**MED3ATB**

**Sepsis worksheet**

**Instructions**

Fill out the following worksheet while working through the *Sepsis* lesson on LMS. You must write all answers in your own words (paraphrase). Do not plagiarize from the text or videos provided!

Bring your worksheet to the workshop. You will be tested on your knowledge of this module in the weekly quiz.

1. In the context of polymicrobial sepsis, inflammation is a necessary evil. Discuss (4-5 sentences) **5 Marks**

Sepsis is a result of an excessively reactive immune system mediating an overproduction of pro-inflammatory cytokines in response to the pathogens in the blood.

As this over secretion of pro-inflammatory cytokines causes tissue damage, in response, host immune system produces anti-inflammatory mediators to compensate for and limit the pro-inflammatory effect.

Consequently, lymphopenia and immune suppression are promoted as a result of these anti-inflammatory mediators stimulating apoptosis of the immune cells.

Although tissue damage could be prevented through inhibiting inflammation, excessive inhibition could disturb the functionality of the immune system to defend against pathogens. For an example, opportunistic pathogens such as pseudomonas and hepatitis B cause approximately 85% of the deaths due to polymicrobial sepsis.

Thus, inflammation is a necessity although an excessive degree of inflammation could lead to septic shock.

1. In the last 25 years, about 100 clinical trials for treating sepsis have failed. Discuss the reason for this high rate of failure. **5 Marks**

In the last 25 years, the main approach of sepsis therapeutics has been to block the inflammatory pathway which can mediate cytokine storms by producing excessive amounts of pro-inflammatory cytokines. However, production of adequate amounts of pro-inflammatory cytokines is essential in the process of recruiting adaptive immune cells to fight off and clear the infection. Therefore, potential sepsis therapeutics which are known to have a mechanism of action to block the inflammatory pathway have been withdrawn from the market as they interfere with the immune system’s normal functionality. For an example, binding of Eritoran (which is structurally analogous to LPS) to the receptor of LPS, TLR4, inhibits the initiation of an inflammatory pathway that is otherwise activated. Currently, Eritoran has been withdrawn from the market.

Moreover, attempts have been made to design antibody-based therapies for sepsis which target specific cytokines. However, one such drug that targets TNFα has proven to be ineffective as multiple other cytokines are also involved in the inflammatory pathways that are crucial in sepsis.

1. Explain the mouse model for studying sepsis. **3 Marks**

A commonly studied mouse model is the cecal ligation and puncture (CLP) mouse model in which polymicrobial sepsis is closely related to human sepsis characteristics and progression. The cecum of the mouse is punctured in this mouse model to let intestinal content leak into the peritoneal cavity. TLR4 in the host immune system recognizes LPS on the cell wall of gram-negative bacteria that is predominant in the fecal matter now present in the peritoneal cavity. This TLR4-LPS interaction leads to sepsis.