**Probability on bacterial infections when suppressing inflammation.**

Extending wound healing time in order to have less scarring. A large inflammatory response of adults results in faster healing but causes more extensive scarring. It is clear that prolonged and/or excessive inflammation in the early stages of burn injury leads to excessive fibrosis and scarring. This scarring is caused by excessive TGFB and collagen synthesis caused by the inflammation.

For scarless healing we need: Few inflammatory cells, much anti-inflammatory cytokines, few pro-inflammatory cytokines, low TGFB levels and low collagen type 1 levels. Anti-inflammatory cytokines can be used for their anti-scarring effects. However, suppressing inflammation can possibly lead to bacterial infections as inflammation cells won’t be recruited to the wound site full of bacteria.

**Biomarkers of bacterial infection [1-8]**

White blood cell (neutrophils, lymphocytes, eosinophils, monocytes, basophils) count (WBC), absolute neutrophil count (ANC) , erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), pro-adrenomedullin (ProADM), serum procalcitonin (PCT), mid-regional pro-atrial natriuretic peptide (ANP), pancreatic stone protein (PSP)/regenerating protein (reg), interleukin-6 (IL-6), IL-8, IL-27, soluble urokinase-type plasminogen activator receptor (suPAR) among others, N have been recognized as potential biomarkers of increased risk on bacterial infections.

In the HIIS model, the probability on acute bacterial infection can only be measured using neutrophil count, as the rest of the cell types are not included in the model. In addition, ANC is most sensitive in most cases and easy to reproduce.

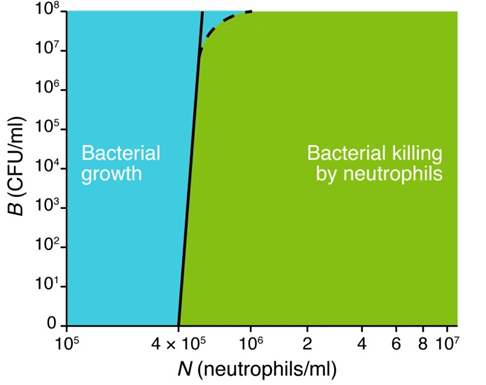
**ANC**

**Neutropenia:**

The neutrophil count usually is between 1.6 and 7.4 x 109/L blood.Because each neutrophil in suspension can kill >20 bacteria ([4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2212745/#bib4)), there is a large apparent excess in neutrophil capacity to kill bacteria. Yet, in neutropenic hosts, bacteria survive and grow in blood.

There is a correlation between the neutrophil count and the risk of bacterial infection. Neutropenia is an abnormally low concentration of neutrophils in the blood. Neutropenia can be measured using ANC. Congenital neutropenia is determined by blood neutrophil counts ANC < 0.5 × 109/L. An absolute count of 500-1,000 per mm3 is associated with moderately increased risk. A count below 500 per mm3 is invariably associated with serious infection. Neutropenia occurs spontaneously in treatment with immunosuppressive or cytotoxic drugs.

Thus, while a blood N value of 5 × 105 neutrophils/ml is a call for vigilance, it is an imprecise measure of the likelihood of infection. This is so because blood is primarily the conduit by which neutrophils travel from bone marrow to tissues, and the blood N reflects the sum of the rates at which neutrophils are produced and released from bone marrow into the circulation, and the rates at which they are consumed in tissues ([14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3533502/#B14)) and/or recycled to spleen and bone marrow for destruction ([15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3533502/#B15)).



**Neutrophilia**

Neutrophilia is defined as an increased absolute neutrophil count (ANC) in PB above 2SD of the mean value for healthy individuals, i.e. above 7.5 x 109/l.

Some notes on the model

Possibilities to model chance on bacterial infection:

1. Macrophages – ITM ratio (killing of bacteria)
2. Neutrophil count (neutropenia, chance on infection)

* HIIS model does include bacteria count (ITM), macrophages and neutrophils mostly phagocyte the ITMs. macrophages are agranulocytes which work as phagocytes inside the tissues.
* HIIS model does not have a constant flow of newly generated neutrophils.
* HIIS model starts with a preset number of neutrophils and activates all of them.
* HIIS model calculates neutrophil count in cells/mm3, activated, resting and apoptotic
* Setup cell counts can be adjusted
* Adjust inflammatory cell influx by changing activation rate neutrophils
* Cytokine levels can be adjusted to slow down the inflammation (neutrophil, macrophage activation)

**Some thoughts on testing bacterial infection probability.**

For scarless healing we need: Few inflammatory cells, many anti-inflammatory cytokines and, few pro-inflammatory cytokines. Therefore, we have to adjust the initial setup of these values.

Create continuous influx of resting neutrophils in blood flow to simulate the constant flow of neutrophils, to be able to calculate the ANC as bacterial infection risk factor. Adjust the initial neutrophil count few times and measure rate of activation and neutrophils in blood. Whenever this work, we can start playing around with the cytokine levels to see how this infleunces the ANC.

Lower CH (Pro-inflammatory):  
lower epithelial permeability

Lower Neutrophil activation

Lower activated macrophages

Higher ACH (anti-inflammatory):  
slower activation neutrophils and macrophages

ACH controls CH, high ACH means low CH, so will suppress inflammation.

Or cytokine delay:

**Continuous influx of neutrophils**

The normal human neutrophil production rate is 0.85 to 1.6 × 109 cells/kg per day. The HIIS model uses 80 kg.

**Burn infection**

Infection is defined as the presence of high concentrations (>105 organisms/g of tissue) of bacteria in the burn wound and scab.

SIRS -> WBC <4x109/L (<4000/mm³), >12x109/L (>12,000/mm³)

A hallmark of sepsis and severe systemic inflammatory response syndrome (SIRS) is the massive recruitment of immature neutrophils from the bone marrow into the circulation. The absolute neutrophil count was not well correlated with the SIRS classification using binary combinations of temperature, pulse, respiratory rate and absolute neutrophil count to classify (Fig. 2).

**Leukopenia**

Leukopenia is a decrease in the number of leukocytes. Found in the blood, they are the white blood cells, and are the body's primary defense against infection. Thus, leukopenia places individuals at increased risk of infection. However, HIIS model only uses neutrophils and macrophages, and not the rest of the leukocytes, so not really useful.

Linking models

HIIS – Wound contraction

Add differential equations of macrophage – TGFB – fibroblast link

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