VIEWPOINT

Does Atelectasis Cause Fever After Surgery? Putting a Damper on Dogma

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Fever and atelectasis are common after surgery, and in the absence of infectious causative mechanisms, atelectasis is commonly thought to be a cause of fever. The notion is entrenched in surgical textbooks and frequently discussed on morning rounds in the hospital. The therapeutic implication of atelectasis as a putative cause of postoperative fever has been the widespread adoption of incentive spirometry to reduce atelectasis.

Despite the ubiquity of this view, evidence that atelectasis is a cause of fever is scarce; indeed, many studies have failed to demonstrate an association between fever and atelectasis.[1] Moreover, in several randomized clinical trials, incentive spirometry has not been shown to reduce the incidence of fever.[2]

Here we propose an alternative explanation—the danger model of immunity—to explain how fever may develop after surgery in the absence of a clear pathogen. According to this theory, an immune response is initiated when cells are injured or distressed. We believe this self-limiting inflammatory response better accounts for noninfectious postoperative fever than atelectasis, and we suggest that current treatment to reduce fever with incentive spirometry may not be necessary.

Atelectasis and Fever After Surgery

Although infections such as pneumonia, intra-abdominal abscess, or urinary tract infection account for a small proportion of postoperative fevers, many cases have no identifiable cause. Surgical textbooks have adopted the notion that atelectasis causes fever, with claims such as "atelectasis is responsible for over 90 percent of febrile episodes"[3(p35)] after an operation. In spite of the confidence of textbooks, the available data suggest that atelectasis is not associated with fever at all. A systematic review[1] identified 8 studies that collectively included 998 patients, and only 1 study reported a significant association between atelectasis and postoperative fever. The authors concluded that there is no evidence supporting the concept that atelectasis is associated with postoperative fever.[1]

Why do textbooks persist in depicting a link between atelectasis and fever? The molecular mechanism most commonly cited to support a causal role for atelectasis in postoperative fever is increased production of fever-inducing cytokines such as interleukin 1 (IL-1) or tumor necrosis factor by alveolar macrophages. This is based on a study in which whole-lung atelectasis was modeled in rats by ligating the left main stem bronchus while maintaining ventilation of the right lung. Alveolar macrophages were subsequently harvested, and in vitro assays showed increased production of IL-1 and tumor necrosis factor.[4] The obvious confounder in the interpretation of this study is the significant tissue trauma involved in surgically exposing and ligating the left main stem bronchus. According to the danger model, it may be that the alveolar macrophages in this study were not responding to atelectasis per se but rather to the tissue damage caused by the surgery.

The Danger Model

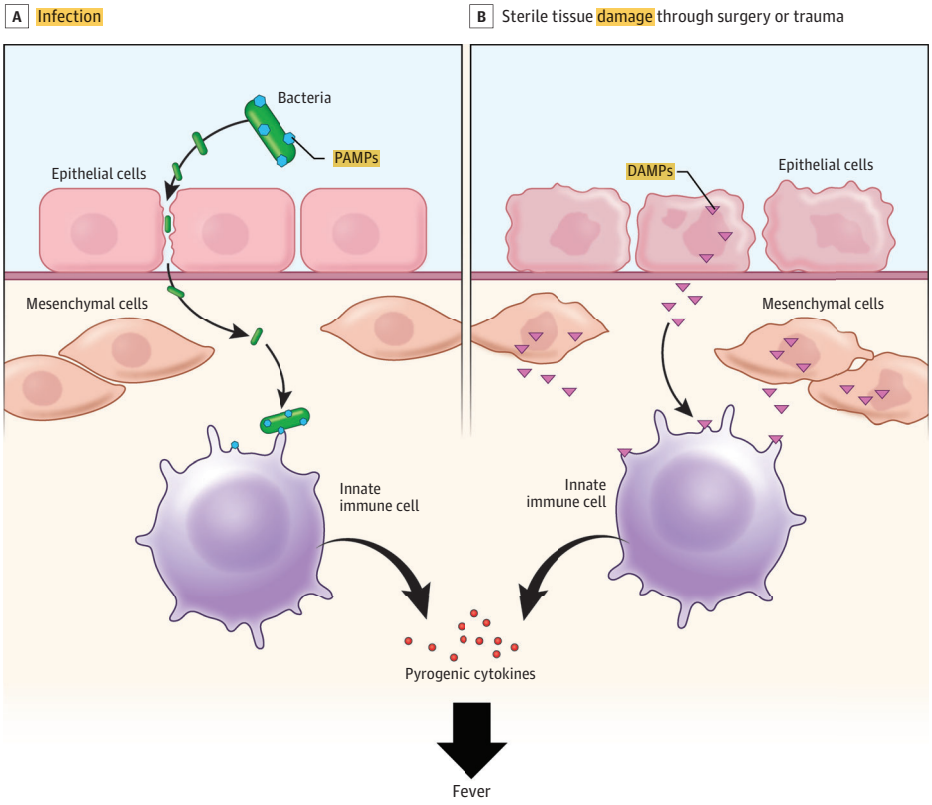
There are 3 dominant theories to explain how the immune system is activated.[5] In 1954, Macfarlane Burnet, MD, PhD, proposed the immune system distinguishes self from nonself by eliminating leukocytes that recognize self in early life. By 1989, however, enough anomalies had piled up that Charles Janeway, MD, proposed a mechanism whereby the immune system distinguishes noninfectious self from infectious nonself (ie, pathogens), proposing that immune cells possess genetically encoded pattern-recognition receptors (later identified as Toll-like receptors) capable of recognizing conserved common structures on evolutionarily distant organisms, such as pathogens; Janeway called these *pathogen-associated molecular patterns* (or PAMPs). Once activated by PAMPs, macrophages capture molecules from pathogens and present them to lymphocytes to stimulate an immune response.[5]

Although this extended nonself theory explains how the immune system reacts to pathogens, it does not account for rejection of transplanted organs, spontaneous rejection of tumors, autoimmunity, or an immune response to toxins. Nor can it explain how the immune system discriminates between pathogens and commensal organisms. These are best explained by the third major model of immunity, the Matzinger danger model,[5] based on the assumption that the immune system responds to things that create damage and does not respond to any entity, whether self or nonself, that does not create damage. The idea is that damaged cells send alarm signals that activate innate immune cells. Thus, immunity to transplant is initiated by preparation of the donor organ and stress of surgery; immunity to cancer occurs with tumor necrosis; autoimmunity occurs because of inappropriate alarm signals or their receptors; and the distinction between commensal organisms and pathogens lies with their tendency to produce tissue damage.

The alarm signals are termed *damage-associated molecular patterns* (DAMPs). The last decade has seen the discovery of a number of them, including uric acid, DNA, RNA, heat-shock proteins, type I interferons, adenosine triphosphate, and formyl-methionine peptides.

With regard to fever, DAMPs, similar to PAMPs, trigger immune cells to release pyrogenic cytokines such as IL-1 and IL-6, which induce fever by acting on the hypothalamus (**Figure**). Thus, fever is a result of tissue

Figure. Damage-Associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs)



Two different mechanisms describe how the immune system induces fever after an operation. A, Pathogens in the postoperative period can cause fever when Toll-like receptors are activated by PAMPs, such as lipopolysaccharide, which in turn induce innate immune cells to release interleukin 1 and interleukin 6. B, Tissue damage from surgery releases nuclear and cytosolic molecules such as uric acid, DNA, and adenosine triphosphate, called DAMPs, that are capable of activating immune cells that subsequently release pyrogens such as interleukin 1 and interleukin 6.

damage, whether from pathogens, surgery, trauma, or other mechanisms whereby DAMPs are released.

Therapeutic Implications of the Danger Model

The danger model of immunity challenges the premise of our current therapeutic approach in treating noninfectious causes of postoperative fever. The clinical benefit of interventions targeting atelectasis as a cause of postoperative fever, such as incentive spirometry, need to be reassessed. The first report of incentive spirometry as treatment for atelectasis was described in 1972.[1] Although still widely used, a Cochrane review[2] of 12 randomized clinical trials that included 1834 patients concluded that there is no evidence to support the use of incentive spirometry in preventing fever after surgery. We have limited focus here on the role of incentive spirometry to reduce fever after surgery, not other pulmonary complications, for which it may have clinical benefit.

The danger model provides an understanding of noninfectious postoperative fever that is not owing to atelectasis and does not require treatment with incentive spirometry. In the absence of symptoms or signs of infection such as leukocytosis, we believe that early postoperative fever can be attributed to DAMPs, not PAMPs—a physiologic self-limiting phenomenon that does not require therapeutic intervention.

ARTICLE INFORMATION

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REFERENCES

1. Mavros MN, Velmahos GC, Falagas ME. Atelectasis as a cause of postoperative fever: where is the clinical evidence? *Chest*. 2011;140(2):418-424. doi:10.1378/chest.11-0127

2. do Nascimento Junior P, Módolo NS, Andrade S, Guimarães MM, Braz LG, El Dib R. Incentive spirometry for prevention of postoperative pulmonary complications in upper abdominal surgery. *Cochrane Database Syst Rev*. 2014;(2):CD006058.

3. Doherty G. *Current Diagnosis and Treatment Surgery, 13th Edition*. New York, NY: McGraw-Hill Companies, Inc; 2010.

4. Kisala JM, Ayala A, Stephan RN, Chaudry IH. A model of pulmonary atelectasis in rats: activation of alveolar macrophage and cytokine release. *Am J Physiol*. 1993;264(3 Pt 2):R610-R614.

5. Matzinger P. Tolerance, danger, and the extended family. *Annu Rev Immunol*. 1994;12:991-1045. doi:10.1146/annurev.iy.12.040194.005015