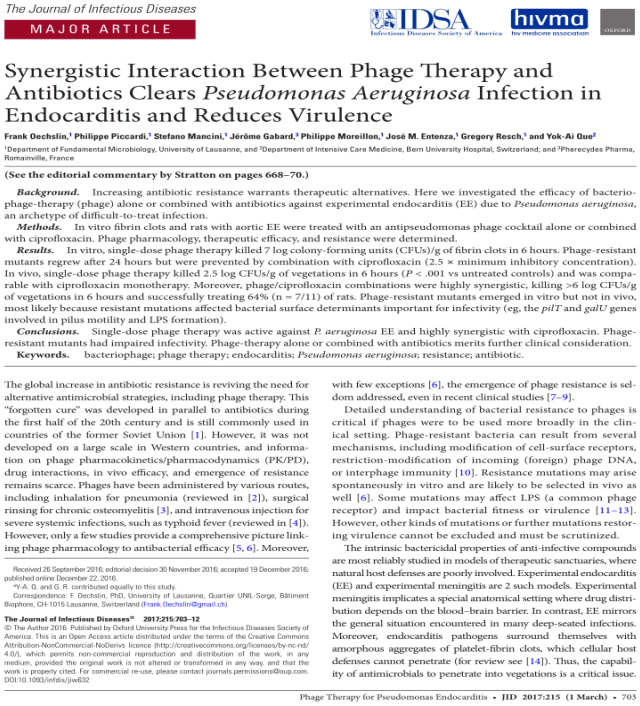
Pseudomonas Aeruginosa Infections and Treatment (Infectious Disease and Therapy)



The Journal of Infectious Diseases
MAJOR ARTICLE

Synergistic Interaction Between Phage Therapy and Antibiotics Clears *Pseudomonas Aeruginosa* Infection in Endocarditis and Reduces Virulence

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(See the editorial commentary by Stratton on pages 668–70.)

Background. Increasing antibiotic resistance warrants therapeutic alternatives. Here we investigated the efficacy of bacteriophage-therapy (phage) alone or combined with antibiotics against experimental endocarditis (EE) due to *Pseudomonas aeruginosa*, an archetype of difficult-to-treat infection.

Methods. In vitro fibrin clots and rats with aortic EE were treated with an antipseudomonas phage cocktail alone or combined with ciprofloxacin. Phage pharmacology, therapeutic efficacy, and resistance were determined.

Results. In vitro, single-dose phage therapy killed 7 log colony-forming units (CFUs)/g of fibrin clots in 6 hours. Phage-resistant mutants regrew after 24 hours but were prevented by combination with ciprofloxacin (2.5 × minimum inhibitory concentration). In vivo, single-dose phage therapy killed 2.5 log CFUs/g of vegetations in 6 hours ($P < .001$ vs untreated controls) and was comparable with ciprofloxacin monotherapy. Moreover, phage/ciprofloxacin combinations were highly synergistic, killing >6 log CFUs/g of vegetations in 6 hours and successfully treating 64% (n = 7/11) of rats. Phage-resistant mutants emerged in vitro but not in vivo, most likely because resistant mutations affected bacterial surface determinants important for infectivity (eg, the *pilT* and *galU* genes involved in pilus motility and LPS formation).

Conclusions. Single-dose phage therapy was active against *P. aeruginosa* EE and highly synergistic with ciprofloxacin. Phage-resistant mutants had impaired infectivity. Phage-therapy alone or combined with antibiotics merits further clinical consideration.

Keywords. bacteriophage; phage therapy; endocarditis; *Pseudomonas aeruginosa*; resistance; antibiotic.

The global increase in antibiotic resistance is reviving the need for alternative antimicrobial strategies, including phage therapy. This "forgotten cure" was developed in parallel to antibiotics during the first half of the 20th century and is still commonly used in countries of the former Soviet Union [1]. However, it was not developed on a large scale in Western countries, and information on phage pharmacokinetics/pharmacodynamics (PK/PD), drug interactions, in vivo efficacy, and emergence of resistance remains scarce. Phages have been administered by various routes, including inhalation for pneumonia (reviewed in [2]), surgical rinsing for chronic osteomyelitis [3], and intravenous injection for severe systemic infections, such as typhoid fever (reviewed in [4]). However, only a few studies provide a comprehensive picture linking phage pharmacology to antibacterial efficacy [5, 6]. Moreover, with few exceptions [6], the emergence of phage resistance is seldom addressed, even in recent clinical studies [7–9].

Detailed understanding of bacterial resistance to phages is critical if phages were to be used more broadly in the clinical setting. Phage-resistant bacteria can result from several mechanisms, including modification of cell-surface receptors, restriction-modification of incoming (foreign) phage DNA, or interphage immunity [10]. Resistance mutations may arise spontaneously in vitro and are likely to be selected in vivo as well [6]. Some mutations may affect LPS (a common phage receptor) and impact bacterial fitness or virulence [11–13]. However, other kinds of mutations or further mutations restoring virulence cannot be excluded and must be scrutinized.

The intrinsic bactericidal properties of anti-infective compounds are most reliably studied in models of therapeutic sanctuaries, where natural host defenses are poorly involved. Experimental endocarditis (EE) and experimental meningitis are 2 such models. Experimental meningitis implicates a special anatomical setting where drug distribution depends on the blood–brain barrier. In contrast, EE mirrors the general situation encountered in many deep-seated infections. Moreover, endocarditis pathogens surround themselves with amorphous aggregates of platelet-fibrin clots, which cellular host defenses cannot penetrate (for review see [14]). Thus, the capability of antimicrobials to penetrate into vegetations is a critical issue.

Received 26 September 2016; editorial decision 30 November 2016; accepted 19 December 2016; published online December 22, 2016.
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The Journal of Infectious Diseases® 2017;215:703–12

DOI:10.1093/infdis/jiw632

Pseudomonas Aeruginosa Infections and Treatment (Infectious Disease and Therapy) [Aldona L. Baltch, Raymond P. Smith] on rutaciclistacastillosybatallas.com *FREE* shipping.Pseudomonas aeruginosa infections may be effectively treated with phage therapy. The results from this study demonstrated that phage therapy was an effective treatment against P. aeruginosa in chronic lung infections and in a cystic fibrosis lung-type environment.Two antipseudomonal drug combination therapy (eg, a beta-lactam antibiotic with an aminoglycoside) is usually recommended for the initial empiric treatment of a pseudomonal infection, especially for patients with neutropenia, bacteremia, sepsis, severe upper respiratory infections (URIs), or abscess formation.processing. Drugs & Diseases > Infectious Diseases. Pseudomonas aeruginosa Infections Treatment & Management. Updated: Dec 01, Author: Marcus.Pseudomonas aeruginosa has become an important cause of gram-negative infection, especially in patients with compromised host defense mechanisms. It is the most common pathogen isolated from patients who have been hospitalized longer than 1 week, and it is a frequent cause of nosocomial infections.The principles of antimicrobial treatment of infections caused by P. Safety Network at the Centers for Disease Control and Prevention, Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical.The optimal treatment strategies for P. aeruginosa infection are still . obtaining samples from young patients, or those with milder disease.Pseudomonas aeruginosa (P. aeruginosa) is an aerobic, . of 12 patients with MDR P. aeruginosa infections, salvage therapy with Note: This is an edited version of an upcoming paper in Current Infectious Diseases Reports. in the treatment of complicated intra-abdominal infection: results from a.Most pseudomonads known to cause disease in humans are associated with opportunistic Pseudomonas aeruginosa infection is a serious problem in patients In burn patients, topical therapy of the burn with antimicrobial agents such as .. to treat severe Pseudomonas infections, especially in patients with leukopenia.Antimicrobial therapy for pulmonary pathogenic colonisation and infection by Treatment of patients following the first isolation of P. aeruginosa, but with no Oral ciprofloxacin is recommended for patients with mild pulmonary disease.Most of the infections caused by P. aeruginosa are strikingly difficult to treat using .. therapy: a revitalized therapy against bacterial infectious diseases. J Infect.Infections caused by multidrug-resistant Pseudomonas aeruginosa Infections were classified according to the criteria of the Centers for Disease Control and of ceftolozane-tazobactam treatment as salvage therapy for MDRPA infection.Single-dose phage therapy was active against P. aeruginosa EE and This forgotten cure was developed in parallel to antibiotics during the quantified prior to infection (24 hours after surgery), prior to therapy (18 .. Supplementary materials are available at The Journal of Infectious Diseases online.Chronic infection leads to progressive lung disease in cystic fibrosis, frequently .. when choosing empiric therapy for treatment of P. aeruginosa infections.Pseudomonas aeruginosa is a major cause of nosocomial infections. Empirical treatment usually involves combination therapy, selected on the .. the American

Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA).extensive therapy to master the infection. Pseudomonas Infection in the Immunosuppressed or patients with these diseases and cures may be anticipated.