Sepsis and the killer platelets

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Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” (1) (Sepsis 3) and is typically diagnosed using the Sequential Organ Failure Assessment (SOFA) score. While sepsis typically arises in response to a bacterial infection, surprisingly, around 40% of cases are culture-negative. The cause of culture-negative sepsis is unclear but could be due to bacterial species that are difficult to grow in the lab.

So what are killer platelets and why do they kill?

So, if sepsis is due to bacteria growing in the blood, how does that kill a patient? The clue here is in the definition of sepsis: it is the dysregulated host response that causes death, not the bacteria. Since the host response is supposed to recognise bacteria, how can this lead to sepsis and death?

The majority of sepsis patients develop a coagulation disorder (coagulopathy) known as disseminated intravascular coagulation (DIC). Bacterial infection leads to the formation of microthrombi that can occlude some of the small blood vessels supplying organs such as the liver, kidney, brain, etc. As these blood clots block blood flow, ischemic damage occurs around the clot. As more blood clots form, the ischemic damage spreads, ultimately leading to organ failure. As these clots are forming in multiple organs, this leads to multi-organ failure, which is the primary cause of death in sepsis.

There is clear evidence to support this thrombus formation. Patients with sepsis have high D-dimer levels, which is a direct marker of clot formation. This then creates an obvious drug target for sepsis – anti-coagulants. Protein C is an anti-coagulant protein synthesised by the body. Activated protein C (aPC) was found to be very effective at improving survival in animal models of sepsis. As a result, aPC was brought to the market with expectations that it would revolutionise the treatment of sepsis.

However, ten years later, it was withdrawn from the market due to a lack of evidence for benefit. Furthermore, studies with the standard anti-coagulants (anti-thrombin agents) were equally very disappointing. This was a dilemma. Mortality in sepsis is due to a coagulopathy associated with high D-dimer levels indicative of thrombin activation. Still, despite very positive animal studies, strategies that target thrombin activation have been unsuccessful.

The nature of thrombosis

The key to this dilemma is the nature of thrombosis. The two major components of a thrombus are the fibrin mesh and platelets. In the venous system, clots are primarily composed of a fibrin mesh generated by the actions of thrombin on fibrinogen. As this mesh traps blood cells, it is often called a red clot. However, activation of platelets leads to the formation of platelet aggregates where platelets are cross-linked by fibrinogen. These platelet-rich thrombi typically form in the arterial circulation and are known as white clots.

If anti-thrombins are not effective in sepsis coagulopathy it is unlikely that fibrin formation is driving DIC. This suggests that platelet-rich clots may be the drivers, and evidence supports this. One meta-analysis of 700,000 patients showed that prior use of aspirin was associated with a reduction in mortality of 7%.

Another meta-analysis found that the risk ratio for death in critically ill patients on aspirin was 0.81 and that the benefit was only seen in septic patients. Furthermore, a meta-analysis of 135,000 patients on aspirin for cardiovascular protection found a 15% reduction in vascular mortality. Yet, aspirin is the standard of care for cardiovascular protection and treatment, while it is not used in sepsis management.

Thrombocytopenia, megakaryocytes and more

Further evidence for a role of platelets is the common occurrence of thrombocytopenia (low platelet count) in sepsis, and furthermore, the extent of the thrombocytopenia is predictive of mortality. Thrombocytopenia can be due to a failure to produce new platelets or a consumption of platelets.

While there is evidence that infection can affect megakaryocytes this is unlikely to be a factor in the thrombocytopenia. With a life span of 10 days, it would take nine days before thrombocytopenia was severe enough to require intervention. Furthermore, decreased platelet production will lead to bleeding rather than the thrombosis seen in sepsis.

There are two possible mechanisms for platelet activation – direct activation or innocent bystander. Sepsis is characterised by a hyper-inflammatory state with a large number of circulating pro-inflammatory cytokines. In this scenario, platelets are innocent bystanders caught up in this inflammatory response. This is known as thromboinflammation, where thrombosis is part of the inflammatory process. However, platelets can also be directly activated by a pathogen in a process known as immunothrombosis.

There is evidence to support both scenarios. Most cases of sepsis are due to Gram-positive bacteria such as Staphylococci spp and Streptococci spp and Gram-negative bacteria like Escherichia coli and Klebsiella pneumoniae. Most sepsis-causing bacteria have been shown to activate platelets directly. However, around 40% of sepsis cases are culture-negative,

making it unlikely that platelets are being directly activated by viable but nonculturable (VBNC) bacteria. Patients presenting with sepsis have a similar risk of having a subsequent myocardial infarction as patients presenting with chest pain.

Killer platelet activation

A common mechanism of platelet activation by these bacteria is FcγRIIa, the receptor for the Fc portion of IgG. While bacteria often use multiple receptors, including GPIIb/IIIa and GPIb, to activate platelets, they all induce platelet aggregation in an FcγRIIa- dependent manner. Blocking FcγRIIa inhibits platelet aggregation induced by all of these bacteria. This may explain the results of the animal studies of sepsis. Mice do not express FcγRIIa; thus, the coagulopathy in mouse models of sepsis is driven by thrombin generation, but in humans, it is driven by FcγRIIa-mediated platelet activation.

Bacteria are not the only cause of DIC as viruses cause a similar coagulopathy – basically a viral sepsis. Multi-organ failure is the primary cause of death in COVID-19. Furthermore, high-dose intravenous IgG (IVIg), which acts as an inhibitor of FcγRIIa, improved survival in severe COVID-19. Dengue virus can cause a haemorrhagic fever that has been shown to be FcγRIIa-dependent.

Thus, DIC is a severe coagulopathy that arises from systemic infection by either bacteria or viruses. Many different organisms can cause DIC, making it very difficult to develop a single agent that can target them all. However, platelets play a critical role in the pathogenesis of sepsis and targeting platelets can potentially help treat sepsis.

Anti-platelet agents will not cure sepsis, but by preventing the onset of DIC, they will buy time for the clinicians to identify the cause and appropriate anti-microbial agent. Furthermore, they should also reduce the incidence and severity of post-sepsis syndrome, which is due to organ damage from the thrombosis.

Reference

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