Turning the Phage on Treatment of Antimicrobial-Resistant Pneumonia

Lower respiratory tract infections cause 79% of all infectious disease deaths in the United States each year (1). Many of these pneumonia deaths are from community-acquired pneumonia or severe viral pneumonia, but hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), continues to play a major role. Sixty-four percent of the infections being treated in the ICU on any single day are pneumonia (2).

The development of multidrug-resistant, extremely drug-resistant, and pandrug-resistant bacterial pathogens is forcing changes in the manual of nosocomial pneumonia treatment. For decades, the backbone of antibiotic treatment for serious gram-negative pneumonia has been a β-lactam (penicillins, cephalosporins, or carbapenems). Of particular concern with regard to antimicrobial-resistant (AMR) pneumonia are new and emerging carbapenem-resistant pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter* spp., and carbapenem-resistant Enterobacteriaceae.

Previous "new" chapters in AMR pneumonia treatment have really been edits of prior chapters—adding various β-lactamase inhibitors to address specific resistance mechanisms (3, 4), optimizing pharmacokinetic/pharmacodynamics to treat borderline resistance (5), and even aerosolizing antibiotics to address adverse tissue penetration issues (6). A rereading of truly early chapters has been needed to correctly dose colistin and be reminded of its associated nephrotoxicity (4). Not since linezolid came on the market has a truly new class of antibiotics for HAP/VAP been introduced. The availability of this class of drugs has resulted in substantially less concern regarding the adequacy of treatment for methicillin-resistant *S. aureus* (MRSA) HAP/VAP (7) and the rare vancomycin-resistant Enterococcal pneumonia in immunocompromised patients.

Two complementary studies published in this issue of the *Journal* suggest that we may be turning the page to a truly new chapter of AMR pneumonia treatment. Both papers demonstrate the potential and the limitations of lytic bacteriophage therapy for pneumonia owing to AMR pathogens. In contrast to the more common temperate phages, which integrate into the host bacterial chromosome as prophages, lytic phages are rapidly bactericidal. In this issue of the *Journal*, Prazak and colleagues (pp. 1126–1133) present a comprehensive evaluation of the benefit of an intravenous cocktail of four bacteriophages in a mouse MRSA pneumonia model (8). They demonstrate that the phage cocktail was equivalent to treatment with teicoplanin, a glycopeptide equivalent to vancomycin. Unfortunately, neither additive nor synergistic effects of combination antibiotic and phage therapy were demonstrated. In contrast to the disappointing results of the animal study, Maddocks and colleagues (pp. 1179–1181) report a case of multilobar cavitary extremely drug-resistant *Pseudomonas* VAP, complicated by an infected bronchopleurocutaneous fistula, that responded dramatically to both intravenous and aerosol treatment with a customized four-phage cocktail (9). Not only did the patient respond clinically, but repeat sampling could not detect any further *P. aeruginosa*. A beneficial response of this degree is virtually unknown with conventional antibiotic treatment.

Some would claim that phage therapy is the oldest chapter in the treatment of bacterial infections, dating back to work during the preantibiotic era in Russia. However, research at that time was never challenged by AMR pathogens, and antibiotic therapy rightly eclipsed phage therapy because it showed equal or greater efficacy and was substantially easier to administer, as was shown in the mouse model (8). Conversely, phage involvement in human bacterial pneumonia has likely been occurring occultly for years. Shotgun metagenomic sequencing of BAL fluid from a culture-positive pneumonia occasionally reveals lytic bacteriophages (10). The occult presence of bacteriophages may explain some of the variable response to antibiotic treatment in AMR HAP/VAP.

The challenges of phage therapy for AMR pneumonia are not insignificant. A great advantage of phage therapy is its high specificity; however, this approach requires a more accurate etiologic diagnosis than is currently used for broad-spectrum antibiotics. Even a clear-cut pneumonia diagnosis may be required, as Prazak and colleagues found that phages did not appear in the lung without the presence of pneumonia, and instead were cleared by the spleen (8). Whether tracheal colonization or even purulent tracheobronchitis would respond to phage therapy is questionable.

Although they are generally specific, some *S. aureus* bacteriophages can also infect other gram-positive bacteria, including other staphylococci and streptococci. Because streptococci are a common component of the normal lung and upper-respiratory microbiomes (11), the effect of a large therapeutic inoculum of an *S. aureus* lytic phage on the lung microbiome is currently unclear and a potential limitation of therapy. However, a *Pseudomonas* phage poses substantially less concern in this regard.

Just as with antibiotics, susceptibility testing is required for phage therapy. This is currently only available at specialized centers and requires growth of the actual pathogen before submission to these centers. Phage therapy will take longer than the current delay in antibiotic susceptibilities and will not be immediately available for patients with HAP/VAP who are in septic shock. Logistics will therefore be a major limitation for early adoption.

Concerns about the development of resistance over time with monotherapy led to the use of multiphage cocktails in both studies. A multiphage approach clearly limits this development of resistance (*see* Figure E1 in the online supplement of Reference 8). Bacteria have a repertoire of antiphage responses that likely exceeds that of antibacterial strategies, given the much longer exposure in nature. The emergence of resistance was found to be a cause of treatment failure in a wound infection study, one of the very few randomized controlled trials of phage treatment to be conducted in humans (12). The bacterial clearance in the *Pseudomonas* pneumonia case despite the likely high bacterial load is therefore that much more impressive (9).

The optimal method for delivering phage therapy for pneumonia is also unclear. Addition of aerosolized phages resulted

Originally Published in Press as DOI: 10.1164/rccm.201908-1561ED on August 27, 2019

in dramatic bacterial clearance in the *Pseudomonas* case (9), but intravenous-only administration did not result in eradication of MRSA in the experimental model (8). A higher lung necrosis score was associated with nonsurvival (*see* Figure E3 in Reference 8), raising concerns about intravenous delivery of both phage and antibiotic to the lumen of cavitary pneumonia. Phage therapy is not neutral for the host: phages may transcytose host cells and stimulate Toll-like receptor 9 and other pattern recognition molecules (13). Generally, phage infusions or mucosal applications are well tolerated without an inflammatory signal, as was seen in the mouse model (8). More importantly, neutralizing antibodies are common in individuals exposed to naturally occurring phages, and may blunt the benefit of intravenous therapeutic phage therapy. Because aerosolization is less likely to induce neutralizing antiphage antibodies and less likely to be blunted by preformed antibodies, this route may be preferred for pneumonia treatment in the critically ill.

Validation of the benefit of routine phage treatment of AMR pneumonia requires much more work. Only further data will demonstrate whether phage therapy is truly a new chapter in pneumonia treatment or just another interesting footnote. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Richard G. Wunderink, M.D.
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

ORCID ID: 0000-0002-8527-4195 (R.G.W.).

References

1. El Bcheraoui C, Mokdad AH, Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, Morozoff C, *et al*. Trends and patterns of differences in infectious disease mortality among US counties, 1980-2014. *JAMA* 2018;319: 1248–1260.
2. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, *et al*.; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;302:2323–2329.
3. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, *et al*. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis* 2018;18: 285–295.
4. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J, *et al*. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. *Infect Dis Ther* 2018;7:439–455.
5. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. *Nat Rev Microbiol* 2004;2:289–300.
6. Kollef MH, Ricard JD, Roux D, Francois B, Ischaki E, Rozgonyi Z, *et al*. A randomized trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of Gram-negative ventilator-associated pneumonia: IASIS Trial. *Chest* 2017;151:1239–1246.
7. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, *et al*. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis* 2012;54:621–629.
8. Prazak J, Iten M, Cameron DR, Save J, Grandgirard D, Resch G, *et al*. Bacteriophages improve outcomes in experimental *Staphylococcus aureus* ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2019;200:1126–1133.
9. Maddocks S, Petrovic Fabijan A, Ho J, Lin RCY, Ben Zakour NL, Dugan C, *et al*. Bacteriophage therapy of ventilator-associated pneumonia and empyema caused by *Pseudomonas aeruginosa* [letter]. *Am J Respir Crit Care Med* 2019;200:1179–1181.
10. Qi C, Hountras P, Pickens CO, Walter JM, Kruser JM, Singer BD, *et al*. Detection of respiratory pathogens in clinical samples using metagenomic shotgun sequencing. *J Med Microbiol* 2019;68: 996–1002.
11. Charlson ES, Bittinger K, Haas AR, Fitzgerald AS, Frank I, Yadav A, *et al*. Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med* 2011;184:957–963.
12. Jault P, Leclerc T, Jennes S, Pirnay JP, Que YA, Resch G, *et al*. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect Dis* 2019;19: 35–45.
13. Van Belleghem JD, Dąbrowska K, Vaneechoutte M, Barr JJ, Bollyky PL. Interactions between bacteriophage, bacteria, and the mammalian immune system. *Viruses* 2018;11:E10.

Another Warning Sign: High Nicotine Content in Electronic Cigarettes Disrupts Mucociliary Clearance, the Essential Defense Mechanism of the Lung

Electronic cigarette (e-cigarette) usage has become popular at an alarming rate and continues to rise, especially among younger populations in the United States. In 2018 alone, there was an ~40% increase in usage (from 12% to 21%) compared with 2017 among high school students, according to a recent Centers for Disease Control and Prevention report (1). Many incorrectly believe that smoking e-cigarettes (vaping) is not harmful to health. The general misconception by the public that "e-cigarettes are safe," however, has been challenged or overturned by many recent studies revealing the association between e-cigarettes and adverse cardiovascular, pulmonary, and systemic health effects.

As a nicotine delivery system, e-cigarette liquids typically contain *1*) a vehicle (propylene glycol/vegetable glycerin [PG/VG]), *2*) a chemical that gives an appealing flavor, and *3*) various

Supported by the NIH/NHLBI/FDA (P50HL120100).

Originally Published in Press as DOI: 10.1164/rccm.201905-1080ED on June 14, 2019