



ARLG

Antibacterial Resistance Leadership Group

Considerations for the Use of Phages in Clinical Practice

Gina Suh, M.D. (Mayo Clinic)

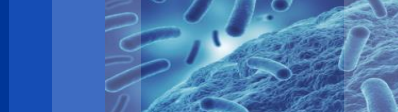
Thomas Lodise, Pharm.D., Ph.D (Albany College of Pharmacy and Health Sciences)

Robin Patel, M.D. (Mayo Clinic)

November 4, 2022

ARLG Grand Rounds





Disclosures

- Gina Suh has a business agreement with Adaptive Phage Therapeutics (APT) and is a principal investigator in planned clinical trials with APT and Phagelux
- Robin Patel reports grants from ContraFect, TenNor Therapeutics Limited, and BioFire. Dr. Patel is a consultant to PhAST, Torus Biosystems, Day Zero Diagnostics, Mammoth Biosciences, and HealthTrackRx; monies are paid to Mayo Clinic. Mayo Clinic and she have a relationship with Pathogenomix. She has research supported by Adaptive Phage Therapeutics. Mayo Clinic has a royalty-bearing know-how agreement and equity in Adaptive Phage Therapeutics. She is also a consultant to Netflix, Abbott Laboratories, and CARB-X. In addition, she has a patent on *Bordetella pertussis/parapertussis* PCR issued, a patent on a device/method for sonication with royalties paid by Samsung to Mayo Clinic, and a patent on an anti-biofilm substance issued. She receives honoraria from the NBME, Up-to-Date and the Infectious Diseases Board Review Course.
- Tom Lodise has no disclosures related to the presentation. Disclosures outside the presentation include: AbbVie (Consultant), BioFire Diagnostics (Grant/Research Support), Cidara (Advisor/Consultant), Entasis (Grant/Research Support), Ferring (Advisor/Consultant/Speaker), Genentech (Consultant), ICPD (Consultant), Johnson and Johnson (Consultant), Melinta (Advisor/Consultant), Merck (Advisor/Consultant, Grant/Research Support), Paratek (Advisor/Consultant), Roche (Consultant), Shionogi (Advisor/Consultant/Speaker), Spero (Advisor/Consultant), Wockhardt (Grant/Research Support), and Venatrox (Advisor/Consultant).

What Are Phages?



The viruses that infect bacteria



Nature's "check" on bacteria



Most abundant organism
 10^{31} phages



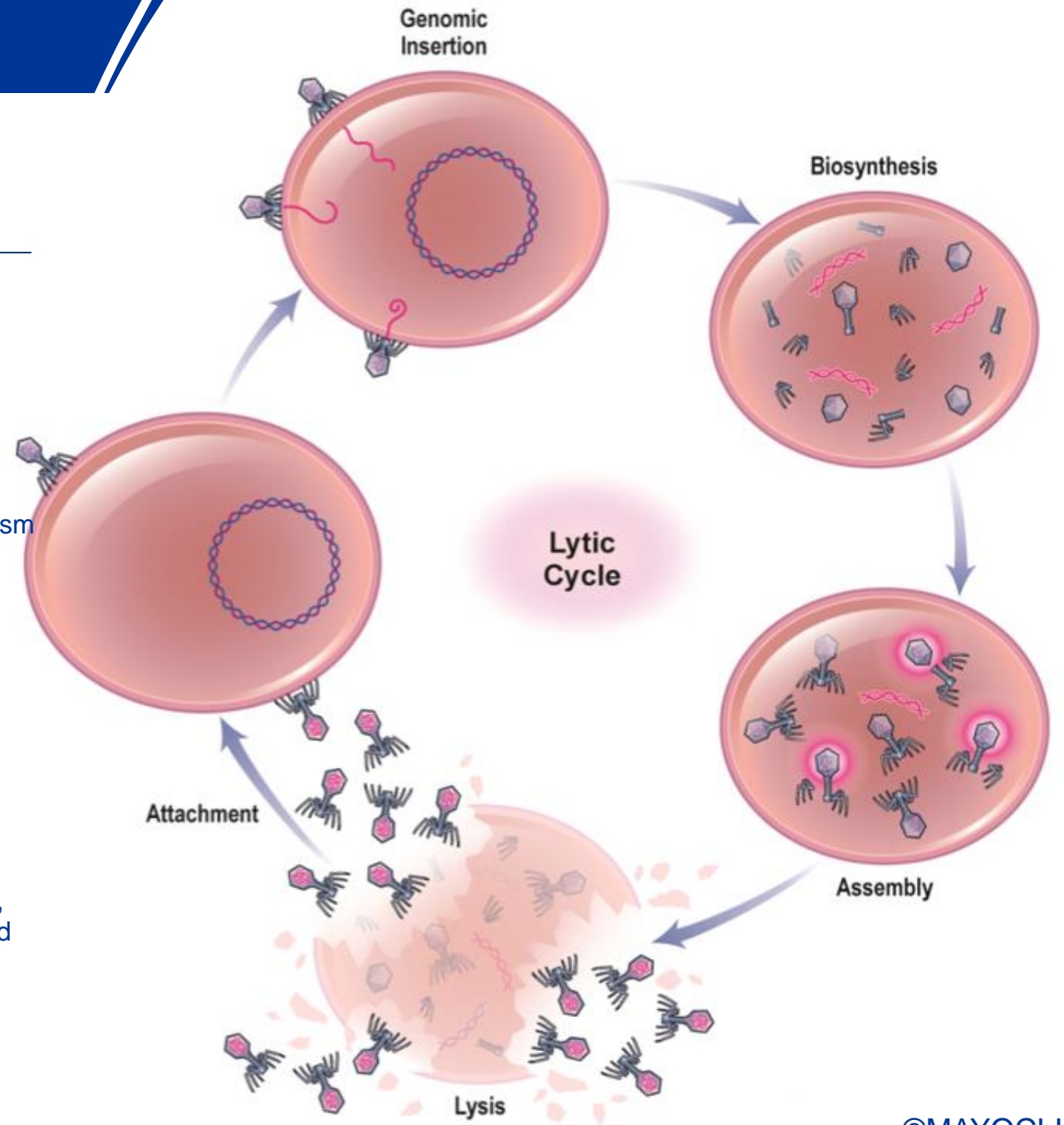
Highly specific



Harnessed as treatment for last 100 years but not FDA approved

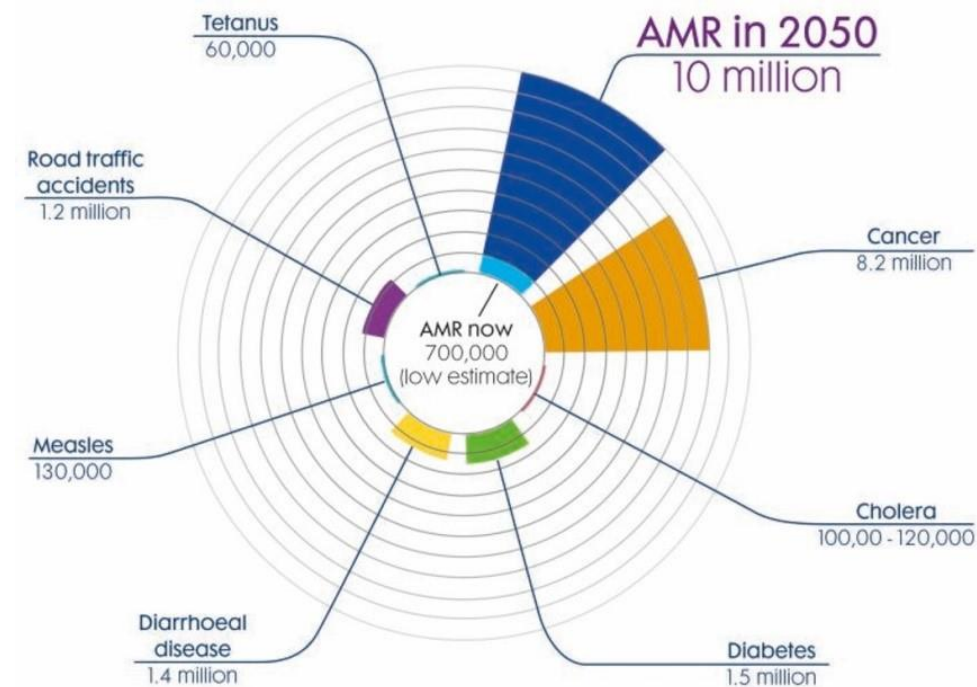


Good safety profile, generally considered safe



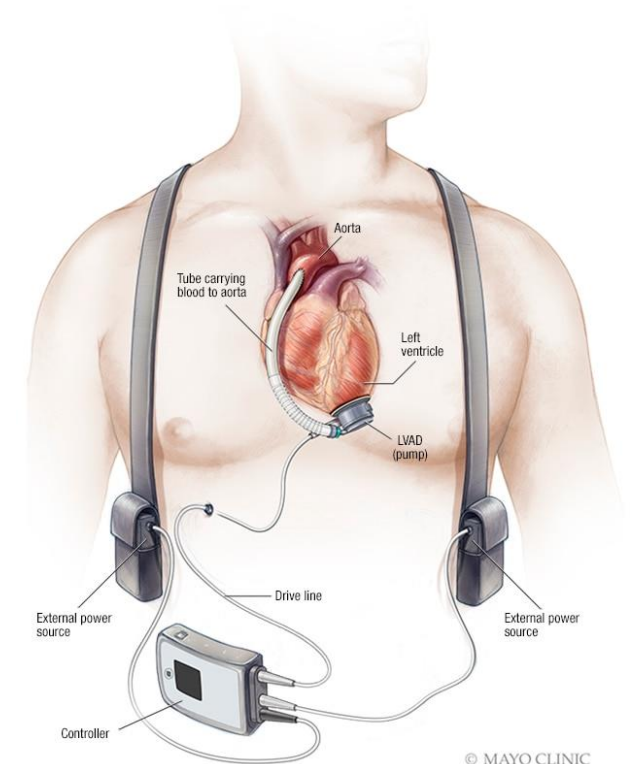
Why Phages?

Antimicrobial Resistance

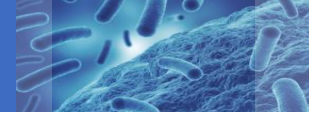


United Nations. High-Level Meeting on Antimicrobial Resistance.
2016

Medicine is Changing



Geng et al Exp Ther Med 2016



Rich History of Phage Therapy



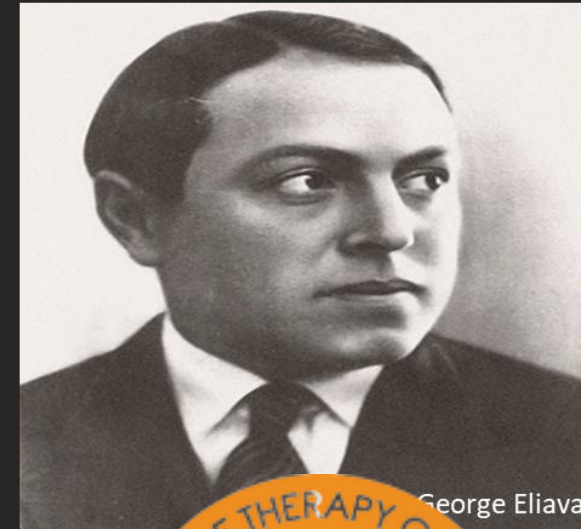
Ernest Hankin



Frederick Twort



Felix D'Herelle



George Eliava



Antibiotics vs. Phages

- Static molecule
- Broad host range
- Easier to commercialize
- Dynamic, living organisms
- Extremely narrow host range
- Highly individualized
- Commercialization challenging
- Appears effective against biofilms

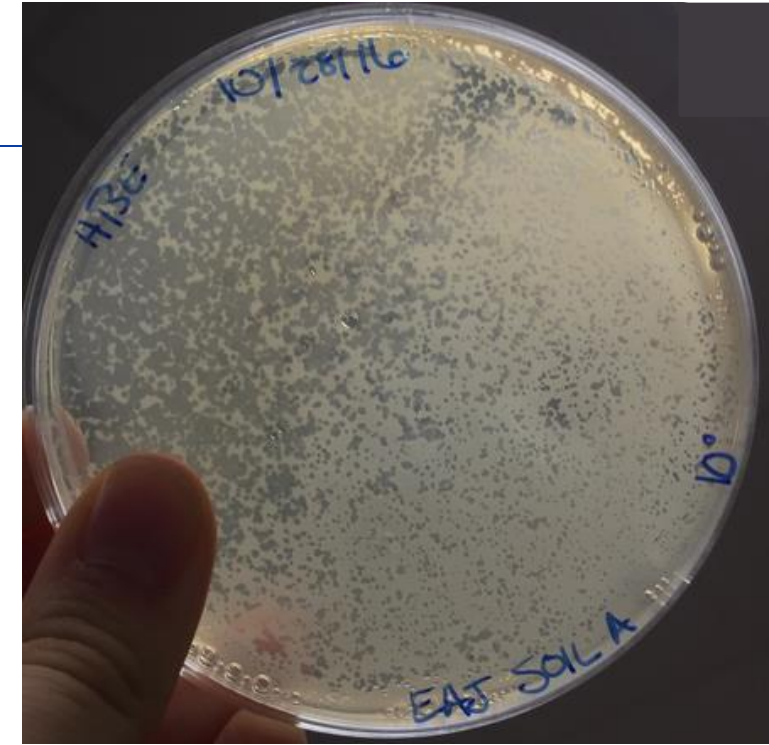
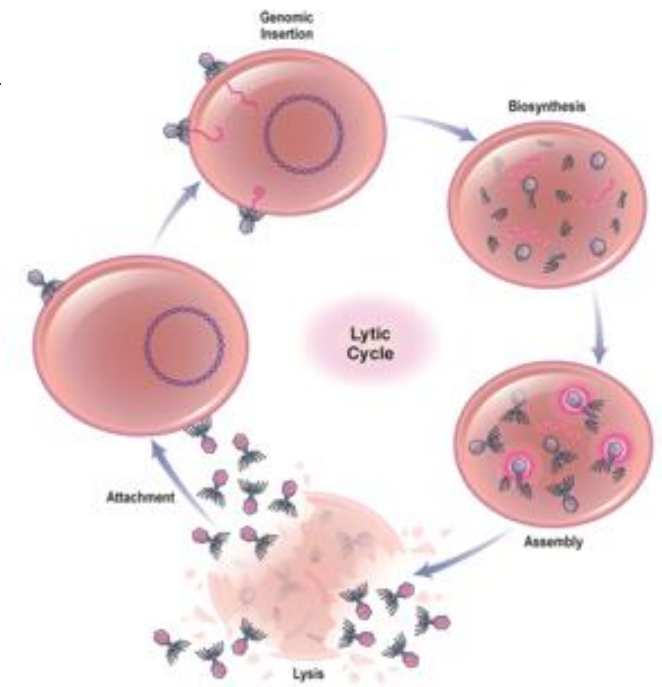
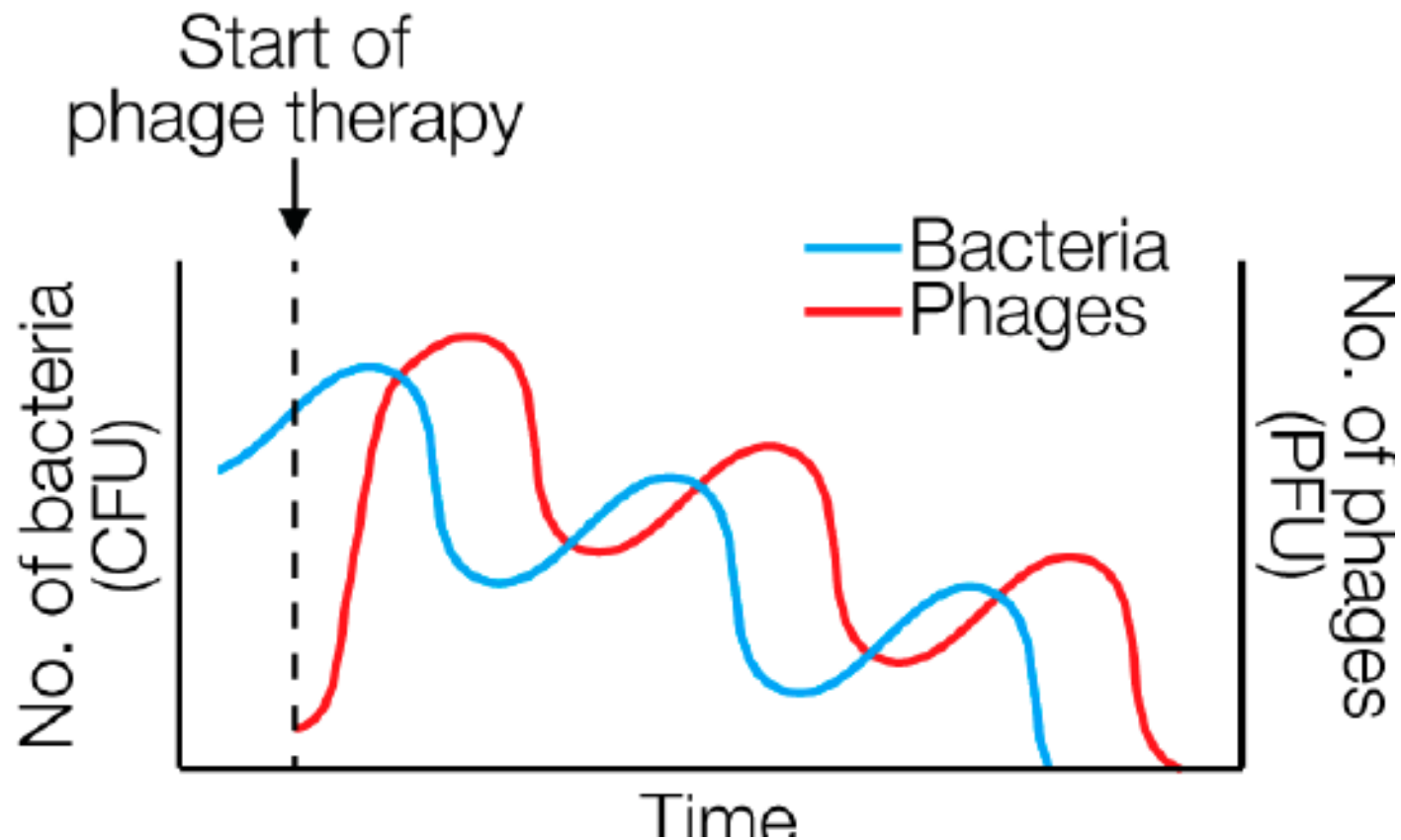
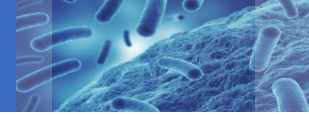


Photo courtesy K Totten

Phages Are Self-Amplifying



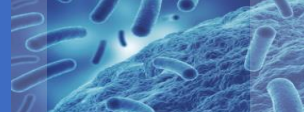
- Lytic cycles continue until bacteria are no longer present
- Phages dissipate when bacterial host are gone



Much is still unknown

- Efficacy
- Dosing/Dosing intervals
- PK/PD
- Optimizing stability
- Determinants of specificity
- Determinants of host range
- Optimizing delivery of phage to site of infection
- *In vivo* vs. *in vitro* discordance
- Role of human immune response
- Optimizing concurrent antibiotic therapy





ARLG PHAGE TASKFORCE

- **NIH (DMID), ARLG (with input from the FDA)**
- **Jane Knisely**
- **Gina Suh**
- **Thomas Lodise**
- **Robin Patel**
- Pranita Tamma
- Jose Alexander
- Saima Aslam
- Erica Bizzell
- Katherine Totten
- Joseph Campbell
- Benjamin Chan
- Scott Cunningham
- Katherine Goodman
- Kerryl Greenwood-Quaintance
- Anthony Harris
- Shayla Hesse
- Anthony Maresso
- Veronique Nussenblatt
- David Pride
- Michael Rybak
- Zoe Sund
- David van Duin
- Daria Van Tyne



Methodology

- Professional medical librarian (Karen Barton)
- Medline (Ovid), Embase (Elsevier), and Cochrane Central Registry of Controlled Trials (Wiley)
- 2000 - August 2021
- English-language only
- Excluded: Editorials, comments, letters, conference abstracts
- 14,841 abstracts screened
- 968 manuscripts reviewed



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Antibacterial Resistance Leadership Group

Considerations for the Use of Phage Therapy in Clinical Practice

 Gina A. Suh,^a  Thomas P. Lodise,^b  Pranita D. Tamma,^c Jane M. Knisely,^d Jose Alexander,^e Saima Aslam,^f Karen D. Barton,^g Erica Bizzell,^d  Katherine M. C. Totten,^a Joseph L. Campbell,^d Benjamin K. Chan,^h Scott A. Cunningham,^a Katherine E. Goodman,ⁱ Kerryl E. Greenwood-Quaintance,^a Anthony D. Harris,ⁱ  Shayla Hesse,^d Anthony Maresso,^j Veronique Nussenblatt,^d  David Pride,^f  Michael J. Rybak,^k Zoe Sund,^g  David van Duin,^l  Daria Van Tyne,^m  Robin Patel,^a for the Antibacterial Resistance Leadership Group

Question 1: For which infections can phage therapy be considered?

Question 2: Should antibiotics be administered concurrently with phages?

Question 3: Is phage therapy safe for clinical use as an anti-infective?

Question 4: What are some practical considerations when considering phages as anti-infective therapy?

Question 5: Which regulations govern use of phages in clinical settings?

Question 6: What types of phage products are available, and which are preferred for treatment of patients with acute and chronic bacterial infections?

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Question 10: Under which conditions should PST be used to select phages for therapeutic use?

Question 11: Which parameters should emerging PST platforms consider?

Question 12: Which parameters should test methods for assessment of phage activity in combination with antibiotics consider?

Question 13: Which immune system components are likely to impact safety and efficacy of phage therapy, and how can these be tested?

Question 14: What are current acceptable standards needed for safe phage administration?

Question 15: Under which conditions should phage be quantified in clinical specimens and which parameters might be important features of assays to quantify phage in clinical specimens?



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Antibacterial Resistance Leadership Group

Clinical Considerations for Phage Therapy

November 4, 2022

ARLG Grand Rounds

Gina Suh, M.D.





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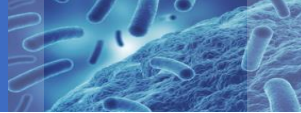
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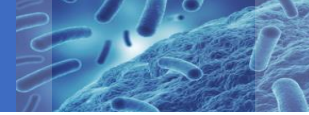
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For which infections can phage therapy be considered?

SUGGESTION

- Experimental phage therapy can be considered for a variety of infections refractory to conventional antibiotics, including respiratory tract infections, infections involving devices that cannot be removed, osteoarticular infections, UTIs, gastrointestinal infections, endovascular infections, and other source infections.
- Bacteriophage therapy is a consideration for bacterial but not fungal, viral, or parasitic infection.



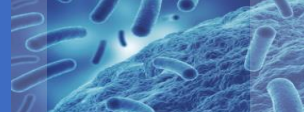
For which infections can phage therapy be considered?

RATIONALE

- 65 cases total
- Age range 2-88 years
- Sex
 - Female 17 (26%)
 - Male 44 (68%)
 - Unknown 4 (6%)

- **Indwelling devices 23**
 - PJI 12
 - Aortic graft infection 6
 - LVAD 2
 - Craniotomy site 1
 - Infusion pump infection 1
 - PV IE 1
- **Pneumonia 14**
 - Pneumonia in transplant 5
 - Pneumonia in COVID 4
 - Pneumonia in CF 3
 - Pneumonia/empyema 1
 - Pneumonia in chronic bronchiectasis 1
- **Osteomyelitis 8**
- **UTI 5**
- **Skin and skin structure 2**
- **Sternal infection 2**
- **Bacterial keratitis 1**
- **Necrotizing pancreatitis 1**
- **Pressure ulcer 1**
- **Prostatitis 1**
- **Skin graft infection 1**

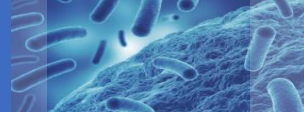
- *P. aeruginosa* 22
- *S. aureus* 22
- *Acinetobacter* 7
- Polymicrobial 7
- *K. pneumoniae* 6
- *S. epidermidis* 3
- *Achromobacter* 2
- *E. coli* 2
- *M. abscessus* 2
- *Burkholderia dolosa* 1
- *E. faecalis* 1
- *E. faecium* 1
- GBS 1



For which infections can phage therapy be considered?

GAPS IN KNOWLEDGE

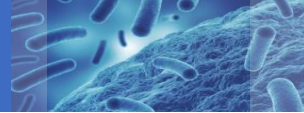
- Lack of randomized controlled trials of phage therapy
- Trials which should use standardized dosing regimens urgently needed
- Analysis and publication of studies with negative outcomes
- Systematic data collection from compassionate use cases including clinical failures
- Many questions remain about selection of cases, treatment indications, stages of illness, and acuity/chronicity of illness



Should antibiotics be administered concurrently with phages?

SUGGESTION

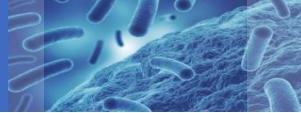
- The ARLG Phage Taskforce suggests that if phage therapy is used, it should be in conjunction with conventional antibiotics.



Should antibiotics be administered concurrently with phages?

RATIONALE

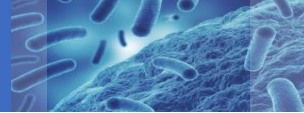
- Concurrent antibiotic use in nearly all clinical cases
- Potential to reinstate susceptibility of the targeted bacteria to antibiotics by manipulating bacterium-phage coevolutionary strategies
- *In vitro* demonstration of phage-antibiotic synergy



Should antibiotics be administered concurrently with phages?

GAPS IN KNOWLEDGE

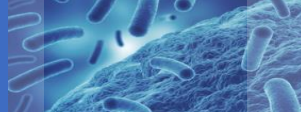
- Lack of controlled clinical trial data on the effectiveness of phage-antibiotic combinations
- Clinical trials comparing antibiotic alone versus antibiotic plus phages are needed
- Subsequent trials might consider assessing phage alone versus antibiotics plus phage
- Bacterial isolates before and after phage therapy should be tested for antibiotic and phage susceptibility
- Further research is needed to investigate potential for attenuated bacterial virulence after initiation of phage therapy



Is phage therapy safe for clinical use as an anti-infective?

SUGGESTION

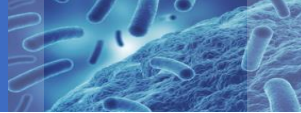
- Phage therapy is generally safe to administer, with adverse events rarely reported
- Patients receiving their first dose of phages should be observed for allergic and other adverse reactions
- Monitoring of renal function, liver function, complete blood count at minimum until robust safety data are established



Is phage therapy safe for clinical use as an anti-infective?

RATIONALE

- Relatively few reported adverse events (AEs)
- Most published accounts report no AEs after phage
- Transient AEs have been observed, but their association with the administered phages unclear
 - Fever, transient SOB, transient hypotension, sweats, flushing, chills, reversible transaminitis, transient pain at infection site
- Clinical trial data available
 - Single-arm safety trial in patients with *Staph* bacteremia reported no AEs
 - Topical phage therapy burn patients – mild AEs deemed unrelated to PT
 - Otitis media and nasal irrigation trial reported no serious AEs



Which regulations govern use of phages in clinical settings (in the U.S.)?

SUGGESTION

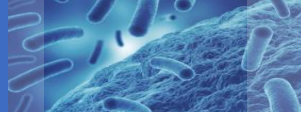
- Expanded access (commonly known as compassionate use) is a viable regulatory pathway for treatment of individual patients with phage therapy



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RATIONALE

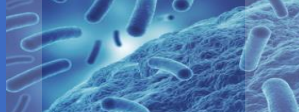
- Currently, no FDA approved phage products for clinical use
- Phages regulated as biological products by FDA *Center for Biologics Evaluation and Research (CBER)*
- Application for investigational new drug (IND) application required
- Most common pathway for investigational drugs outside of clinical trials is expanded access (compassionate use)
 - Purpose is to treat the patient, not support licensure
 - Defined safety and quality criteria must be fulfilled
- Emergency expanded-access can be granted in life-threatening cases
- Not a substitute for rigorous trials



What are some practical considerations when considering phages as anti-infective therapy?

SUGGESTION

- A detailed plan outlining uncertain clinical outcomes, lack of proven efficacy, lack of standardized dosing or administration, potential adverse events, costs, and other logistics be discussed with patients as part of the informed consent process before administering phage therapy



What are some practical considerations when considering phages as anti-infective therapy?

- What is the first step?
 - The bacterial isolate is needed to identify phage(s) with lytic activity; storage of the patient's bacterial isolate(s) often required
 - Assessment of the clinical status of the patient and urgency
 - Median time from request to phage administration ranges 28-386 days, with a median of 171 days
- What are the costs associated with phage therapy?
 - Not reimbursable by insurance
 - Some academic laboratories provide at no cost or charging for phage preparation
 - Other costs covered by patients or insurance (infusion therapy centers, PICC lines, etc)
- Pathway for compassionate use treatment should be developed

International Phage Grand Rounds



- Collaborative effort
 - Dr. Jon Iredell (Australia)
 - Dr. Greg German (Canada)
 - Dr. Ran Nir-Paz (Israel)
 - Dr. Gina Suh (U.S.)
 - Network of interested phage clinicians
- Classical GR format
- De-identified case discussions
 - Clinical decision points incorporating translational science
- Alternating hosts across time zones
- Quarterly
- Coming soon



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Antibacterial Resistance Leadership Group

Dosing and PK and PK/PD Considerations with Phage Therapy

Friday, 4th November 2022

ARLG Grand Rounds

Thomas Lodise, Pharm.D., Ph.D





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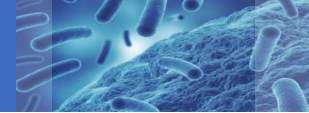
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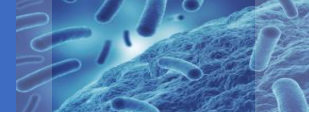


Available Phage Products for Use

- Available phage product for clinical use
 - Monophage vs cocktails
 - Nature versus bioengineered
 - Pre-biomanufactured (i.e., off the shelf) or manufactured in real-time
- **ARLG Phage Taskforce endorses the use of a phage product that has microbiologic activity against the target pathogen(s).**
- **ARLG Phage Taskforce encourages clinicians to send the bacterial pathogen(s) to phage testing center for optimal phage selection.**

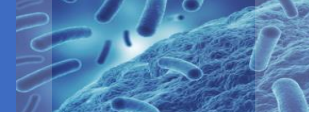
Studies are needed to determine if monophage versus cocktails should be used

Rapid screening methods are needed to identify optimal phage(s) against patients' bacterial pathogens and minimize production time of on-demand phages



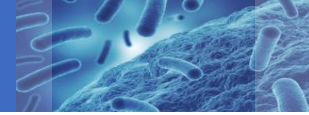
Considerations with Selection of Cocktail vs Monophage Product

- Both cocktails and monophage are available as pre-biomanufactured and on-demand phage products.
 - *On demand products offer the potential to modify phages based on phage susceptibility testing (PST) results but take considerable time to manufacture.*
- Cocktails may be preferred to maximize the number of phages that target a specific bacterium and/or to broaden the bacterial spectrum.
- Cocktails may theoretically optimize bacterial killing over time and minimize the potential for resistance emergence.
- A drawback with cocktails is that individual phages usually require a decrease in concentration when mixed into a single dose.
 - *Due to size of phages and purification processes, a phage suspension cannot contain more than $\sim 10^{11}$ plaque-forming units/mL (PFU/mL).*
- There is also the potential that component phages agglomerate or interfere with one another by competing for the same bacterial receptor or drive cross-resistance.



PK/PD Consideration with Phage Dose Selection

- **The ARLG Phage Taskforce suggests using the highest safe and tolerated dose of a phage product with endotoxin levels below the acceptable FDA limits.**
 - Maximize phage concentrations at infection site, infect as many host cells as possible with the first dose, and promote self-amplification.
- **Repeat dosing is preferred to maximize concentrations at site of infection when given systemically.**
 - Due to large size, protein content, and removal by the mononuclear phagocyte system (MPS), concentrations at the infection site are assumed to be substantially lower than the initial dose delivered systemically before phage replication.

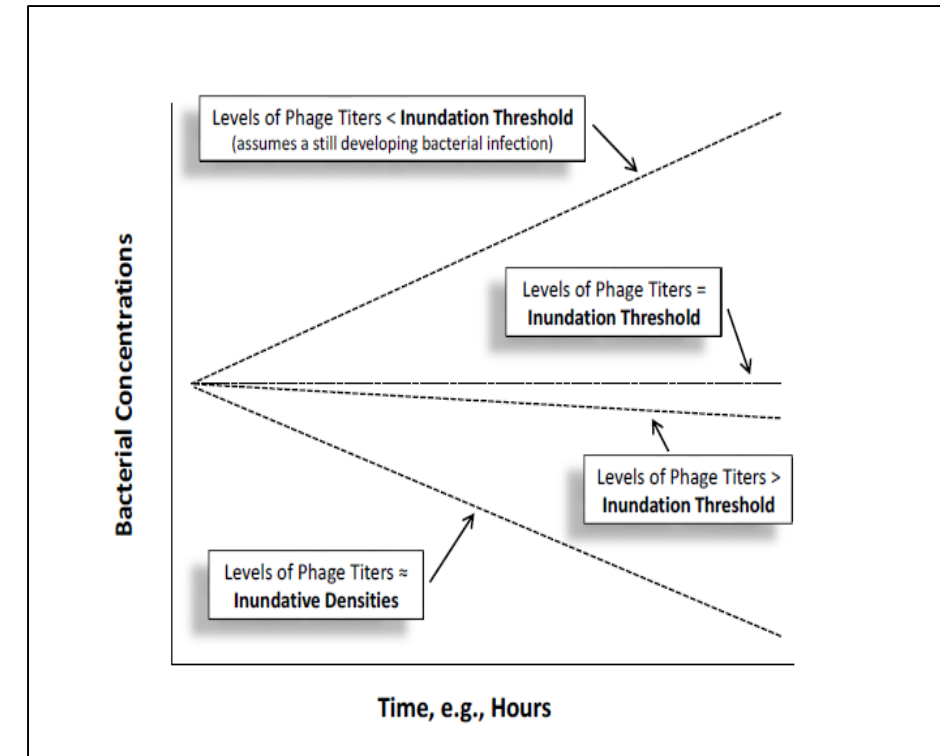


Ideal PK/PD Properties of Phage Products

- **High microbiological susceptibility**
- **High concentrations of phage(s) at site of infection**
- **High adsorption rates of phages**
 - *Infectivity of phages*
- **Large burst sizes**
 - *Number of phage progeny produced from a single cell*
 - *Based on pre-clinical data, it has been proposed bacterial cell densities need to be $>10^4$ CFU/ml for self-amplification to occur*
- **Short latency periods**
 - *Time of phage replication within bacterial cells*

Required Number of Phages at Infection Site

- Numbers of phages at sites of infection required for optimal net bacterial killing has not been established.
 - The ratio of adsorbed phages to targeted bacteria, termed actual multiplicity of infection (MOI_{actual}) ratio has been proposed to be 10.
 - Some data indicate that the MOI_{actual} should result in phage densities that far exceed the inundation threshold
 - Other suggest that a reasonable phage density capable of maximizing net bacterial killing at the infection site in a timely manner is 10^8 PFU/ml.



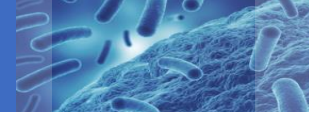
All reported MOI_{actual} and inundative phage density targets are based on mathematical modeling of pre-clinical infection model data and are limited by model assumptions

Standardization of PK/PD methodologies and their evaluations are required



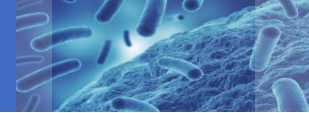
Some Important Considerations with Mathematical Modeling of Pre-Clinical Infection Model Data

- Ratios of viable to nonviable phage particles and numbers of absorbed phages to numbers of bacteria at infection sites are difficult to quantify and likely variable over a treatment course
 - *Limit ability to estimate MOI_{actual}*
- Phages may bind bacterial debris from lysed bacteria and are heterogeneously distributed at infection sites
 - *Limit ability to determine the actual number of active phages at an infection site that can infect cells*
- Often do not account for contributions of the immune system, bacterial host defense mechanisms [e.g., bacterial membrane vesicle production, which reduces phage virulence], concurrent receipt of antibiotics, and local host environments
 - *Well-recognized factors that affect phage therapy outcomes*
- Modeling studies often lack clinical validation



Potential Routes of Phage Therapy Administration

- **Common routes of administration**
 - *Systemic injection*
 - *Oral*
 - *Direct administration*
- **The Taskforce endorses IV phage administration for treatment of patients with infections that involve organs or systems in which phages have been shown to achieve titers/concentrate if benefits outweigh the risks.**
 - *Skeletal muscles, brain, heart, thymus, bone marrow, kidneys, bladder, lung, and GI tract*
- **The Taskforce endorses direct administration when available data indicate the specific direct administration modality with a given phage product achieves viable phage titers at the intended infection site.**
- **The Taskforce suggests limiting use of orals to infections of the gastrointestinal tract or in combination with other routes of phage administration until more clinical data.**



Key Considerations with Each Phage Administration Modality

▪ Systemic

- *Rapidly cleared from bloodstream by MPS and subject to inactivation by complement and circulating neutralizing antibodies.*
- *Penetration into site of infection varies by organ system and appears to be dose dependent.*

▪ Direct or topical

- *Phages have reduced efficacy when the selected route of administration does not facilitate timely and sustained distribution within spatially structured bacterial populations at the infection site.*
- *Components of direct administration applications may inactivate phages, limiting clinical utility.*

▪ Oral

- *Ability to survive in the human GI tract is uncertain.*
- *Less efficient means for achieving systemic therapeutic phage concentrations relative to other routes.*



Dosing and Frequency of Phage Products

- Data suggest that phages need to be re-dosed to maximize phage concentrations at infection sites, but ideal frequencies and durations of administration are unclear.
 - *Dosing practices are largely empirical based PK considerations.*
- The literature regarding the clinical use of phage therapy has not indicated clear safety concerns, supporting the use of repeated dosing for extended durations, especially to maximize concentrations at infection sites.
- **Members of the ARLG Phage Taskforce suggest that patient responses inform durations of therapy and mimic those employed for antibiotics.**

PST should be in place to confirm susceptibility of the involved bacteria to the phage to make sure the administered phage is still viable as resistance may develop



ARLG

Antibacterial Resistance Leadership Group

Diagnostic Considerations for the Clinical Use of Phage Therapy

Friday, 4th November 2022
ARLG Grand Rounds

Robin Patel, M.D.
Director, ARLG Laboratory Center





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Antimicrobial Agents
and Chemotherapy®



ARLG

Antibacterial Resistance Leadership Group

Considerations for the Use of Phage Therapy in Clinical Practice

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Question 1: For which infections can phage therapy be considered?

Question 2: Should antibiotics be administered concurrently with phages?

Question 3: Is phage therapy safe for clinical use as an anti-infective?

Question 4: What are some practical considerations when considering phages as anti-infective therapy?

Question 5: Which regulations govern use of phages in clinical settings?

Question 6: What types of phage products are available, and which are preferred for treatment of patients with acute and chronic bacterial infections?

Question 7: What are the key pharmacokinetic and pharmacodynamic considerations with selecting initial phage doses?

Question 8: What are potential routes of administration for phage therapy and how should they be selected?

Question 9: What dosing frequency and duration for phage therapy should be used?

Question 10: Under which conditions should PST be used to select phages for therapeutic use?

Question 11: Which parameters should emerging PST platforms consider?

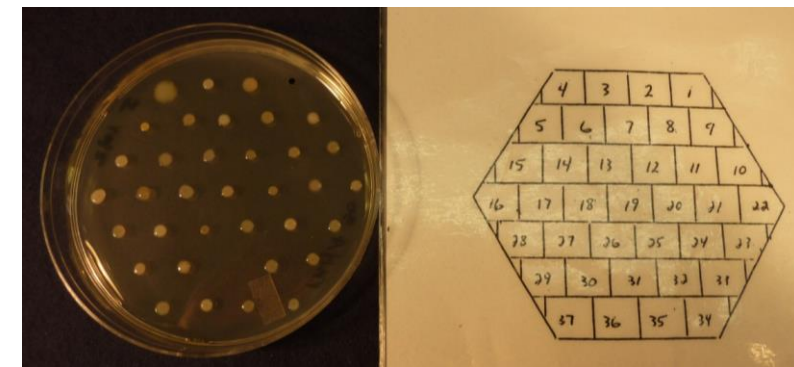
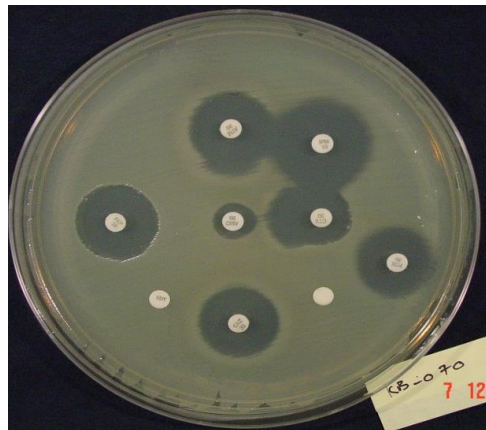
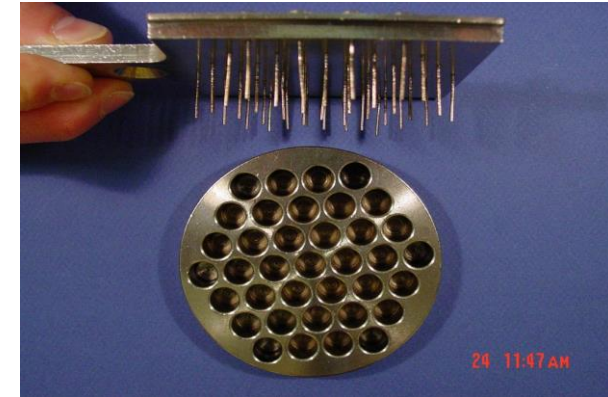
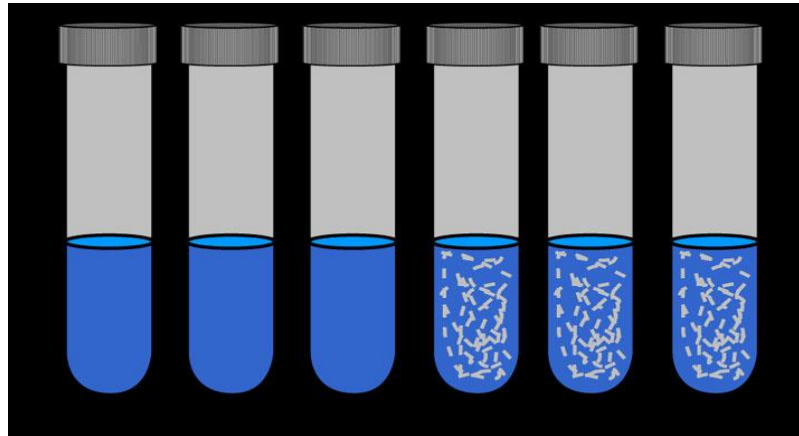
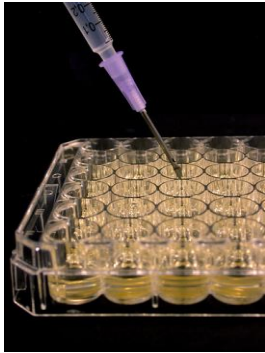
Question 12: Which parameters should test methods for assessment of phage activity in combination with antibiotics consider?

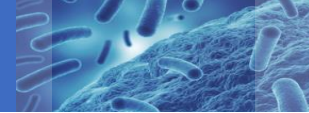
Question 13: Which immune system components are likely to impact safety and efficacy of phage therapy, and how can these be tested?

Question 14: What are current acceptable standards needed for safe phage administration?

Question 15: Under which conditions should phage be quantified in clinical specimens and which parameters might be important features of assays to quantify phage in clinical specimens?

Antimicrobial Susceptibility Testing (AST)





UNDER WHICH CONDITIONS SHOULD PHAGE SUSCEPTIBILITY TESTING (PST) BE USED TO SELECT PHAGES FOR THERAPEUTIC USE?

SUGGESTION:

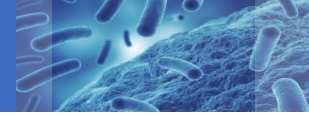
- It would be ideal to perform PST before phage administration so that a phage or phages active against infecting bacterium selected
 - However, standardized, accurate, and reproducible methods, reported with validated interpretive criteria lacking
 - Once such methods available, routine use suggested before phage administration



UNDER WHICH CONDITIONS SHOULD PST BE USED TO SELECT PHAGES FOR THERAPEUTIC USE?

RATIONALE AND OTHER CONSIDERTIONS:

- No reliable activity against all strains of a bacterial species
- Because of potential for resistance development during treatment, confirmation of continued activity likely helpful for clinical failures
- PST may involve testing panel of phages
- Dynamic tension with testing time
 - Phage cocktails/phage broad host ranges, may allow empiric therapy (emergency situations); confirming activity still ideal



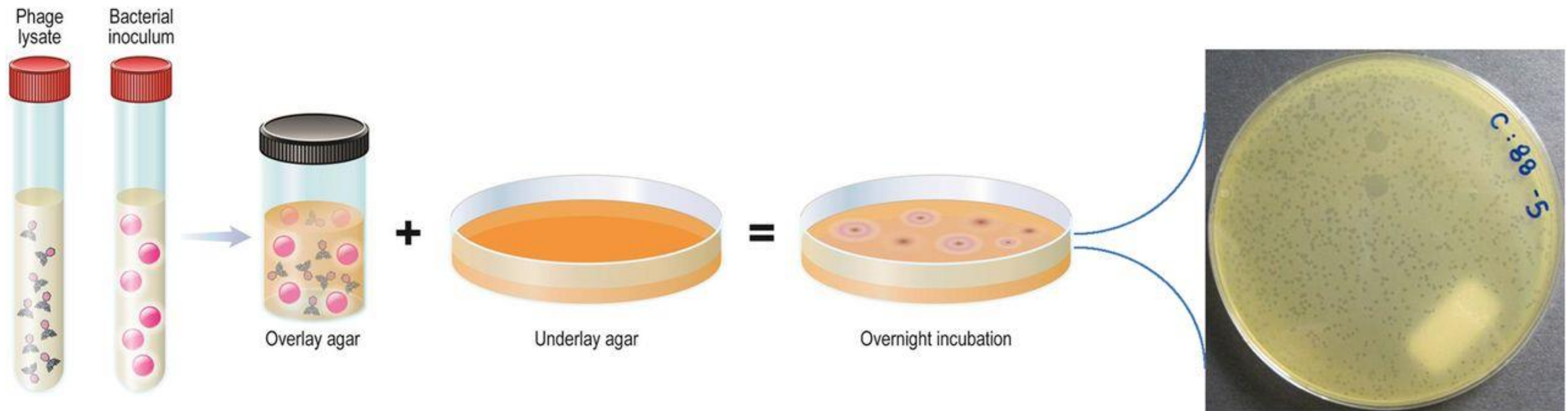
WHICH PARAMETERS SHOULD EMERGING PST PLATFORMS CONSIDER?

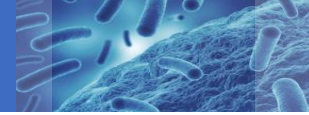
SUGGESTION:

- Identified several laboratory testing strategies for assessing phage activity against individual bacterial isolates
 - No reference gold standard method
- Standardized, accurate, reproducible, rapid, test multiple phages at once, and report out using interpretive criteria that predict clinical activity needed
 - No criteria yet exist

Lytic/Plaque PST Example

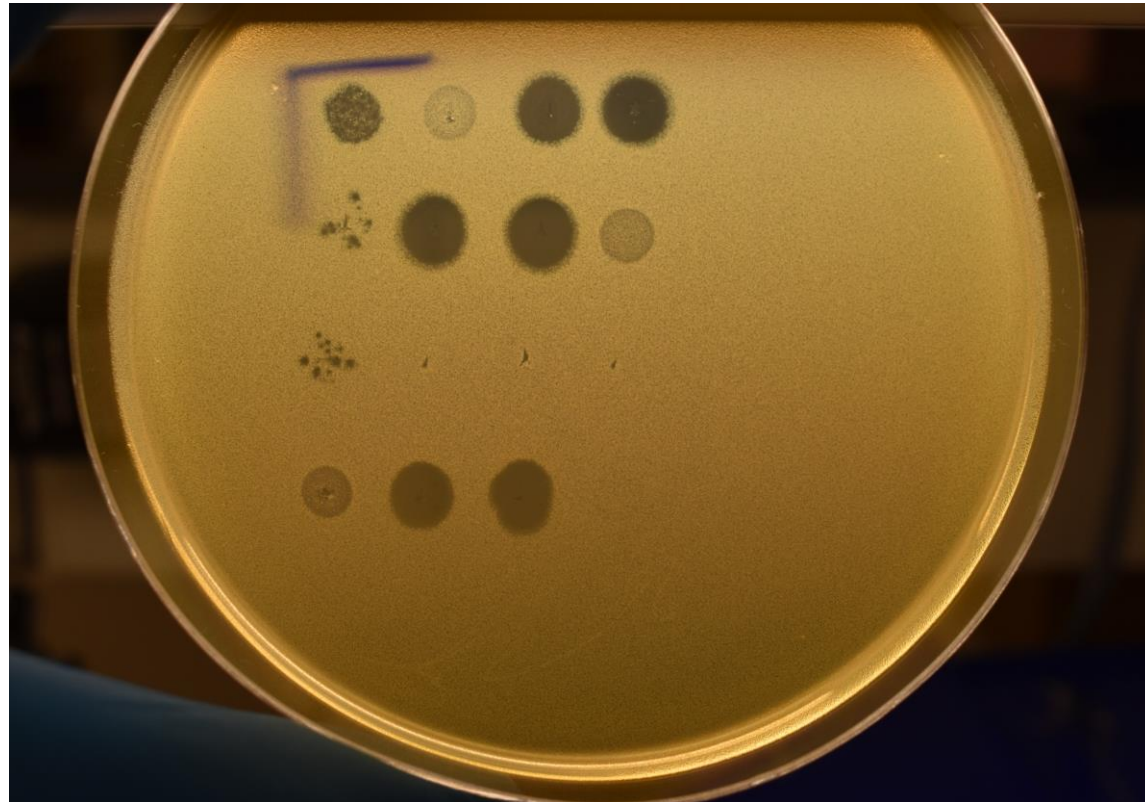
Example: Double-Overlay Plaque Assay





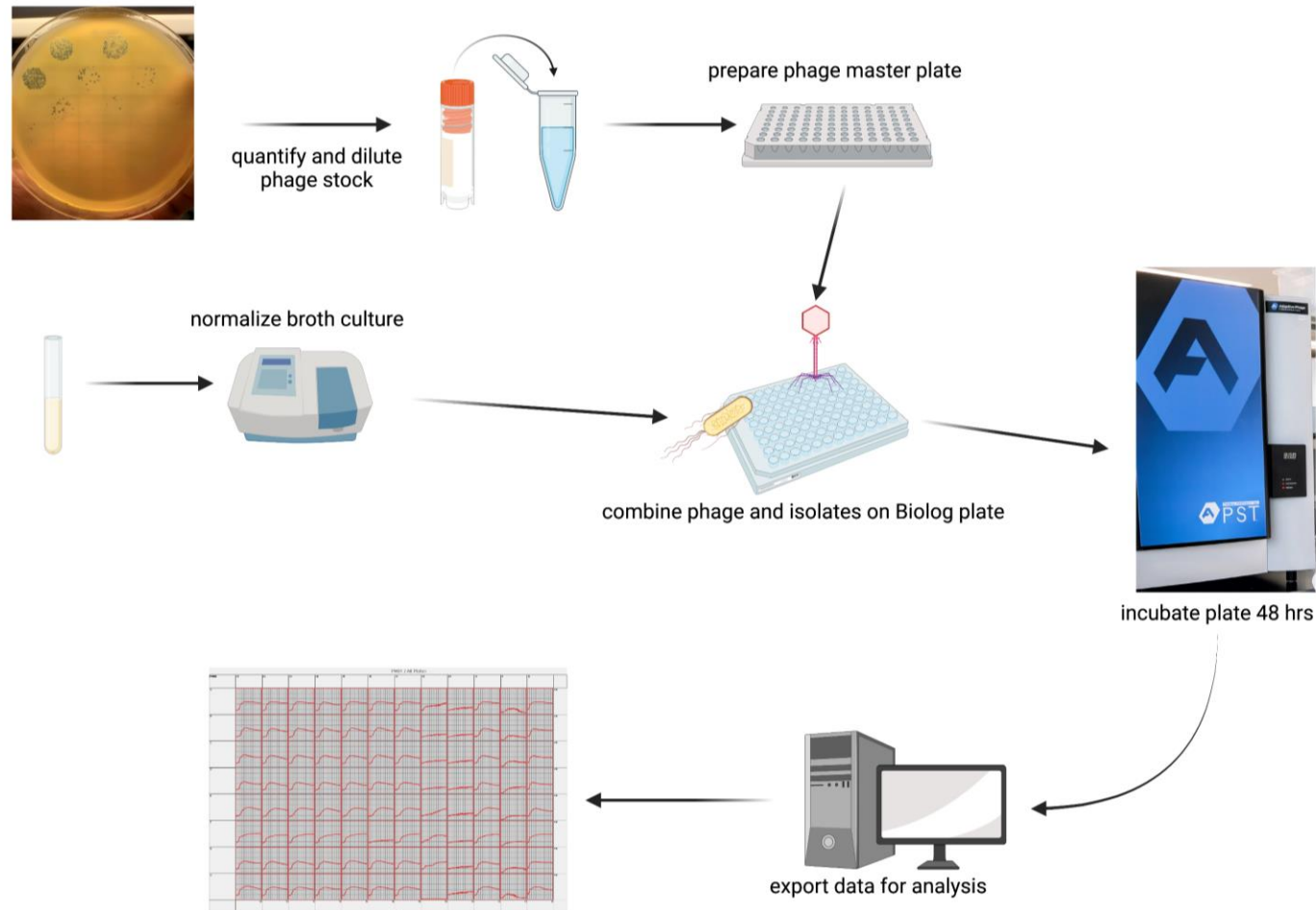
Lytic/Plaque PST Example

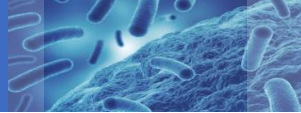
Example: Spot Modification



Liquid Media PST Example

Example: PhageBank Susceptibility Testing™

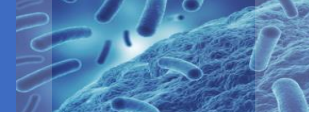




WHICH PARAMETERS SHOULD EMERGING PST PLATFORMS CONSIDER?

GAPS IN KNOWLEDGE:

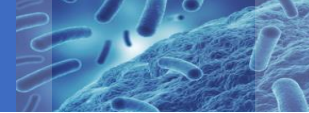
- No reference standard method
- Lack interpretive criteria
 - *In vitro* parameters predictive of clinical efficacy unknown
- Reporting
 - “Active” and “inactive”; or
 - “Susceptible,” “intermediate,” and “resistant”
- Universal or different breakpoints for all phage-bacterium combinations?
- Testing cocktails?
- Standardized phage concentrations, media compositions & concentrations (if relevant), incubation temperatures & durations thereof, bacterial densities & growth phases, quality control, results interpretation



WHICH PARAMETERS SHOULD TEST METHODS FOR ASSESSMENT OF PHAGE ACTIVITY IN COMBINATION WITH ANTIBIOTICS CONSIDER?

SUGGESTION:

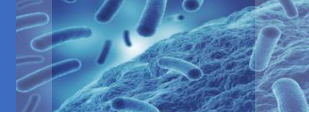
- No standard method for phage-antibiotic combination testing identified
- May be helpful to predict effects of specific phage-antibiotic combinations on bacterial population reductions, addressing synergy and antagonism



WHICH IMMUNE SYSTEM COMPONENTS ARE LIKELY TO IMPACT SAFETY AND EFFICACY OF PHAGE THERAPY, AND HOW CAN THESE BE TESTED?

SUGGESTION:

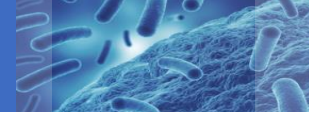
- Unable to recommend specific assessment of immunologic parameters that correlate with phage activity that should be assessed due to significant knowledge gap
 - Suggest considering tests for neutralizing antibodies with prolonged phage administration (although standardized assays for such measurements unavailable)
- Monitor renal, liver, and hematologic function



WHAT ARE CURRENT ACCEPTABLE STANDARDS NEEDED FOR SAFE PHAGE ADMINISTRATION?

SUGGESTION:

- Phages should...
 - Not harbor antibiotic resistance or toxin genes
 - Not be capable of undergoing lysogeny
 - Be sequenced - absence identifiable antibiotic resistance elements, bacterial toxin genes, integrase genes, regulators of integrase genes, integrase-like genomic elements
- Bacterial hosts for phage propagation should...
 - Be sequenced – no toxin or antibiotic resistance genes
- Phage therapy formulations should
 - Be sterile according to U.S. Pharmacopeia 71
 - Tested to confirm low levels of endotoxin



UNDER WHICH CONDITIONS SHOULD PHAGE BE QUANTIFIED IN CLINICAL SPECIMENS AND WHICH PARAMETERS MIGHT BE IMPORTANT FEATURES OF ASSAYS TO QUANTIFY PHAGE IN CLINICAL SPECIMENS?

SUGGESTION:

- Given uncertainty as to number of phages required at infection site for maximal effect, unable to make recommendation as to circumstances under which phage concentrations should be measured in clinical samples
- Determination of phage concentrations at sites of infection limited to animal and clinical research studies
 - Assess amount of phage required at infection sites for ideal effects
- No standard method for phage enumeration in clinical specimens

Questions?

This study was supported in part by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health and under the Award Number UM1AI104681. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.