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Articles selected and commented on by: Yuye Zhang and Yuanlin Song, Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, PR China
A small-molecule fusion inhibitor of influenza virus is orally active in mice.

Authors: van Dongen, et al.
URL: https://doi.org/10.1126/science.aar6221

Comments: Nowadays, the prevention and treatment of influenza is mainly based on seasonal influenza vaccines and a small amount of antiviral drugs, but because of the rapid evolution of viruses, the effectiveness of the vaccines is limited. Broadly neutralizing antibodies (bnAbs) could neutralize a wide range of viruses within and across influenza virus subtypes, but they are not widely used due to their inconvenience in administration and relatively high price. In this study, the authors identified an orally active small molecule against influenza A hemagglutinin which is a bnAbs CR6261-based designed small protein and mimics bnAb binding and functionality. Like bnAbs, the compound could also effectively neutralize a broad spectrum of influenza A viruses in vitro and protected mice from lethal and sub-lethal viral challenge. The compound could dramatically reduce the viral titers in a reconstituted three-dimensional cell culture of fully differentiated human bronchial epithelial cells. This compound has potential practical utility in the context of human airway infection. This compound provides hope for the development of universal vaccines for influenza infection.

Duration of antibiotic treatment for common infections in English primary care: cross sectional analysis and comparison with guidelines.

Authors: Pouwels KB, et al.
URL: https://doi.org/10.1136/bmj.l440

Comments: This is cross sectional study to evaluate the duration of prescriptions for antibiotic treatment for a wide range of common infections in English primary care and to compare this with guideline recommendations. This study shows that a substantial proportion of antibiotic prescriptions have durations exceeding those recommended in guidelines, especially for respiratory tract infections. Antibiotic treatments for respiratory indications accounted for more than two thirds of the total prescriptions considered, and 80% or more of these treatment courses exceeded guideline recommendations. The results indicate that unnecessary antibiotics use may be substantially reduced safely by aligning the course length more with guidelines. With the development of evidence-based medicine, access to guidelines is very easy. However, primary care institutions have very poor guideline adherence which causes a serious antibiotic overuse in primary care. Just as the author says, highlighting the magnitude of this issue is only a first step. We need to identify why doctors don’t follow the guidelines, and take effective measures to improve guideline adherence, which can radically reduce antibiotic abuse.

Authors: Burstein B, et al.
URL: https://doi.org/10.1001/jama.2018.9245
Comments: Bronchiolitis is one of the most common infectious diseases in children and the most common cause of hospitalization in infants. Clinical practice guidelines recommend that radiography should not be routinely obtained in the diagnosis of bronchiolitis because studies have shown that they do not affect clinical outcomes, but rather lead to antibiotics overdose and longer hospital stays. This study used a large representative sample of infants in emergency departments between 2007 and 2015 to do a longitudinal assessment of the proportion of infants diagnosed with bronchiolitis undergoing radiography. Unfortunately, there was no decrease in radiography by year (P for trend =.87), as confirmed in multivariable analysis (adjusted odds ratio for effect of year, 0.99 [95%CI, 0.91-1.08]). In spite of AAP bronchiolitis guidelines in 2006 and 2014 and Choosing Wisely recommendations in 2013, the results show that turning the guidelines into practice is very difficult and requires more nationwide support.

Effector T_{H17} Cells Give Rise to Long-Lived T_{RM} Cells that Are Essential for an Immediate Response against Bacterial Infection.

Authors: Amezcua Vesely MC, et al.
URL: https://doi.org/10.1016/j.cell.2019.07.032
Comments: This study focused on CD4 tissue resident memory T (T_{RM}) cells, and demonstrated the cellular origin of CD4 T_{RM} cells and their contribution to host defense to bacterial infections. The author combined the use of two complementary fate reporter mouse models, next-generation T cell receptor and single-cell sequencing approaches. By using an immunization-infection model with different serotypes of Klebsiella pneumoniae (Kp), they show that a significant fraction of the lung long-lived CD4 T_{RM} cells (exT_{H17} cells) derive from IL-17A-producing effector (T_{H17}) cells. They observed that exT_{H17} T_{RM} cells are maintained by IL-7, which is mainly produced by lymphatic endothelial cells in the lung. Finally, they reveal that exT_{H17} T_{RM} cells play essential roles that can resist an carbapenem-resistant strain of Kp. What’s more, they also found long-lived exT_{H17} cells after Candida albicans and Bacillus Calmette-Guérin infections, which means that the longevity and presence of T_{H17} effector derived T_{RM} cells may not only occur in the Kp infection but they are also generated in other infections where IL-17A plays an important role. In summary, their study describes the origin and function of airway CD4 T_{RM} cells during bacterial infection, and provides a new strategy for vaccine design of carbapenem-resistant Kp.
Omadacycline for Community-Acquired Bacterial Pneumonia.

Authors: Stets R, et al.
URL: https://doi.org/10.1056/NEJMoa1800201

Comments: Omadacycline is a new type of oral or intravenous antibiotic with broad-spectrum activity against gram-positive, gram-negative and atypical bacteria (Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae). This trial was a phase 3, double-blind, double-dummy, randomized, noninferiority trial of the drug conducted at 86 sites in Europe, North America, South America, the Middle East, Africa, and Asia involving community-acquired bacterial pneumonia. The results show that once-daily omadacycline, administered intravenously with the option to transition to oral administration, was noninferior to moxifloxacin with early clinical response as the primary efficacy end point. Drug-resistant infections are a health threat that has already occurred, and this threat will become more serious. Omadacycline overcomes the efflux and ribosomal protection mechanisms of tetracycline resistance, and does not have cross-resistance with beta-lactam antibiotics, polymyxins, aminoglycosides, and fluoroquinolones. However, patients which have infection with a suspected drug-resistant pathogen (e.g., fluoroquinolone-resistant Klebsiella pneumoniae) were excluded from the trial. Whether or not omadacycline is effective for the treatment of infections caused by carbapenem-resistant Enterobacteriaceae and species of Acinetobacter is still a question. It is difficult to study the synthesis and structure-activity relationship of antibiotics, and it is not easy to find new analogs such as Omadacycline that show non-inferiority. The chemical structure of Omadacycline differs from that of tigecycline, which was launched 10 years ago, only one carbonyl group, and the key pharmacophores of all tetracyclines have not changed. High-quality clinical trials are still needed to verify whether this innovation is likely to effectively cope with the invasion of super-resistant bacteria.
Dynamics of IFN-β Responses During Respiratory Viral Infection: Insights for Therapeutic Strategies.

Authors: Watson A, et al.


URL: https://www.atsjournals.org/doi/10.1164/rccm.201901-0214OC

Comments: In this study, the authors describe the dynamics of IFN-β activity in an in vitro model that mimics the prophylactic and therapeutic effects of exogenous IFN-β on virally infected cells. They used monocyte-derived macrophages (MDMs), alveolar macrophages (AMs) and primary bronchial epithelial cells (PBECs) isolated from healthy controls and COPD patients lung. The results show that exogenous IFN-β prophylaxis but not treatment modulates influenza infection of MDMs, AMs, and PBECs. They also investigated the duration of the IFN-β response and found that exogenous IFN-β modulates influenza infection in MDMs and PBECs 1 week and 72 h after its removal, respectively, although this effect was reduced compared to 24 h following infection. This study provides guidance for future applications of preventive use of exogenous IFN-β during viral seasons and explores the potential for repeated intermittent prophylactic doses of IFN-β, which in turn can be used to prevent exacerbations in both asthma and COPD.

Multiple Respiratory Microbiota Profiles Are Associated With Lower Airway Inflammation in Children With Protracted Bacterial Bronchitis.

Authors: Marsh RL, et al.


URL: https://doi.org/10.1016/j.chest.2019.01.002

Comments: The pathogenic mechanisms of protracted bacterial bronchitis (PBB) are still unclear about the disease recurrence and progression to bronchiectasis. This study evaluated the relationship between BAL microbiota, bacterial biomass, and inflammatory markers in children with PBB and age-matched control patients, in order to clarify contributions of ongoing airway infection and inflammation. The results show that neutrophilic inflammation in children with PBB was associated with culture of one or more respiratory pathogens. And there were significant associations between inflammatory markers and bacterial biomass, but not alpha diversity, suggest that inflammation in children with PBB cannot be attributed to single pathogenic species. This study provides a better understanding of about the airway microbiota and inflammation in children with PBB, and more research is needed to clarify the relationship between different PBB microbiota profiles and clinical outcomes to better guide clinical practice and prevent the PBB recurrence and progression.
**Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry.**

**Authors:** Dhar R, et al.

**Reference:** Lancet Glob Health. 2019 Sep;7(9):e1269-e1279.

**URL:** https://doi.org/10.1016/S2214-109X(19)30327-4

**Comments:** This is a multicentre, prospective, observational cohort study to describe characteristics, severity of disease, microbiology, and treatment of patients with bronchiectasis in India, and compare differences between India, Europe, and the USA. The results show that the disease characteristics of patients with bronchiectasis in India were quite different from those in Europe and the United States, which means that data from Europe and the United States might not be well applied to clinical practice in low-income and middle-income countries such as India. Indian patients were younger, more likely to be male, and exhibited high frequency of severe cystic bronchiectasis. Tuberculosis and other serious infections were the most frequently reported underlying causes. Risk factors for exacerbations included *Pseudomonas aeruginosa* infection, and a history of pulmonary tuberculosis. Indian patients had a high burden of symptoms and were admitted to the hospital frequently because of severe disease progression. Patients in India had poor adherence to guideline-recommended care, and could not currently receive evidence-based low-cost interventions such as chest physiotherapy. This is first published data for the burden of bronchiectasis in India, which could help to improve medical quality in India and other similar countries with a high prevalence of tuberculosis and severe respiratory infections.

**Precision mouse models with expanded tropism for human pathogens.**

**Authors:** Wahl A, et al.


**URL:** https://doi.org/10.1038/s41587-019-0225-9

**Comments:** The creation of human/mouse chimeric models (humanized mice) provides the possibility of related research on human-specific pathogens. However, current humanized mouse models primarily enable the analysis of pathogens that infect hematopoietic cells. In this study, they implanted human lung tissue subcutaneously into the back of immune-deficient mice to create humanized lung-only mice (LoM), and repopulated lung implants with autologous human innate and adaptive immune cells to create BLT-lung (BLT-L) mice. They also demonstrated that these models could support the infection and replication of important human viral and bacterial pathogens, such as MERS-CoV, ZIKV, mycobacteria, RSV and HCMV. These models could be used to verify the effect of human pathogens on human lung tissue, which in turn can aid in *in vivo* studies of treatment and preventive measures against these pathogens.
Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with Pseudomonas aeruginosa (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials.

Authors: Haworth CS, et al.
URL: https://doi.org/10.1016/S2213-2600(18)30427-2

Comments: This study investigated the safety and efficacy of inhaled liposomal ciprofloxacin (ARD-3150) for patients with non-cystic fibrosis bronchiectasis and chronic lung infection with Pseudomonas aeruginosa in two international, randomized, double-blind, placebo-controlled, phase 3 trials (ORBIT-3 and ORBIT-4) run concurrently in similar geographical regions. However, the results of the two clinical trials are inconsistent. ARD-3150 led to a statistically significantly longer median time to first pulmonary exacerbation compared with placebo in ORBIT-4, but not in ORBIT-3 or the pooled analysis. For subgroup analysis in ORBIT-3, ORBIT-4, and pooled analysis, patients with at least four pulmonary exacerbations in the past year had a greater reduction in pulmonary exacerbation frequency when treated with ARD-3150 versus placebo compared with patients with two or three pulmonary exacerbations in the past year, which indicates that patients with frequent pulmonary exacerbations are more likely to benefit from inhaled antibiotic treatment. The numbers of adverse events and serious adverse events were similar in both groups in ORBIT-3 and ORBIT-4. The primary endpoint of both ORBIT-3 and ORBIT-4 was time to first pulmonary exacerbation from the date of randomization to week 48. However, it is not a universally accepted endpoint. Because for a chronic disease with the potential for frequent pulmonary exacerbations, prolonged time to first pulmonary exacerbation may not a good representation for estimate the reduction in the number of pulmonary exacerbations. And it may be one underlying reason for the inconsistency between the results of two trials. Overall, ARD-3150 might provide benefit to patients with non-cystic fibrosis bronchiectasis with frequent pulmonary exacerbations, which provides guidance for patient selection in clinical practice. Further research is needed to find an appropriate outcome measures for inhaled antibiotics.

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Paediatric and Adult Bronchiectasis

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