The Enemy of My Enemy: 
Bacteriophage Therapy to Treat Multi-drug Resistant Bacterial Infections

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Harold Simon Distinguished Professor, 
Co-director, IPATH

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Senior Director, International Initiatives, UC San Diego 
Distinguished Professor, 
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Disclosures

• Steffanie Strathdee holds stock in Adaptive Phage Therapeutics.

• All patient photos shown are used with permission.
# Uniklinick Antibiogramm

**Name:** Patterson  
**Vorname:** Thomas Leroy (M)  
**Geb. Datum:** *18.02.1947*

### Anforderung:
Mikrobiologische Untersuchung

### Befund:

1. **Acinetobacter baumannii (4MRGN)** vereinzelt  
   *Keine Spezies-spezifischen Grenzwerte vorhanden.*

2. **Candida albicans** reichlich

3. **Candida glabrata** reichlich  
   Das Antymykogramm siehe Befund 61569953.

### Bemerkung/Bewertung:
Die anaeroben Kulturen werden weiterbebrütet. Nur im positiven Falle erhalten Sie einen erneuten Befund.  
Telefonische Befunddurchsage erfolgte am 10.12.2015 um 10:03 Uhr  
Faxmitteilung erfolgte am 10.12.2015 um 10:17 Uhr  
4MRGN: Multiresistentes gramnegatives Stäbchenbakterium mit Resistenz in 4 Antibiotikagruppen (KRINKO-Definition).  
Aufgrund der Meldepflicht nach Hessischer Verordnung für besondere Antibiotikaresistenz ist dieser Befund an das Amt für Gesundheit gemeldet worden.

### Antibiogramm

<table>
<thead>
<tr>
<th>Keim</th>
<th>1</th>
<th>MHIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazidim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td>&gt;=32</td>
</tr>
<tr>
<td>Gantamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td>&gt;=256</td>
</tr>
<tr>
<td>Co-Trimoxazol</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Fosfomycin i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciproflaxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minocyclin</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Colistin</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ampicillin/Sulbactam</td>
<td></td>
<td>&gt;=256</td>
</tr>
</tbody>
</table>

### Antymykogramm

<table>
<thead>
<tr>
<th>Keim</th>
<th>3</th>
<th>MHIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>S</td>
<td>1,125</td>
</tr>
</tbody>
</table>

### Erläuterung:
*S = sensibel, I = intermediär, R = resistent  
Numerische Angaben sind MHIK in µg/ml
By 2050, Superbugs Could Kill 10 Million People a Year

Will cost $100 trillion to the global economy through loss of productivity

Source: Review On Antimicrobial Resistance
Emerging therapies for multidrug resistant *Acinetobacter baumannii*

Meritxell García-Quintanilla*, Marina R. Pulido*, Rafael López-Rojas, Jerónimo Pachón, and Michael J. McConnell

Unit of Infectious Disease, Microbiology, and Preventive Medicine, Institute of Biomedicine of Sevilla (IBIS), University Hospital Virgen del Rodeo/CSIC/University of Sevilla, 41013, Sevilla, Spain

The global emergence of multidrug resistant *Acinetobacter baumannii* has reduced the number of clinically available antibiotics that retain activity against this pathogen. For this reason, the development of novel prevention and treatment strategies for infections caused by *A. baumannii* is necessary. Several studies have begun to characterize nonantibiotic approaches that utilize novel mechanisms of action to achieve antibacterial activity. Recent advances in phage therapy, iron chelation therapy, antimicrobial peptides, prophylactic vaccination, photodynamic therapy, and nitric oxide (NO)-based therapies have all been shown to have activity against *A. baumannii*. However, before these approaches can be used clinically there are still limitations and remaining questions that must be addressed.

**Phage therapy**

Bacteriophages, or phages, are viruses that infect, and in some cases lyse, bacterial cells. The potential use of bacteriophages as antibacterial agents was recognized at almost the same time as their discovery nearly a century ago [9]. However, the dawn of the antibiotic era slowed interest in this area in western countries. In the present context of infections caused by multidrug-resistant bacteria for which there are a decreasing number of active antimicrobials, research exploring the use of phage therapy as an alternative treatment has been renewed in 2010.

Trends in Microbiology, 2013
Early Pioneers

Charles Hankin

Bronislaw Fejgen

Felix d’Herelle

Frederick Twort

Nicolai Gamaleya

Giorgi Eliava

Phage Therapy Unit
Wrocław, Poland
Thanks to PENICILLIN
...He Will Come Home!
The Phage Hunt Begins...

Dr Ry Young

Texas A&M- Center for Phage Technology
Contacting the FDA....

Dr Robert (Chip) Schooley, UCSD

Dr Cara Fiore, FDA
US Navy Biological Defense Research Directorate

Photo Courtesy of the Naval Medical Research Center
The Endotoxin Issue:
San Diego State University to the Rescue

Anca Segall, PhD

Forest Rohwer, PhD

Jeremy Barr, PhD
The Dosing Dilemma

How much phage to administer?

What routes?

How often?

How long?
<table>
<thead>
<tr>
<th>Bacteriophage cocktail (AB1, AB4, AB7, AB17 phages)</th>
<th>5 x 10^9 in 5 mL lactated ringers, IV bolus only</th>
</tr>
</thead>
</table>

**Route:** Intravenous  
**Due Time:** 3/18/18 0900  
**Pharmacy instruction:** Obtain 0.5 mL of 1x 10^11 PFU/mL

*Note: Properly handle as hazardous agent*
Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection

Schooley et al, AAC, 2017
Tom’s A.baumannii isolate being attacked by Navy phages

Courtesy of Dr. Robert Pope, National Biodefense Analysis & Countermeasures Center, Dept of Homeland Security
Could gargling a virus that eats bacteria solve the SUPERBUG CRISIS? As overused antibiotics become less and less effective, a tantalising discovery may revolutionise healthcare

- Stefanie Stratford feared the worst when husband Tom Patterson comatose
- Husband of 15 years lay in a deep coma, the victim of an aggressive superbug.
- His heart, lungs and major organs were all shutting down with little hope left.
- A previously unknown recovery to result of natural phenomenon that could combat growth of antibiotic-resistant infections and also treat sore throats.
U.S. center will fight infections with viruses
Proving ground for phage therapy will organize full clinical trials of the approach
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Underlying Condition</th>
<th>Organism</th>
<th>Start Date</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>Disseminated infection</td>
<td>A. Baumannii</td>
<td>May 2016</td>
<td>Treatment success</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>Bilateral lung transplant</td>
<td>P. Aeruginosa</td>
<td>May 2017</td>
<td>Treatment success</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>Open head trauma</td>
<td>A. Baumannii</td>
<td>June 2017</td>
<td>Treatment success</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>CF; pre lung transplant</td>
<td>P. Aeruginosa</td>
<td>September 2017</td>
<td>Treatment success</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>Infected LVAD</td>
<td>P. aeruginosa +</td>
<td>December 2017</td>
<td>Failure</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>Infected LVAD</td>
<td>S. Aureus</td>
<td>April 2018</td>
<td>Treatment success</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>Infected left knee prosthesis</td>
<td>S. Aureus</td>
<td>March 2019 September 2019</td>
<td>First treatment failed, second treatment success</td>
</tr>
<tr>
<td>8</td>
<td>83</td>
<td>Infected LVAD</td>
<td>P. aeruginosa</td>
<td>August 2019</td>
<td>Treatment failure, patient passed away</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>Recurrent UTI</td>
<td>ESBL E. coli</td>
<td>February 2020</td>
<td>Partial success</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>Recurrent bacteremia, aortic graft infection</td>
<td>P. Aeruginosa</td>
<td>March 2020</td>
<td>Treatment success</td>
</tr>
<tr>
<td>11</td>
<td>65</td>
<td>Bacteremia</td>
<td>ESBL E. Coli</td>
<td>July 2020</td>
<td>Outcome pending</td>
</tr>
<tr>
<td>12</td>
<td>77</td>
<td>Lung infection</td>
<td>P. aeruginosa</td>
<td>September 2020</td>
<td>Outcome pending</td>
</tr>
</tbody>
</table>
Phage Therapy for Limb-threatening Prosthetic Knee Klebsiella pneumoniae Infection: Case Report and In Vitro Characterization of Anti-biofilm Activity

Successful Treatment of Antibiotic-resistant, Poly-microbial Bone Infection With Bacteriophages and Antibiotics Combination

Successful adjunctive use of bacteriophage therapy for treatment of multidrug-resistant *Pseudomonas aeruginosa* infection in a cystic fibrosis patient

A Case Series of Emergency Investigational New Drug Applications for Bacteriophages Treating Recalcitrant Multi-drug Resistant Bacterial Infections: Confirmed Safety and a Signal of Efficacy

Bacteriophage Application for Difficult-To-Treat Musculoskeletal Infections: Development of a Standardized Multidisciplinary Treatment Protocol
Phage Referrals to IPATH

All referrals from 6/1/2018-9/30/2021 N=1,171

Viral Infection: 9
Non-infectious etiology: 45
Non-medical conditions: 78
Incomplete details: 51
Not indicated: 784

Phage Hunt Recommended: N=204
No isolate Provided: 34

Phage Hunt Initiated: N=170
Phage not found: 45
Died before phage: 13
Infection resolved: 9
Unknown outcome: 7
Phage hunt ongoing: 14

Lytic Phages Found N=82
Deceased before administration: 13
Infection resolved: 20
Regulatory barrier: 2
Financial barrier: 1
Unknown reason: 5

Patients Treated N=30 (11 pending)

2.6%
# Selected Organisms in Play

Data from 06/01/18 – 9/30/21

<table>
<thead>
<tr>
<th>Organism</th>
<th>#Requests</th>
<th>Phage Hunt Initiated</th>
<th>Lytic Phage Found</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em></td>
<td>145</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>50</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>47</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>34</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><em>Achromobacter species</em></td>
<td>12</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><em>E. aerogenes</em></td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>E. species</em></td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><em>S. marcessens</em></td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>M. abscessus</em></td>
<td>68</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td><em>M. chimera</em></td>
<td>10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><em>M. avium</em></td>
<td>35</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>B. burgdorferi</em></td>
<td>55</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Building a Phage Library

P. AERUGINOSA

A. BAUMANNII

M. ABSCESSUS
Treat phage like living antibiotics

Bacteriophage therapeutics has emerged as one of the few potential beacons that represent possible solutions to the growing global crisis of antimicrobial resistance. Bringing science to the bedside (and vice versa) will maximize the potential of this compelling opportunity.

Robert T. Schooley and Steffanie Strathdee

The most important caveat is that phages are living antimicrobials that evolve with their bacterial targets. The guiding conceptual framework of clinical development thus requires working at the interface between bacteriology and virology — developing the clinical and translational research agenda with both disciplines in mind.

The process for developing an understanding of absorption, distribution, metabolism and excretion characteristics of antibiotics is well established and relies heavily on preclinical animal studies in uninfected animals. Many antibiotics have failed simply because they cannot be delivered to their sites of infection or because rapid metabolism and excretion make clinical administration impractical.

One of the major advantages of phage therapeutics may well be that replication within their bacterial hosts at the site of infection will make them much more forgiving than antibiotics in terms of delivery; however, phage therapeutics will require the introduction of new considerations, such as multiplicity of infection, physical configuration and size of the bacterial target population, and the rate of bacterial evolution in the setting of selective pressures by one (or likely more than one) phages during treatment. These investigations should be aided by the
NIH Funds First Phage Therapy Trial ($12 M) through the Antibacterial Resistance Leadership Group

December 13th, 2019

Design: Adaptive Phase 2 Trial

Enrollment to start in 2022

PI: Robert T. Schooley
Next Steps

• Translational studies:
  – PK/PD, Valency, Dose, Routes of administration
  – Potential synergy with antibiotics

• Clinical trials needed to determine efficacy:
  – Fixed vs. personalized cocktails

• Develop a phage library to enable phage to be matched to superbugs within 2 days.

• Genetic engineering to optimize natural phage or develop synthetic phage
Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*

Rebekah M. Dedrick\(^1\), Carlos A. Guerrero-Bustamante\(^1\), Rebecca A. Garlena\(^1\), Daniel A. Russell\(^1\), Katrina Ford\(^2\), Kathryn Harris\(^2\), Kimberly C. Gilmour\(^2\), James Soothill\(^2\), Deborah Jacobs-Sera\(^1\), Robert T. Schooley\(^3\), Graham F. Hatfull\(^1\)* and Helen Spencer\(^2\)*
Significant increase in standardized incidence rates for:

- Central line associated bloodstream infections
- Catheter-associated UTIs
- Ventilator associated associated events
- MRSA bacteremia
Acknowledgements

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- Jason Gill
- Mei Liu
- Carlos Gonzalez

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- Biswajit Biswas
- Kim Bishop-Lilly

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- Vance Fowler
- Pranita Tamma