill hemodynamically unstable patients, other modalities such as thrombolytics and antiplatelets may be tried if they continue being hypoxaemic despite anticoagulation.
- Antiplatelets should be considered in those patients with elevated troponins and cardiac dysfunctions
- Caution should be exercised in those patients with acute kidney injury, especially when contrast media are to be administered; low fibrinogen levels, late stage disease with thrombocytopenia with platelet count below 50 (either heparin induced thrombocytopenia or disease induced). If platelet count is below 25 x 10^3/μL, anticoagulants should not be administered owing to increased risk of bleeding.
- If heparin induced thrombocytopenia (HIT) is suspected or confirmed, argatroban or bivalirudin anticoagulation should be used instead
- In severe COVID-19 patients with liver failure, plasma exchange is recommended
- PLEASE NOTE: D-dimer levels should not be the criteria to start anticoagulation, but instead useful to estimate disease severity
- Patients with pre-COVID thrombosis should receive therapeutic anticoagulation irrespective of the stage of the COVID-19 illness. Prophylactic treatment should be continued for at least 14 days post discharge for those patients who had stage 1 disease and did not progress to the next stage,
- Patients who are already receiving anticoagulant and/or antiplateletmedications prior to diagnosis of COVID-19 should continue with medications
- Patients with COVID-19 who experience incidental thromboembolic events, or who are highly suspected to have thromboembolic disease at a time when imaging is impossible or not available should be managed with therapeutic doses of anticoagulant therapy as per standard of care for patients without COVID-19
- For patients who have severe disease and have significant bleeding, treatment should be by blood products based on dose titration: fresh frozen plasma for fibrinogen cut-off of <2 g/L; and platelet concentrate for cut-off < 20 x 103/μL.
- The recommended treatment regimens are summarized in table 1 and a flowchart provided in figure 2 to aid clinician decision making.

Table 1

Guide on the type of anticoagulant, dosage for either prophylaxis or therapeutic usage

	Prophylactic Dose	**Therapeutic Dose**
UFH	5000U subcut q12h	80U/kg bolus then 18U/kg/h infusion
Enoxaparin	40mg subcut q24h	1mg/kg subcut q12h
Fondaparinux	2.5mg subcut q24h	5mg subcut q24h (<50kg) 7.5mg subcut q24h (50-100kg) 10mg subcut q24h (>100kg)
Apixaban	2.5mg PO q12h	-
Rivaroxaban	10mg PO q24h	-

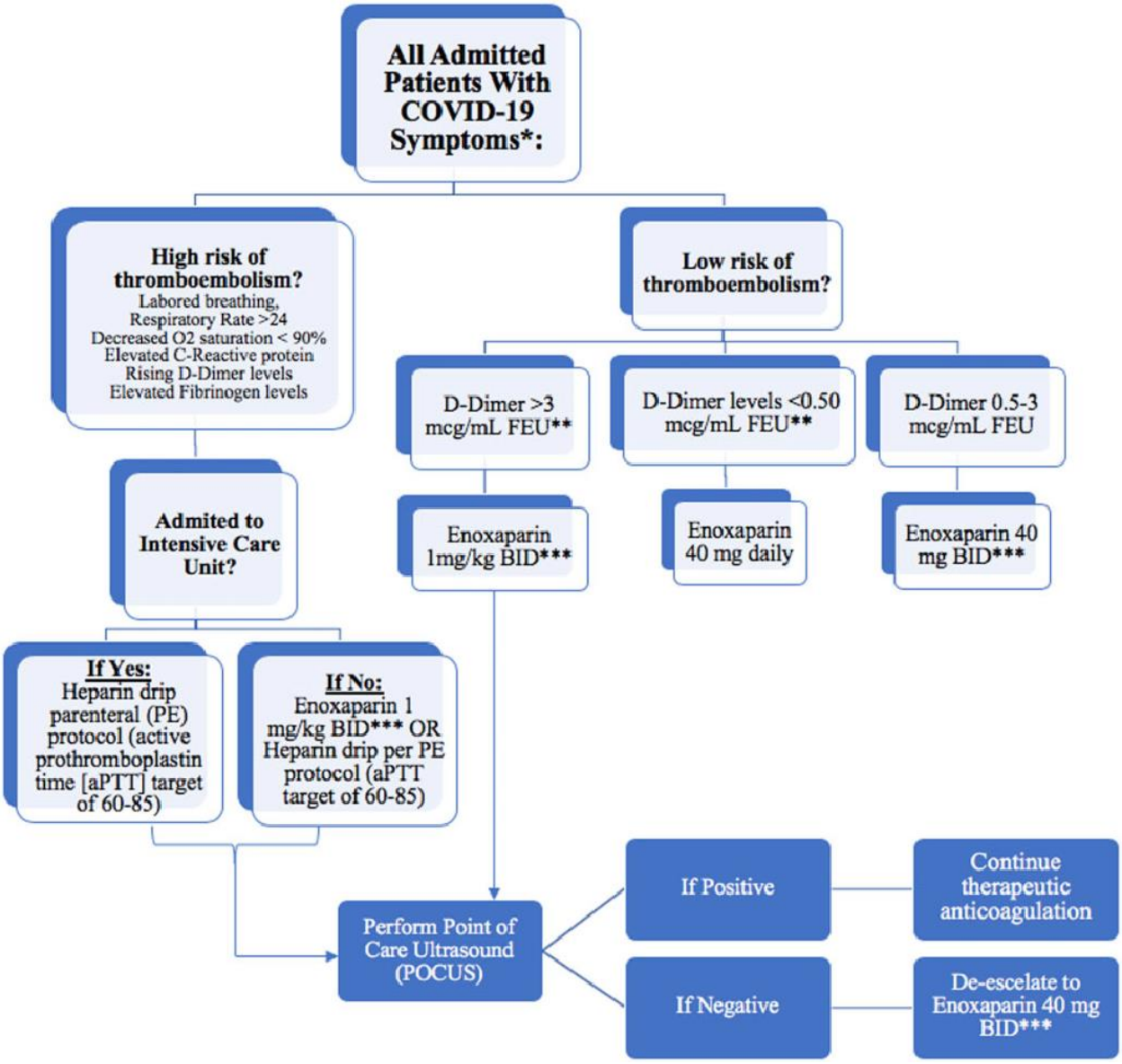

Figure 2: Flow chart depicting algorithm for management of Coagulopathy in COVID-19 patients. High risk bleeding excluded; FEU, Fibrinogen Equivalent Units; Adjust Enoxaparin dose to renal failure. Adapted from Atallah et al (7)

Note: the flow charts contain many drugs that are not discussed extensively in the text. The authors main consideration was familiarity/clinical experience in Kenya. Drugs such as Nadroparin, Apixaban, Fondaparinux and Rivaroxaban though available in Kenya, are limited to a few centers and relatively expensive as well as not many clinicians are NOT experienced in their prescription. Furthermore, not much literature in COVID-19. Nevertheless, they are listed to avoid biases despite the aforementioned.

CONCLUSION

We believe that these guidelines will greatly improve patient outcomes in severe COVID 19 as well as preventing thrombotic complications in affected patients. We undertake to periodically review these guidelines to take into consideration

emerging local and global data and/or treatment recommendations.

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