Thrombosis and Antithrombotic Therapy

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1. Thrombosis

The physiology of coagulation is complex. However, it can be simplified as a delicate balance between procoagulant and anticoagulant forces. The competing risks of imbalance are haemorrhage and thrombosis. Both can be devastating. However, whilst veterinarians have often given much attention to preventing or treating haemorrhage, there has been less attention on thrombosis. Thrombosis risk increases with any of the three elements of Virchow's triad: static or turbulent blood flow, endothelial injury or activation, and hypercoagulability of the blood.

Thrombosis can cause devastating clinical consequences due to obstruction to blood flow, with resultant tissue ischaemia, congestion, or even obstructive shock. The clinical manifestations of thrombosis are dependent of the location of the thrombus. Broadly, this can be divided into arterial and venous thrombosis. Arterial thrombi are platelet rich. Clinically relevant arterial thrombosis most commonly occurs at the aortic trifurcation, but can also manifest in other limb arteries, as a cerebrovascular accident, a myocardial infarction, or infarction of another organ. Venous thrombi are fibrin rich. The manifestations of venous thrombosis likewise depend upon the location. The most acutely devastating is embolism of a systemic venous thrombus to the pulmonary circulation: a pulmonary thromboembolism. Other common manifestations of venous thrombosis include vena cava thrombosis and thrombosis of the portal system.

2. Diagnostics to Assess Thrombosis Risk

Across the broad spectrum of emergency and critical illnesses, some laboratory diagnostics may aid in determining whether thromboprophylaxis is indicated. However, interpretation can be complex and there is no one test that reliably identifies a patient at risk of thrombosis. Broadly, there are two patterns of test results that might prompt thromboprophylaxis. The first of these is a pattern of results that indicate hypercoagulability, one of the aspects of Virchow's triad. This is mostly assessed by viscoelastic methods such as thromboelastography (TEG), rotational thromboelastometry (ROTEM), or point-of-care devices such as the VCM-Vet. Shortened traditional coagulation times (PT and aPTT) may also suggest hypercoagulability based on one study in dogs. The other pattern is one that suggests thrombosis (micro or macro) is already occurring. Evidence for this may include consumptive thrombocytopenia, prolongation of coagulation times, hypocoagulable viscoelastic testing, and an elevation in D-Dimers. It is often a challenging 'leap of faith' for practitioners to initiate thromboprophylaxis based on hypocoagulable test results. There is often substantial concern for hemorrhage. These cases

do need to be monitored closely for hemorrhage. However, often the only thing that can stop worsening of the hypocoagulable state is preventing further platelet and factor consumption with thromboprophylaxis. It is also worth remembering that most cases of hemorrhage can be treated, provided sufficient resources are available, whilst severe thromboembolic complications are often difficult to treat.

3. Antithrombotic Therapy

Medications aimed at preventing thrombosis are broadly termed antithrombotic agents or thromboprophylaxis. These are two broad categories: antiplatelet agents and anticoagulants. Historically, the major antiplatelet agent employed in small animal medicine was aspirin. However, due to unpredictable pharmacokinetics and pharmacodynamics, it is no longer recommended as a first line. Inhibitors of the ADP receptor $P2Y_{12}$, such as clopidogrel, are now considered standard of care. Anticoagulants inhibit the function of coagulation factors. They include the heparins (unfractionated and low molecular weight), vitamin K antagonists such as warfarin, and a newer class of drugs called direct oral anticoagulants (DOACs). Heparins are heavily utilized in hospitalised small animals. However, the need for frequent injection limits their utility after hospital discharge. Historically, the only oral anticoagulant option was vitamin K antagonists such as warfarin. Due to highly unpredictable pharmacokinetics, the need for frequent monitoring, and the high risk of haemorrhage, these agents are not recommended. The newer DOACs such as rivaroxaban are thought to be more predictable in their dose-response relationship and carry a lower risk of haemorrhage. Thus, their usage in veterinary medicine is greatly expanding.

Choosing whether to administer an antiplatelet agent, an anticoagulant, or both is challenging. As noted above, a broad simplification is that arterial thrombi are platelet-rich, while venous thrombi are platelet-poor. Thus, if the primary risk is of arterial thrombosis, an antiplatelet agent is commonly the first line, whilst anticoagulants are first line for preventing venous thrombosis. However, in conditions where there is risk of both arterial and venous thrombosis, or the overall thrombosis risk is considered very high, it is reasonable to administer an anticoagulant and antiplatelet agent together.

It is challenging for the small animal clinician to know when thromboprophylaxis, the administration of antithrombotic agents to prevent thrombosis, is indicated. For this reason, the American College of Veterinary Emergency and Critical Care created the Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE) guidelines. These guidelines discuss conditions associated with a high risk of thrombosis, such as immune mediated haemolytic anaemia in dogs, protein losing nephropathy and enteropathy in dogs, heartworm disease in dogs, and feline cardiomyopathy. Additionally, it discusses many conditions associated with an intermediate thrombosis risk, such as pancreatitis, sepsis, and neoplasia. This consensus statement summarises a wealth of information about the current state of knowledge regarding thrombosis in small animals and is highly recommended reading.

The CURATIVE statement also discusses many recommendations about antithrombotic choice, dosing, monitoring, and discontinuation. Routine monitoring is generally not employed in veterinary medicine but is an area of ongoing research. Antithrombotic therapy is generally discontinued when there is no ongoing risk factor and no evidence of thrombosis. However, there is often some concern about what to do if a patient requires an invasive procedure while receiving thromboprophylaxis. CURATIVE bases its recommendations for this on how high the thrombosis risk is. High risk patients should have their therapy continued through the perioperative period.

4. Complications of Antithrombotic Therapy

Assessment of hemorrhage in patients receiving thromboprophylaxis warrants broad diagnostic investigation. Evaluation for local factors predisposing to bleeding should be considered. Tests of systemic hemostasis should include platelet count, traditional secondary coagulation assays and/or viscoelastic tests, and specific monitoring tests if available. There should also be consideration of platelet function assays for animals receiving antiplatelet therapy. Excessive antithrombotic therapy may cause evidence of hypocoagulability on these tests, but normal results do not rule out a contribution of the medication.

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