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Towards an Ecology of the Lung: New Conceptual Models of Pulmonary Microbiology and Pneumonia Pathogenesis

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Summary

Pneumonia is a major cause of morbidity and mortality for which no new methods of treatment have entered clinical practice since the discovery of antibiotics. Innovations in the techniques of culture-independent microbial identification have shown that the lungs, previously deemed sterile in the absence of infection, contain diverse and dynamic communities of microbes. In this Personal View, we argue that these observations have shown the inadequacy of traditional conceptual models of lung microbiology and the pathogenesis of pneumonia, hampering progress in research and practice. We propose three new conceptual models to replace the traditional models of lung microbiology: an adapted island model of lung biogeography, the effect of environmental gradients on lung microbiota, and pneumonia as an emergent phenomenon propelled by unexplored positive feedback loops. We argue that the ecosystem of lung microbiota has all of the features of a complex adaptive system: diverse entities interacting with each other within a common space, showing interdependent actions and possessing the capacity to adapt to changes in conditions. Complex adaptive systems are fundamentally different in behaviour from the simple, linear systems typified by the traditional model of pneumonia pathogenesis, and need distinct analytical approaches.

Introduction

A century ago, two decades after Pasteur's initial description of the pneumococcus,¹ Sir William Osler described pneumonia as “captain of the men of death”, the “most widespread and fatal of all acute diseases”, “a self-limited disease, which can neither be aborted nor cut short by any known means at our command”.² The subsequent discovery and development of antibiotics and vaccines improved the treatment and prevention of pneumonia, and its prominence as a major public health concern decreased in the second half of the 20th century.³ However, antibiotic development has stagnated, drug-resistant organisms are

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Declaration of interests

We declare that we have no competing interests.

increasingly common,⁴ and no novel treatment methods for management of pneumonia have been incorporated into practice since the beginning of antibiotic therapy 75 years ago. Respiratory infections remain a huge source of mortality and morbidity, responsible for a greater global burden of disease than are cancer, ischaemic heart disease, or diabetes.⁵

In the past decade, novel culture-independent techniques have shown that the lower respiratory tract, previously deemed sterile, contains diverse communities of microbes, even without clinical evidence of infection.⁶ Novel insights have shown a previously unappreciated complexity to lung microbiology and the pathogenesis of respiratory infections. We argue that the conventional model of the pathogenesis of pneumonia—the rapid growth of an invasive organism in a previously sterile area of the body—has proven inadequate for the appropriate contextualisation of observations from modern lung microbiome studies, and has probably hampered progress in treatment and prevention of pneumonia. The use of inappropriate conceptual frameworks results in imprecise terms, poorly framed debates, and confines the imaginations and approaches of researchers and clinicians.

In this Personal View, we propose three new concepts to replace the traditional models of lung microbiology that shape our understanding of pneumonia and its emergence from a previously healthy lung environment. These concepts include an adapted island model of lung biogeography, the effect of environmental gradients on lung microbiota, and pneumonia as an emergent phenomenon propelled by largely unexplored positive feedback loops. For each proposed conceptual model, we summarise the conventional method it is designed to replace, discuss our proposed model, review relevant published work, and provide areas of further study and potential implications for clinical care.

Conceptual model 1: an adapted island model of lung biogeography

Modern textbooks of pathology⁷ and clinical medicine⁸ follow the long tradition of dividing the anatomy of the respiratory tract and its associated infections into those of upper and lower compartments, typically defined as the airways and parenchyma above and below the larynx or trachea. The term pneumonia is often used interchangeably with lower respiratory tract infection.

The upper airways have long been known to be replete with diverse and abundant communities of microbes, but even recent textbooks have taught that “the normal lung is free from bacteria”.⁷ This claim of lower airway sterility stems from 130 years of our defining bacterial presence by our ability to culture organisms from tissue samples. In the past decade, new culture-independent techniques have called this conventional wisdom into question via greatly improved sensitivity in the identification of microbes. No study using modern techniques of molecular microbial identification has confirmed that the lower respiratory tract in healthy humans is sterile^{9–16}—microbial DNA is always detectable in respiratory samples. An active debate developed early in the study of the lung microbiome about how much of the microbial signal detected in lower respiratory tract specimens indicates a true lung microbiome, and how much instead indicates contamination via artifacts of tissue acquisition or periprocedural aspiration.¹⁷

We believe that the terms of this debate—are the lungs sterile and is there a unique lung microbiome?—presuppose the simplistic and outdated dichotomy of discrete compartments of the respiratory tract. We propose that a richer and more useful conceptual model can be derived from the equilibrium model of island biogeography proposed by MacArthur and Wilson in 1963.¹⁸ With this model, MacArthur and Wilson aimed to characterise and integrate the factors that define the number of plant and animal species (species richness) of islands. They observed that among the Pacific islands in what is now called Oceania, species richness was negatively correlated with distance from New Guinea (the nearest large land mass). MacArthur and Wilson speculated that proximity to a major land mass, the presumed source of each island's colonist ancestors, was the primary determinant of its immigration rate—the rate at which new species are introduced to an island's ecosystem. MacArthur and Wilson separately observed that the larger an island's land mass, the greater its species richness; they speculated that island size was the primary determinant of its extinction rate—the rate at which species go extinct. The integration of these two functions (immigration and extinction rates) on the same x-axis (figure 1A) provided a conceptual model that then enabled prediction of an island's species richness in various theoretical contexts (figure 1B).

Figure 1A and B show the elegance and usefulness of the island biogeography model. When an island has low species richness, the immigration rate from the species-rich zone (land mass) is high, because each arriving species is likely to be new. When an island's species richness is high, the immigration rate is low, because fewer of the arriving species are likely to be novel to the island. The immigration rate is zero when the species richness of the island equals that of the land mass that is the source of new species. The converse relationship is true for species extinction rates and species richness. In areas of low species richness, the extinction rate is low because of the small pool of potential species that might go extinct. As species richness increases, the number of potential species for extinction rises and competition among species for fixed resources increases, thereby leading to an increased extinction rate. Thus, a small island that is far from the mainland would be expected to have low species richness (figure 1B, **point X**); the opposite would be expected of a large island that is close to the mainland (figure 1B, **point Y**). For a particular island's set of conditions, a predicted equilibrium point of species richness exists (figure 1A, **S**), above or below which the system will return from if disturbed. Although the equilibrium point might be constant, the population of the island is dynamic, with a constant turnover of newly immigrated and extinct species.

Figure 1C and 1D show an adaption of this model to lung microbiology. For a given site along the respiratory tract, microbial species richness is a function of the immigration and extinction of microbes that originate in the upper airway. Microbial species are introduced to the lower airways via direct mucosal extension, microaspiration (which occurs commonly among even asymptomatic, healthy people^{19–21}), and inhalation of air (which contains 10^4 – 10^6 bacterial cells per cubic metre^{22–25}). The microbial species extinction rate at the same site is a function of cough (which is frequent even in healthy people without respiratory complaints^{26,27}), ciliary clearance, and the antimicrobial mechanisms of innate and adaptive immunity.

Figure 1D lists anatomical, physiological, and clinical factors that probably affect the slopes and y intercepts of lung microbial immigration and extinction curves. Factors such as close proximity to the larynx, increased oropharyngeal microbial burden, and laryngeal dysfunction probably increase the slope of the immigration curve. Factors such as impairment of the cough reflex, ciliary function, or innate and adaptive immunity probably decrease the slope of the extinction curve. Changes to any of these factors will reset an equilibrium point for species richness, as with the island model. Common clinical interventions might indirectly affect patients' equilibrium points via alterations in immigration rates (such as proton pump inhibitors, which affect the microbiota of the upper aerodigestive tract^{28, 29} and are positively associated with the development of pneumonia^{30–32}) or extinction rates (such as pentobarbital, which inhibits ciliary function,³³ or inhaled corticosteroids, which impair local host defenses^{34, 35} and are positively associated with the development of pneumonia³⁶).

An important limitation of this adapted island model is that it predicts only the effects of various factors on species richness—ie, the total number of species—and does not predict species evenness—ie, the relative populations of species within a community—nor total microbial burden. An analogous, but imperfect, model could be developed to predict microbial burden, which (like species richness) is affected by influx and efflux rates; however, at least in the instance of acute infection, microbial burden is probably affected by the local rate of bacterial reproduction, which is absent from the adapted island model. Despite these limitations, this model does provide a more substantial conceptual footing for hypotheses-testing and mechanistic investigation than do previous models, including the binary model implied by the question of whether the lungs are sterile during health.

Low microbial species richness in the gastrointestinal tract has been associated with obesity, insulin resistance, dyslipidaemia, systemic inflammation, and susceptibility to infection,^{37, 38} but the clinical significance of differences in microbial diversity in the lung has not been established. Studies that have examined the diversity of lung microbiota have compared microbial diversity of respiratory specimens from patients with respiratory diseases with that of specimens from healthy controls, often with conflicting results. For example, compared with that of healthy controls, microbial diversity in patients with COPD has been reported as increased,¹⁵ decreased,¹¹ and equivalent.¹⁶ Results of similar analyses have found microbial diversity to be increased³⁹ and decreased⁴⁰ in recipients of lung transplants. The effects of these diagnoses on lung microbial diversity are likely to be complex and multifactorial, but these conflicting results underscore the need for further study. Direct study of the effect of the factors listed in figure 1D would enable a more direct understanding of the contributors to lung microbial diversity and more consistent, predictable results. To our knowledge, no published studies have investigated associations between the factors shown in figure 1D and diversity of lung microbiota.

Conceptual model 2: the effect of environmental gradients on lung microbiota

As discussed in conceptual model 1, the respiratory tract has traditionally been divided into upper and lower compartments. In characterisation of the microbiology of lower respiratory

tract infections, modern textbooks and reviews list pulmonary pathogens collectively without specifying each microbe's predilection for specific regions of lung anatomy.^{7, 8, 41} With few conspicuous exceptions (aspiration pneumonia favouring dependent zones and reactivation tuberculosis favouring the apices), microbiologists and clinicians have traditionally treated the lower airways as a uniform and homogeneous compartment. Similarly, studies of lung microbiota using culture-independent techniques have largely treated the microbiota detected via bronchoalveolar lavage of single segments as representative of lung microbiota, and have not assessed regional variability in microbiota.⁶ However the two published studies that have compared the microbiota of several segments within the same patient have recorded profound spatial heterogeneity within the lungs (and even lobes) of individual patients.^{11, 42}

There is much physiological and anatomical rationale to suggest that the microbiota of the lung are not uniform. The internal surface area of the lungs is about 30 times that of the skin,⁴³ and the apices and bases differ substantially in relative blood perfusion, oxygen tension, and pH (figure 2A). Figure 2B shows that the temperature of the respiratory tract and the air it contains is not uniform, instead comprising a gradient from near that of inspired air (at the nares) to core body temperature (in the alveoli). Similarly notable differences are present in the regional structure of epithelial cells, presence of cilia, production of mucus, deposition of inhaled particles, and concentration and composition of inflammatory cells.^{47–49} All of these varying factors affect the habitability of the respiratory tract for microbial growth, and probably provide selective advantages for specific species when replication occurs. As mentioned, reactivation tuberculosis has a strong predilection for the apices (though this pattern is less uniform in patients with HIV⁵⁰), which confirms in principle and clinical experience the effect of regional lung differences on microbial growth.

We propose to adopt from ecology the concept of an environmental gradient: a gradual spatial change in an environmental factor such as temperature, salinity, or altitude. The relative species abundance of populations that live along environmental gradients can be strongly affected by these gradients. To use an influential example from ecology, figure 2C shows the results of an experiment in which the relative abundances of two diatoms, *Asterionella formosa* and *Cyclotella meneghiniana*, were accurately predicted by the environmental ratio of silicate to phosphate in different specimens of water collected from Lake Michigan (MI, USA). Analysis of the composition of existing populations in relation to their environmental gradients—ie, gradient analysis—can provide insight into the factors that promote the relative growth of individual species over others and the factors that affect the dynamics of a population. An application of gradient analysis to the microbiology of the lung would compare the local composition of microbial communities in the airways and alveoli with the environmental gradients mentioned (oxygen tension, pH, temperature, host anatomical and immune factors) and others that could be assessed empirically. This analysis could show the factors that affect microbial community structure as well as the factors that mediate the growth of individual species. A consistent relationship between an environmental gradient and a type of microbe would be a powerful argument that bacteria are not only present in the lower airways but are also actively reproducing and susceptible to selective pressure¹⁴—eg, between oxygen tension and the ratio of aerobic to anaerobic

bacterial genera present. An understanding of the relationships between environmental gradients in the lungs and microbial communities could lead to novel hypotheses about manipulation of lung environmental factors for therapeutic benefit and for prevention of infection.

Conceptual model 3: the lung microbial ecosystem is a complex adaptive system within which pneumonia is an emergent and disruptive phenomenon

The conventionally understood mechanism of pathogenesis of bacterial pneumonia is a natural extension of the tenet that the lungs are sterile: a suitably large inoculum of a pathogenic species enters the lower respiratory tract and overwhelms host defences, resulting in rapid and unrestrained growth of a bacterial species. Within this model, few factors should be all that is needed to predict the features of a given pneumonia: size of inoculum, virulence of the bacterial species, and strength of host defences. Changes in any of these three factors should yield proportionate and predictable changes in the frequency and severity of the pneumonia described. However, results of lung microbiome studies have shown the inadequacy of this reductionist, linear model of pneumonia pathogenesis. The pathogenic species that is isolated in a particular pneumonia is merely one of many with access to the lower respiratory tract, each with its own positive and negative growth factors. In many lung microbiome studies, pathogenic species (those that cause acute infections) are also identified in the microbiota of people with no infectious symptoms.^{11,12,51–53}

Consideration of the known mechanisms of bacterial growth and virulence shows the complexity of the system from which acute infection emerges. The growth of a single bacterial species at a single site in the lungs is a function of several factors: nutrient availability; other environmental elements that affect growth, such as temperature, pH, and oxygen tension; the intensity and characteristics of the host inflammatory response; small molecule-mediated interactions with host epithelial cells;⁵⁴ host production of antimicrobial peptides; indirect interactions with other bacterial species via competition for nutrients and ecological niches; direct interactions with other bacterial species via antimicrobial production (table 1); direct interactions with other bacteria via quorum-sensing molecules;⁵⁵ the dynamic influx and efflux of competing and conspiring bacterial species described in conceptual model 1; the presence, absence, or acquisition (via horizontal gene transfer or mutation) of virulence factors; and effect of co-exposure to respiratory viruses on all of these factors and the growth of selective bacterial populations.⁵⁶ Together, these various factors show that the ecosystem of lung microbiota has all the features of a *complex adaptive system*: diverse entities, interacting with each other within a common space, that exhibit interdependent actions and possess the capacity to adapt to changes in conditions.^{57, 58}

Complex adaptive systems are fundamentally different in behaviour from the simple and linear system typified by the traditional model of pneumonia pathogenesis. In linear systems, small changes in conditions result in proportionately small changes in outcomes. By contrast, the outcomes of complex adaptive systems can be profoundly altered by quite small changes in conditions. Whereas a linear system can be modelled by reduction of the

interactions of its elements to a series of differential equations, a complex adaptive system defies reductionist modelling and cannot be understood as a sum of regression analyses of the interactions of its parts.⁵⁹ System behaviour in a complex adaptive system is instead modelled via computational techniques such as agent-based modelling.⁶⁰ Complex adaptive systems give rise to emergent phenomena and phase transitions, in which order or patterns arise seemingly spontaneously (without central coordination)—eg, the formation of ant colonies,⁶¹ spontaneous traffic jams,⁶² and market crashes⁶³—as a consequence of innumerable simple interactions.

Ecosystems have long been recognised and analysed as “prototypical complex adaptive systems”.⁶⁴ When the ecosystem of lung microbiota is considered through this lens, a novel model of the pathogenesis of pneumonia emerges: pneumonia is an abrupt, emergent phenomenon of low microbial diversity, high microbial biomass, and host inflammation that arises from a pre-existing homeostasis of biodiversity. To adopt the language of physiology: if the microbiome is an organ,⁶⁵ acute infection is its decompensated state.

A common means by which order arises from complex systems is via the presence of feedback loops: negative feedback loops, by dampening the instigating signal, tend to promote homeostasis and stability; positive feedback loops, by amplifying the perturbing signal, tend to promote disruption and system instability. The uniform acuity of bacterial pneumonia (arising abruptly over hours to days rather than gradually over weeks to months, even in the absence of a gross aspiration event) bears the hallmark of an underlying positive feedback loop, with a growth-promoting signal that is progressively amplified once initiated. Analogous examples familiar to microbial ecologists include the positive feedback loops that underlie algal blooms⁶⁶ and quorum-sensing behaviour among bacteria.⁶⁷

In figure 3 we propose one of many potential positive feedback loops that might mediate the explosive and acute disruption in homeostasis noted in pneumonia. In homeostasis (in the absence of pneumonia), growth of a single bacterial species is inhibited by at least two tight negative feedback loops, shown by dotted lines at points A and E. Increased bacterial growth provokes increased local inflammation, which kills and clears bacteria, inhibiting further bacterial growth (A). Further, as a bacterial population grows it consumes its available nutrient supply, inhibiting its own subsequent growth (E). But if the provoked inflammation results in enough endothelial and epithelial injury (B) to cause leak of protein-rich and nutrient-rich fluid into the alveolar compartment (C),⁶⁸ the growth-limiting nutrient supply is restored (D) and bacterial growth is promoted (E). This provokes further inflammation, and the feedback loop is repeated, each time amplified with accelerating intensity.

We emphasise that this suggestion is only one of many potential positive feedback loops that might explain the abrupt emergence of pneumonia and the collapse of the lung ecosystem into a low-diversity (typically single-species-dominant), high-biomass state. A similar loop could be proposed using the production of mucus, which is increased in infection and provides another potential nutrient supply for growing bacterial communities. Catecholamines promote the in-vitro growth of many pneumonia-associated bacterial species, including *Streptococcus pneumoniae*⁶⁹ and many Gram-negative rods associated

with health care-associated pneumonia;^{70,71} host production of catecholamines in response to bacteria-induced inflammation could in turn accelerate bacterial growth. Quorum sensing has been used to explain the change in virulence in acute exacerbations of cystic fibrosis,⁵⁵ and could be present in other respiratory infectious processes.

Clinicians already tacitly acknowledge this proposed model in their diagnosis and management of health care-associated pneumonia (HCAP). The strongest risk factor for the development of ventilator-associated pneumonia (stronger even than duration of hospitalisation) was reported more than 20 years ago to be previous treatment with antibiotics.⁷² This observation is taken into account in guidelines for the definition and treatment of HCAP, for which recent antibiotic exposure, even without hospitalisation or nosocomial pathogen exposure, is sufficient to classify a patient's pneumonia as health-care associated rather than community-acquired, implying distinct microbial causes and empirical antibiotic regimens.⁷³ We argue that this observation and recommendation make little sense within the previous model of pneumonia pathogenesis. If the lungs are sterile in health, exposure to antibiotics should have no direct effect on lung microbiology and subsequent pneumonia risk; the association must be either an indirect effect via alteration of pharyngeal microbiota or secondary to some confounding factor, such as the patient's underlying predisposition to infection. However, we believe this clinical observation can be more directly and coherently explained within our proposed model: antibiotic exposure alters the pre-existing ecosystem of the lungs and airways and disrupts the homeostatic feedback loops that keep the complex system in a stable equilibrium. Until the ecosystem matures and restores its stabilising feedback loops, it is vulnerable to collapse via the outgrowth of a selectively favoured species. Clinicians will recognise this explanation as analogous to the well described pathogenesis of *Clostridium difficile* colitis after antibiotic administration.

There is already clinical data to support the hypothesis that therapeutic manipulation of the host microbiome might protect against infection. Several clinical trials, preliminary but promising, have shown a clinical benefit of enterically-administered probiotics (extrinsic microbes administered with therapeutic intent) on the prevention of respiratory infections. These include a randomised controlled trial in 146 patients on mechanical ventilation for whom the rate of ventilator-associated pneumonia was halved in the probiotic group (40% vs 19%),⁷⁴ and two randomised controlled trials, the results of which show decreased frequency of cystic fibrosis exacerbations in patients receiving probiotics.^{75, 76} In view of the anatomical and ecological continuity of the aerodigestive tract, enteric probiotics probably affect the composition and stability of lung microbial communities; modulation of the microbial ecosystem of the respiratory tract is one plausible explanation for the benefit observed in these preliminary trials.

Conclusion

The traditional conceptual models of lung microbiology are inadequate, as shown by observations using culture-independent techniques of bacterial identification. Using pivotal concepts from the fields of ecology and complexity theory, we have proposed three new conceptual models for the study of lung microbiology (table 2). These models provide a

theoretical framework for novel approaches to understanding of the pathogenesis, prevention, and treatment of respiratory infections.

Search strategy and selection criteria

We searched PubMed and Web of Science using the terms “((lung) OR (pulmonary)) AND ((microbiome) OR (16S) OR (pyrosequencing) OR (culture-independent))” with no date or language restrictions to identify relevant studies of the lung microbiome. We then manually screened titles and abstracts to exclude unrelated studies. We read all studies in human beings describing or reviewing bacterial communities in the lung in individuals with and without disease. In developing the conceptual models, we searched the same databases with the terms “(lungs) AND (model) AND (diversity)”, “(lungs) AND (biogeography)”, “(lungs) AND (regional) AND (microbiome)”, “(lungs) AND (environmental gradient) AND (bacteria)”, “(pneumonia) AND (complexity theory)”, and “(pneumonia) AND (emergent phenomenon)”.

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Key messages

- Novel techniques of culture-independent microbial identification have shown that the lungs, even in the absence of infection, contain diverse and dynamic communities of microbes
- These observations have shown the inadequacy of traditional models of lung microbiology and the pathogenesis of pneumonia
- Borrowing pivotal concepts from the fields of ecology and complexity theory, we propose three novel conceptual models of lung microbiology and pneumonia pathogenesis
- The respiratory tract is a single ecosystem extending from the nares to the alveoli, comprising a continuous, and continuously varying, microbial topography
- The number of microbial species at a given site in the respiratory tree is an integrated function of many immigration and extinction factors
- The lungs and airways are spatially heterogeneous in temperature, oxygen tension, pH, nutrient density, and local anatomy and host defence, all of which affect local microbiological growth conditions
- The development of pneumonia is an abrupt and emergent phenomenon of disruption in the complex homeostasis of the lung microbial ecosystem that results from undescribed positive feedback loops arising within a complex adaptive system

Figure 1. An adapted island model of lung biogeography

Immigration and extinction rates for an island as a function of number of species present (A). Effect of island size and proximity to large land mass on the intersection of immigration and extinction curves (B). Application of model to microbiota within the respiratory tract (C). Speculated positive immigration and negative extinction factors for lung microbiota (D). S=equilibrium of species richness. Figure 1A and 1B reproduced with permission from MacArthur and Wilson.¹⁸

A

B

C

Figure 2. Environmental gradients in the lungs

Regional differences in gas exchange in the upright lungs (A). Reproduced with permission from West.⁴⁴ Mean wall and air temperature in the tracheobronchial tree of human beings after hyperventilating cold air (B). Reproduced with permission from Ingenito.⁴⁵ Relative abundance of two diatoms (*Cyclotella* and *Asterionella*) in 78 samples of water from Lake Michigan, USA, plotted against ratio of ambient silicate to phosphate (C). Reproduced with permission from Tilman.⁴⁶ A.f. dominant=*Asterionella formosa* dominant. C.m. dominant=*Cyclotella meneghiniana* dominant.

Figure 3. Example of a potential positive feedback explaining the abrupt emergence of pneumonia from pre-existing homeostasis
Dotted lines indicate inhibition, resulting in negative feedback loops. Solid lines indicate promotion, resulting in a positive feedback loop. This is merely one of many possible feedback loops mediating the pathogenesis of pneumonia

Table 1

Antimicrobials of Microbial Origin

Antimicrobial Class	Microbial Source
Aminoglycosides	<i>Streptomyces spp.</i> (bacteria)
Aztreonam	<i>Chromobacterium violaceum</i> (bacteria)
Bacitracin	<i>Bacillus subtilis</i> (bacteria)
Carbapenems	<i>Streptomyces spp.</i> (bacteria)
Cephalosporins	<i>Acremonium spp.</i> (fungi)
Chloramphenicol	<i>Streptomyces spp.</i> (bacteria)
Colistin, polymyxin B	<i>Bacillus polymyxa</i> (bacteria)
Echinocandins	<i>Papularia sphaerosperma</i> (fungi)
Glycopeptides (e.g. vancomycin)	<i>Amycolatopsis orientalis</i> (bacteria)
Ivermectin	<i>Streptomyces spp.</i> (bacteria)
Lincosamides (e.g. clindamycin)	<i>Streptomyces spp.</i> (bacteria)
Lipopeptides (e.g. daptomycin)	<i>Streptomyces spp.</i> (bacteria)
Macrolides	<i>Streptomyces spp.</i> (bacteria)
Metronidazole	<i>Streptomyces spp.</i> (bacteria)
Mupirocin	<i>Pseudomonas fluorescens</i> (bacteria)
Oxazolidinones (e.g. linezolid)	<i>Streptomyces spp.</i> (bacteria)
Penicillins	<i>Penicillium spp.</i> (fungi)
Polyenes (e.g. amphotericin)	<i>Streptomyces spp.</i> (bacteria)
Rifampin	<i>Amycolatopsis rifamycinica</i> (bacteria)
Tetracyclines	<i>Streptomyces spp.</i> (bacteria)

Table 2

Research and Clinical Implications of New Conceptual Models

Conceptual Model	Model Summary	Questions for Study	Potential Clinical Implications
Model 1: An Adapted Island Model of Lung Biogeography	The respiratory tract is a single ecosystem extending from the nares to the alveoli, comprising a continuous, and continuously varying, microbial topography. The number of microbial species present at a given site in the respiratory tree is an integrated function of numerous immigration and extinction factors.	- How do various clinical and biological factors (Figure 1D) influence the immigration and extinction rates of microbial species in the respiratory tract? - What is the precise relationship between distance from the oropharynx and species richness? - Is there an “extinction point” some distance from the pharynx beyond which the extinction rate exceeds the immigration rate and the average species richness is zero? - Are the immigration and extinction rates for a given patient modifiable and associated with clinically important outcomes?	- For patients with recurrent or refractory respiratory infections, determine if the underlying pathology is a defect in <i>extinction</i> or <i>immigration</i> (Figure 1D). - When initiating interventions with predictable effects on immigration or extinction rates (e.g. dental extraction, proton pump inhibitors, inhaled corticosteroids, cough suppressants), consider their impact on a patient’s equilibrium point of species richness.
Model 2: The Influence of Environmental Gradients on Lung Microbiota	The lungs and airways are spatially heterogeneous with regard to temperature, oxygen tension, pH, nutrient density and local anatomy and host defense, all of which influence local microbiological growth conditions.	- How do environmental gradients in the lungs (e.g. oxygen tension, pH, temperature) relate to microbial community composition? - Does manipulation of these gradients (e.g. tracheostomy and airway temperature, therapeutic hypothermia, supine positioning, increased FiO₂) influence lung microbiota in predictable ways? - Does the emergence of a specific microbe or metagenomic signature from the lung microbiome signal that a specific regional change in airway physiology/ metabolism has occurred? - Do certain constellations of environmental conditions promote or inhibit stability of the microbial ecosystem of the lower airways?	- When patients develop focal respiratory infections, clinicians should consider which local environmental factors made the infected region of the lung selectively hospitable for that specific bacterial overgrowth. - When initiating therapies that alter the environmental gradients of the respiratory tract, clinicians should consider which bacterial species may be selectively favored by this environmental disruption and anticipate their growth in relative community abundance.
Model 3: Pneumonia as an Emergent Phenomenon in the Complex Adaptive System of the Lung Microbial Ecosystem	The development of pneumonia is an abrupt and emergent phenomenon of disruption in the complex homeostasis of the lung microbial ecosystem that results from as-of-yet undescribed positive feedback loops arising	- Can non-reductionist analytic techniques used in the study of complex adaptive systems, such as agent-based modeling, better characterize the homeostasis of lung microbiota and its abrupt erosion in pneumonia? - What are the mediators of the stabilizing and destabilizing	- Clinicians should minimize unneeded patient exposure to known mediators of pathogenic bacterial growth, such as systemic catecholamines^{69–71}, which may perpetuate the positive feedback loops of pneumonia development. - Clinicians should be aware of the impact of antibiotic administration on the dynamic

Conceptual Model	Model Summary	Questions for Study	Potential Clinical Implications
	within a complex adaptive system.	feedback loops of microbial reproduction in the lungs? • Can these identified mediators be used as potential therapeutic targets? • Why does a single dominant species emerge from the lung ecosystem in pneumonia, rather than nonspecific, polymicrobial growth? Do pathogenic species influence the growth of other microbes via direct (e.g. antimicrobial metabolite production) and indirect (e.g. nutrient consumption) interactions? • Are probiotics protective among patients at high risk for respiratory infections, as preliminary studies suggest⁷⁴⁻⁷⁶? If so, by what means?	equilibrium of the lung microbial ecosystem, and should consider HCAP a potential adverse consequence of antibiotic exposure (analogous to <i>C. difficile</i> colitis). • Clinicians should consider enteric probiotic administration in select patients at high risk for respiratory infections as a means of therapeutically modulating a dysbiotic respiratory ecosystem, though clinical data supporting this is preliminary.