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Essay

Within-Host Evolution of Drug-Resistant Bacteria in Immunocompromised Patients: A Case for Adjunct and Alternative Therapies

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Abstract

Antimicrobial resistance is often framed as a problem acquired outside the patient through transmission of resistant strains and genes. This view is important, but it is incomplete for immunocompromised patients, where there is substantial evidence that drug-resistant bacteria can evolve within the host during therapy. In haematological malignancy, transplantation, and other states of impaired immunity, infections persist longer, immune clearance is reduced, and prolonged use of last-line antibiotics creates repeated selection events. These conditions favour stepwise evolution toward the hardest-to-treat phenotypes, including carbapenem resistance, tigecycline resistance, colistin resistance, and resistance to ceftazidime–avibactam, often alongside persistence in reservoirs such as the gastrointestinal tract. This essay argues that antibiotic escalation alone is therefore an incomplete strategy in these settings and that care should be explicitly evolution-aware. Adjunct and alternative approaches should be prioritised earlier to reduce bacterial burden, shorten time under selection, and limit reliance on prolonged sequential antibiotic regimens. Bacteriophages are highlighted as one promising adjunct because they are highly specific, generally well tolerated, can self-amplify at sites where susceptible bacteria are present, and can be iterated through approaches such as training and rational cocktails. Phage–antibiotic synergy is also discussed as a practical strategy to improve killing and reduce escape.

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Essay

One of the most common ways we explain antimicrobial resistance is that it is largely acquired outside the patient [1]. Resistant strains circulate, patients are exposed, and treatment becomes difficult. That is true, and it underpins infection prevention and control. However, it does not fully explain a pattern that is repeatedly documented in immunocompromised care: loss of susceptibility during therapy, relapse after apparent control, and progressive narrowing of options while the patient remains under treatment pressure.

Within-host evolution gives a simpler explanation. Bacteria can evolve during human infection, and antibiotic exposure is one of the strongest pressures shaping what survives [2]. In immunocompromised patients, this evolutionary pressure matters more because infections often last longer, and the immune system provides less help in clearing bacterial populations.

What Is Meant by "Immunocompromised" in This Essay

In this essay, *immunocompromised* refers to patients with a clinically meaningful reduction in immune function that increases infection risk and reduces the ability to clear bacterial populations once infection is established [3]. This includes impaired innate immunity (for example, prolonged neutropenia or neutrophil dysfunction), impaired adaptive immunity (for example, following

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haematopoietic stem cell transplantation or solid-organ transplantation), iatrogenic immunosuppression (for example, high-dose corticosteroids, cytotoxic chemotherapy, or immunomodulatory drugs used in malignancy and transplantation), and advanced systemic conditions where immune function is substantially weakened [4]. The focus is intentionally on haematological malignancy and transplant settings because they carry a high burden of severe drug-resistant infections and commonly require prolonged antibiotic exposure [5,6].

Why Immunocompromisation Changes the Resistance Problem

Immunocompromised states create a wider "evolution window." When immune clearance is weak, bacteria have more time to persist, replicate, and explore resistance pathways. Experimental work supports this directly: immunosuppression can broaden evolutionary routes to drug resistance and increase the chance of treatment failure [7]. This matters because it implies immune status can shape resistance trajectories rather than only changing disease severity.

Clinical evidence aligns with this. Serial isolate studies and longitudinal case reports in transplantation and other high-risk settings document within-host evolution under treatment pressure, including evolution of resistance determinants and changes linked to persistence [8–10].

Why Sequential Last-Line Antibiotic Regimens Can Compound the Problem

In immunocompromised patients, escalation to high-intensity regimens is often unavoidable. The problem is that prolonged, sequential exposure to last-line agents creates repeated selection events inside the same host, enriching whatever can survive each step. This has been observed directly in immunosuppressed settings where sequential pressure included polymyxins, ceftazidime–avibactam and meropenem [9].

The clinical consequence is stepwise movement toward the hardest-to-treat phenotypes. Within-host trajectories show evolution from carbapenem resistance toward additional last-line resistance, including tigecycline resistance and then colistin resistance, with evidence consistent with *mgrB*-pathway disruption [10]. Tigecycline resistance can also emerge rapidly during treatment via *tetA*-linked mechanisms [11]. Colistin resistance has been documented to emerge quickly in KPC-2–producing hypervirulent carbapenem-resistant *Klebsiella pneumoniae*-infected neonates, showing how fast "worst-case" combinations can converge [12].

Ceftazidime–avibactam is not exempt from this logic. High-level resistance has been linked to in-host evolution of *blaKPC* (including variant emergence and increased gene copy number) in a lung transplant recipient [13].

Experimental evidence thus supports the broader point that immunosuppression can widen the evolutionary routes available under antibiotic therapy, increasing the likelihood of resistance-linked failure [14].

The Core Claim

For immunocompromised patients with drug-resistant infections, antibiotic escalation alone is often an incomplete strategy. It can be life-saving in the short term, but it also increases selection pressure in exactly the host environment where bacteria have time to adapt. The practical goal should therefore be twofold: treat the acute infection and reduce the conditions that favour within-host evolution. That means shortening the time bacteria persist, reducing repeated exposure to the strongest antibiotics where possible, and prioritising adjunct and alternative therapies early, before options narrow further [2,9,10].

Where Bacteriophages Fit as a Promising Adjunct

Bacteriophages (often shortened to phages) are viruses that infect bacteria. Therapeutic phage use focuses mainly on lytic phages, which attach to specific bacteria, replicate inside them, and lyse them to release new phage particles [15,16].

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Phage therapy should be presented as an example of a promising adjunct to antibiotics. Its relevance to this discourse is that phages bring several properties that address the main problem that has already been established: rapid within-host evolution of highly adaptable pathogens, including major hospital pathogens such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecium* [9,10].

Why Phages Are a Good Conceptual Match for Immunosuppression

First, specificity and safety. Phages are usually highly specific for their bacterial targets. That specificity is one reason they are often regarded as having a favourable safety profile: they do not directly target human cells, and they can spare much of the commensal microbiota compared with broad-spectrum antibiotics [15]. A systematic review of clinical phage therapy reports a low incidence of adverse events across different routes of administration, supporting the view that phage therapy is generally safe when properly prepared and administered [17]. Trial data also support tolerability, even when efficacy varies by setting and design [18].

Second, self-amplification at the infection site. Unlike most antibiotics, phages can increase in number where susceptible bacteria are present, a feature often described as "auto-dosing" or self-amplification [19]. This matters in immunocompromised infections because bacterial burdens can be high and persistent. A therapy that can intensify at the site of infection, when a suitable target is present, fits the clinical reality better than a fixed-dose approach alone [20].

Third, the ability to keep pace with bacterial adaptation. As mentioned earlier, high-risk pathogens can evolve rapidly under treatment pressure in immunocompromised hosts. A reasonable expectation, then, is that the intervention must be able to respond when bacteria change. Bacteria, however, can and do evolve resistance to phages, especially when a single phage is used. Resistance can also emerge against phage cocktails, although it may occur more slowly because bacteria must overcome more than one phage at once [21]. Intriguingly, phages can also evolve to infect bacteria that have become phage-resistant, because phage infectivity is itself selectable and changeable. This back-and-forth "arms race" between bacterial defence and phage counter-adaptation has shaped bacterial and phage evolution over long evolutionary timescales and is a central reason why phage therapy is conceptually suited to infections where rapid adaptation is expected [22,23].

This evolutionary flexibility can be exploited clinically. One practical approach is phage training, where phages are pre-adapted through coevolution with their target bacteria before therapeutic use [24]. This is relevant for immunocompromised patients because the infections we worry about most, often caused by highly adaptable hospital pathogens such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species, can evolve quickly under strong treatment pressure [25]. In that setting, an adjunct that can be iterated and updated as the bacteria change is a rational fit.

Optimisation of Phage Therapy via Phage Cocktails and Phage–Antibiotic Synergy (PAS)

A major practical limitation of phages is their narrow target range. Two approaches can be taken to improve their suitability for the treatment of infections in immunocompromised individuals:

Phage cocktails. Using mixtures of phages can broaden coverage and reduce the chance that a single bacterial change causes escape. Phage cocktail design is now a formal area of study, including rational approaches aimed at improving breadth while reducing resistance risk [16].

Phage–antibiotic synergy. Combining phages with antibiotics can sometimes increase bacterial killing and reduce escape compared with either agent alone, a phenomenon described as 'synergy'. Reviews summarising the current landscape of phage–antibiotic synergy support this as a realistic strategy, while emphasising the need for careful pairing and method standardisation. This is because synergy is dependent on antibiotic class, dosing relationships, and the specific phage–bacterium pairing [26]. Further, several studies have demonstrated that phage–antibiotic combinations can also steer bacterial evolution in clinically useful directions, by resensitising previously resistant bacteria in certain models [27,28].

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What Should Change in Practice?

If within-host evolution is a major driver of treatment failure in immunocompromised patients, then "treat harder for longer" cannot remain the default logic. A practical, realistic shift would include:

1. Treating immunocompromised drug-resistant infections as high-evolution-risk from the start.
2. Acting early on persistence and reservoirs. If gastrointestinal carriage or other reservoirs are present, treat them as part of the problem, because they prolong the evolutionary window [10].
3. Introducing adjuncts earlier in selected high-risk cases. This includes phage therapy as one option, particularly when infection is persistent, relapsing, device-associated, or when susceptibility is shifting during therapy [17].
4. Using phages responsibly and systematically. That means isolate recovery, phage susceptibility testing, careful product quality control, and monitoring for bacterial escape, then updating the phage approach when needed [15].
5. Prefering strategies that reduce selection pressure. Where clinically feasible, using phage cocktails and phage–antibiotic synergy to add killing power and reduce reliance on prolonged sequences of last-line antibiotics [19].

Conclusion

Immunocompromised patients face infections where pathogens can evolve quickly and repeatedly under treatment pressure. Adjunct and alternative therapies should be prioritised earlier in these cases. Phage therapy is one promising option because it is targeted, generally safe when properly prepared, can amplify where the target bacteria are present, and can be iterated to keep pace with bacterial adaptation.

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