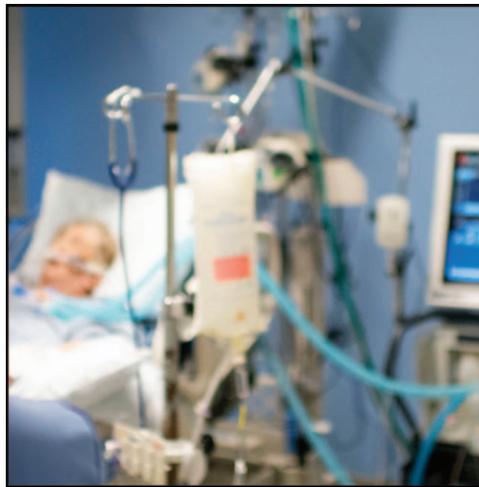


A More Clinically Relevant Model of Ventilator-associated Pneumonia?

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VENTILATOR-ASSOCIATED pneumonia (VAP) is defined as a nosocomial lung infection that develops at least 5 days after endotracheal intubation and is associated with significant mortality and morbidity in intensive care unit patients.¹ Although a variety of microorganisms can be the causative agent in VAP, the most notable is *Pseudomonas aeruginosa*. Several animal models of VAP have been published in order to understand the mechanisms and clinical course of VAP in humans.²⁻⁴ However, none of them has reproduced the most prevalent human etiology or the primary pathogenic mechanism of the disease, that is, aspiration of oropharyngeal pathogens. In this issue of ANESTHESIOLOGY, Li Bassi *et al.*⁵ propose a novel experimental model of VAP in pigs that is induced *via* an oropharyngeal challenge of *P. aeruginosa* that may help to better understand the pathogenesis of VAP and possible therapeutic approaches to prevent and/or treat it in humans.

Recent clinical studies report an incidence from 2 to 16 episodes per 1,000 ventilator days and an attributable mortality of 3 to 17%. Furthermore, not only is VAP a major cause of morbidity, longer stays in the intensive care unit, and longer duration of mechanical ventilation, but it is also the reason for additional hospital costs of up to \$40,000 per episode.¹ Timely, adequate, and accurate administration of antibiotics is predictive of hospital survival; and alternate routes of administration, including aerosolized antibiotics, are being studied to augment treatment effect while diminishing unwanted side effects.^{4,6,7} Finally, it is clear that preventive strategies such as nurse-administered oral hygiene and “ventilator bundles” lower the rate of acquiring VAP.⁶ Given the factors listed above, finding a clinically relevant experimental



“This model closely mimics the human pathology of the disease in both etiology and mechanism[, and] will allow better efficacy testing of a variety of preventive measures for [ventilator-associated pneumonia] ...”

model that closely reflects the human pathogenesis of VAP is paramount to understanding what can be done to further prevent its occurrence and make treatment protocols more efficacious.

To date, numerous animal models of VAP have been published in different animal species.²⁻⁴ The description of the first animal model of nosocomial pneumonia in ventilated animals was published in the 1980s using baboons. With this primate model, the authors were able to confirm pneumonia with histological staining and lung cultures while also testing the effects of various antibiotics. Shortly thereafter, another experimental model of VAP was developed in pigs that had undergone mechanically induced tracheal stenosis and presented with bacterial pneumonia 4 days later.^{8,9} Although these models have enabled us to understand some of the mechanisms of pneumonia including, but not limited to, its pathogenesis, cellular/chemokine/cytokine responses and animal

response to various treatments, there are shortcomings to each of these large animal models of VAP. For instance, when pigs are intubated for a number of days, they will develop VAP, but the inciting pathogen is often *Pasteurella multocida* or *Streptococcus suis* rather than clinically relevant pathogens, such as *P. aeruginosa*. Additionally, there are large differences in underlying pulmonary injury (most patients do not have tracheal stenosis) and methods for bacterial inoculation.

Mouse models of pneumonia have also been used extensively by the scientific community.^{3,10} Mice are useful as a model of pneumonia for several reasons that include their small size, rapid reproductive rate, and laboratory practicality. While measuring bacterial load, mortality, immune responses,

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Corresponding article on page 1205.

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and transmission to other mice is relatively simple, there are some important limitations that include small lungs, a tracheo-bronchial tree that is significantly different than that of the human one, and variable deposition of bacteria in the lungs. In addition, there are genetically manipulated mouse models that may give further insight into the molecular mechanisms of pneumonia.¹⁰ Global knockout, gene overexpression, floxed mice, and conditional-expression systems allow investigators to look at specific genes, control when genes may or may not be present, and even control in which tissues or cells the gene might be present. However, these systems have limitations as well, such as Cre overexposure, leaky promoters, and gene expression (or lack thereof) in nonpulmonary organ systems whose alteration may affect lung or immune functions.

One of the most important limitations of the current animal models of VAP is that these models do not reproduce the primary pathogenic mechanism of the disease (aspiration of oropharyngeal pathogens). Li Bassi *et al.* propose, in the current issue of *ANESTHESIOLOGY*, a novel model of VAP that addresses this major limitation. In their model, pigs were intubated with an endotracheal tube with a Hi-Lo cuff and ventilated for 72 h. The pigs were placed in prone position in reverse Trendelenberg position at 30 degrees. The pigs were challenged orally with *P. aeruginosa* immediately after intubation and again 4 h later. Pigs were monitored for 72 h, sacrificed, autopsied, and histological and microbiological studies were performed to confirm VAP. The strengths of this model are multiple. First, pigs were challenged with a ceftriaxone-resistant *P. aeruginosa* strain (while receiving ceftriaxone) to help ensure pneumonia would develop with the desired microorganism. The second major strength of this model is that VAP occurs in pigs after oropharyngeal challenge. This novel model will allow further study about which types of endotracheal tubes, cuff pressure, and ventilator settings would be useful in decreasing the rate of VAP in humans. Finally, the location of VAP (referring to the right-lower and right-middle lobes of the lung) observed in this pig model is consistent with human pathology. Indeed, it is important to notice that in this model of VAP, the bacterial infection is not completely widespread to the whole lungs, another major limitation of previously published animal models of VAP. The lobar location of pneumonia in the new porcine model of VAP is consistent with human disease and, in particular, will help to better determine the efficacy of aerosolized and intravenous antibiotic treatment.

Although the pig model of VAP proposed by Li Bassi *et al.* is consistent with the human pathology of VAP in many different ways, there are some weaknesses to the model that should be pointed out. First, the authors used a tidal volume of 10 ml/kg and no positive end-expiratory pressure that are ventilator settings not usually used in humans. However, the authors point out that using even small tidal volumes and positive end-expiratory pressure may be injurious to porcine lungs. Therefore, in this porcine model, the use of a protective lung ventilation strategy may not change the incidence of VAP and may not tell us whether this approach could be useful to ventilate intensive care unit patients with VAP. Another weakness of this model is

the inability to demonstrate that the lungs were not seeded by direct inoculation. The authors have done their best to reduce this possibility by increasing the cuff pressure to 40 cm H₂O and adding positive end-expiratory pressure during the challenge and up to 1 h thereafter, although the model may require a better clarification of this point. However, a potential solution to this problem could be to quantify aspiration from the oropharyngeal challenge and confirm that VAP does indeed occur secondary to microaspiration of oropharyngeal contents, as suggested by a recently published study.¹¹ Finally, a new definition of ventilator-associated events has been developed in which the new definition of VAP is a probable lung infection that occurs at least 5 days after onset of mechanical ventilation.¹² Although VAP could be confirmed in the porcine model within 72 h after oropharyngeal bacterial challenge, the clinical course of this experimental VAP appears slightly different from that observed in critically ill patients. If it is feasible, the authors may want to consider slightly modifying their experimental protocol in order to meet the new definition of probable VAP in humans.

In conclusion, the novel porcine model of VAP proposed by Li Bassi *et al.* is an exciting new animal model that will provide investigators and clinicians with valuable information regarding the pathogenesis and clinical course of VAP. This model closely mimics the human pathology of the disease in both etiology and mechanism. In addition, this model will allow better efficacy testing of a variety of preventive measures for VAP including different endotracheal tubes, different cuff pressures, oral hygiene, as well as the relative efficacy of antibiotic or nonantibiotic treatments for this serious complication of mechanical ventilation in humans.

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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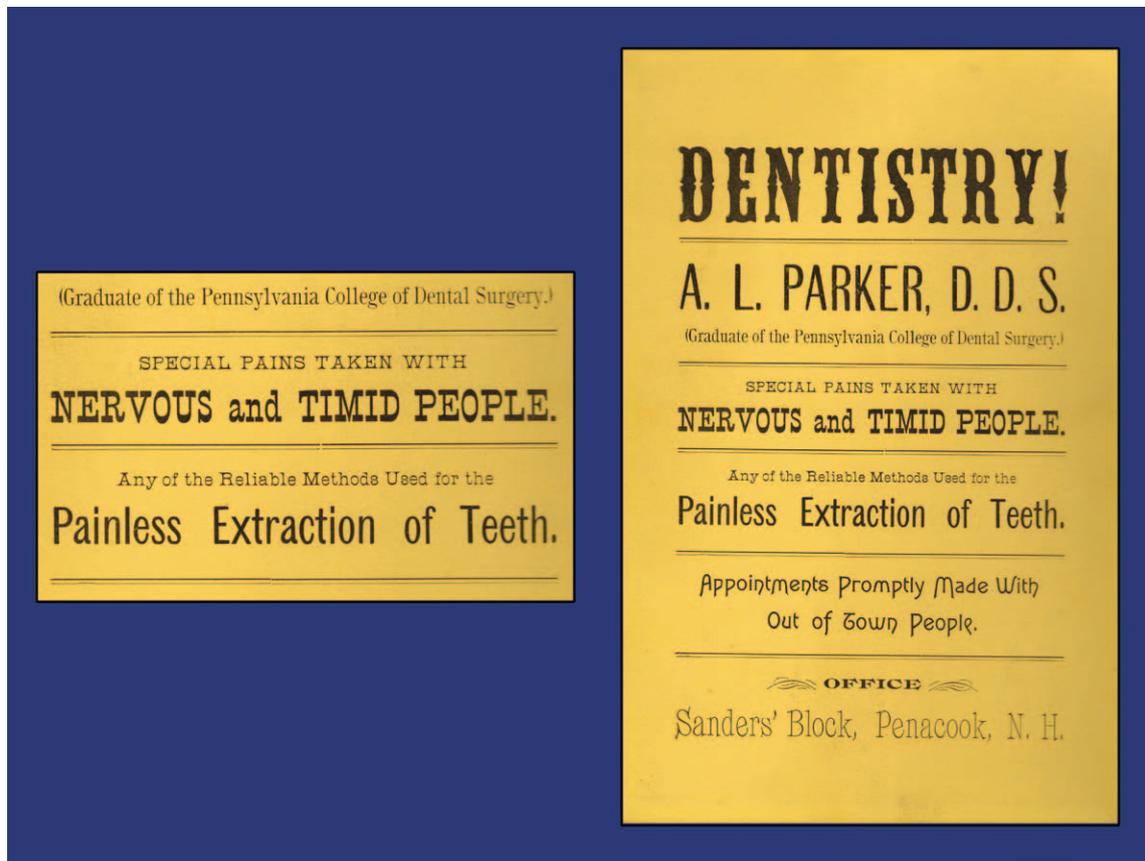
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A.L. Parker's Broadside: "Any... Painless" Anesthetic for Penacook



Arthur Linwood Parker, D.D.S. (1868–1917), directed this side of his Littleton/Penacook broadsheet at Penacook (*right*). For sophisticated villagers who lived there, outside New Hampshire's capital city of Concord, Parker cited the Pennsylvania College of Dental Surgery as his dental alma mater. Knowing that Penacookians expected more anesthetic choices than simply laughing gas, he advertised (*left*) that "Any of the Reliable Methods [are] Used for the Painless Extraction of Teeth." Having lost his first wife in Penacook, Parker had remarried in 1903. However, his personal and professional happiness were soon overtaken by a second tragedy. Parkinson's disease forced him out of dentistry by 1910 and eventually killed him 7 years later. This broadsheet is part of the Wood Library-Museum's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists, Inc.)

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