Pathogenesis of pneumonia due to *Acinetobacter baumannii*: Using a mechanistic model to describe the pathogen-host interaction

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**Objectives:** Increasing prevalence of infections due to multi-drug resistant pathogens, such as *Acinetobacter baumannii*, has led to a growing need for better understanding of bacterial pathogenesis. The objective of this study was to develop a mechanistic model capable of describing the pathogen-host immune response interaction during rat pneumonia infection.

**Methods:** Rat pneumonia data was obtained from Russo et al. [1]. Pulmonary instillation of *A. baumannii* strain 307-0294 was introduced intratracheally in Long-Evans rats to achieve an initial inoculum of 3.5x10⁸ cfu/mL. Animals were sacrificed at 3, 6, 24, 48, 72, and 168h for total lung bacterial quantification and assessment of IL-1β and neutrophil counts in bronchoalveolar lavage fluid. ADAPT5 [2] was used for model development.

**Results:** The model (Figure 1) simultaneously accounted for changes in bacterial concentration (CFU), IL-1β expression (IL-1β), and neutrophil counts (N). Bacterial growth was described by first-order rate constant, $k_c$. CFU stimulates production of IL-1β which stimulates neutrophil recruitment, each with fitted parameters $S_{max}$, $SC_{50}$, and $k_{out}$. Bacterial killing by neutrophil and neutrophil signaling (represented by two transit compartments: T1, T2) were described by second-order rate constants, $k_{dN}$, $k_{dT1}$, and $k_{dT2}$. $T_{max}$ of CFU was predicted to be 25h. Maximal stimulation of IL-1β and N ranged from ~22-35h and ~12-63h with $S_{max}$ estimates of 36.9 (8.0%CV) and 700 (5.6%CV), respectively. Remaining parameter estimates were within physiological ranges or agreed with values reported in the literature.

**Conclusions:** The model captures the maximal stimulatory effects of *A. baumannii* on IL-1β and IL-1β on neutrophils providing a reasonable description of the pathogen-host immune response interaction. Increased proinflammatory cytokine expression drives the neutrophil response that is largely responsible for bacterial clearance [3]. The model can be expanded to include additional biomarkers for a more comprehensive description of bacterial pathogenesis.

**References:**