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Antibiotics: 5 Myths Debunked

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Myths Surrounding Antibiotics

After 80 years of experience, much is known about antibacterial agents. Unfortunately, some of what is "known" is incorrect. To paraphrase Osler, half of everything we're taught is wrong—the problem is, which half?

Here, we seek to debunk five widely believed myths about antibiotics and resistance.

Myth 1: Humans Invented Antibiotics in the 20th Century

The first clinically useful antibacterial agent that was safe and effective was prontosil rubrum, a sulfa drug synthesized in 1931.[1] However, prontosil was not the first antibacterial agent to be invented, and humans were not the initial inventors.

Genetic analysis indicates that bacteria invented antibiotics and an antibiotic-resistance mechanism somewhere between 2 and 2.5 billion years ago.[2-4] Bacteria have been killing each other with these weapons, and using resistance mechanisms to protect themselves against these weapons, for 20 million times longer than we have even known that antibiotics exist.

To underscore the point, in 2011, a study[5] was published in which investigators explored a deep cave in the Carlsbad Caverns system in New Mexico, a geological formation that has been isolated from the surface of the planet for 4 million years. The section of the cave that they explored had never before been accessed by humans.

The investigators cultured many different types of bacteria from the walls of the caves. Every strain of bacteria was resistant to at least one modern antibiotic; most were multidrug-resistant. Not only was resistance found to naturally occurring antibiotics, it was also found to synthetic drugs that were not created until the 1960s-1980s (including fluoroquinolones, daptomycin, and linezolid).

Implications of busting this myth. After 2 billion years of microbial evolutionary warfare, microbes have already invented antibiotics to poison every possible biochemical pathway, and resistance mechanisms to protect every one of those pathways.[4] Thus, resistance mechanisms to antibiotics that have not yet been invented are already widespread in nature. Resistance is inevitable.

Myth 2: Inappropriate Antibiotic Use Causes the Development of Resistance

This myth is often repeated, with the implication that if we could eliminate inappropriate antibiotic use, resistance would no longer develop. However, all antibiotic use causes selective pressure by killing off bacteria. Appropriate use applies the same selective pressure as does inappropriate use. The difference is that we can and should stop inappropriate use because it offers no benefit. In contrast, appropriate antibiotic use is necessary to reduce mortality and morbidity from bacterial infections.

Implications of busting this myth. We accept that there will always be emergence of resistance from appropriate antibiotic use, but the benefit of appropriate antibiotic use to patients and society outweighs the collective harm. In contrast, without a benefit attached to inappropriate use, there is no "pro" to offset the "con" of selective pressure for antibiotic resistance.

In essence, we must seek to eliminate inappropriate antibiotic use not because this will end emergence of resistance, but because it will slow it down without forgoing any meaningful benefit of antibiotic use.

Myth 3: To Prevent Resistance, Patients Must Complete Every Dose of Antibiotics Prescribed, Even After They Feel Better

The origins of this myth are slightly obscure, but appear to date back to the 1940s.[6,7] Despite how widespread and deeply this belief is held, there are no data to support the idea that continuing antibiotics past resolution of signs and

symptoms of infection reduces the emergence of antibiotic resistance.[7]

To the contrary, studies have repeatedly found that shorter-course therapies are less likely to select out for antibiotic resistance, which is consistent with fundamental principles of natural selection.[7] Every randomized clinical trial that has ever compared short-course therapy with longer-course therapy, across multiple types of acute bacterial infections (including cellulitis, acute bacterial sinusitis, community-acquired pneumonia, nosocomial pneumonia/ventilator-associated pneumonia, complicated urinary tract infections, and complicated intra-abdominal infections), has found that shorter-course therapies are just as effective.[7] When evaluated, shorter-course therapies have resulted in less emergence of resistance.

Implications of busting this myth. This myth needs to be replaced by a new antibiotic mantra: "Shorter is better!"[7] Patients should be told that if they feel substantially better, with resolution of symptoms of infection, they should call the clinician to determine whether antibiotics can be stopped early. Clinicians should be receptive to this concept, and not fear customizing the duration of therapy.

Continuing antibiotics past resolution of symptoms for acute bacterial infections (not chronic infections, such as osteomyelitis, tuberculosis [TB], or actinomycosis) does not afford patient benefit and probably selects for antibiotic resistance.

Myth 4: When Antibiotic Resistance Emerges, It Is Usually a Consequence of New Mutations at the Site of Infection

This myth possibly stems from the correct recognition that resistance in TB occurs at the site of infection, owing to spontaneous mutations targeting TB therapy.[8] However, TB has unique features distinct from those of most acute bacterial infections.

There is no environmental reservoir for TB, and TB is not part of our normal flora. Therefore, TB resistance can only occur at the site of infection in the body. TB cavities also contain very high densities of bacilli (ie, > 10^{12} per gram), which predispose to the emergence of resistance on monotherapy, on the basis of the statistical frequency of spontaneous mutations to such drugs as isoniazid and rifampin.

In contrast, when we use typical antibiotics (different from isoniazid, which is specific for TB), they inevitably cause selective pressure among a person's normal bacterial flora. In most cases, resistance emerges not at the site of infection during a course of therapy, but rather among bacteria in the gut or on the skin as a result of genetic sharing of preexisting resistance mechanisms (eg, plasmids, transposons, phages, naked DNA).[8]

Enrichment for resistant normal flora can result in future infections caused by the resistant pathogens, and spread of the resistant pathogens through contact with other people or fomites.

Implications of busting this myth. In most cases, we are not aware when resistance emerges in patients. The fact that the patient's infection resolves with prolonged or unnecessarily broad antibiotic therapy does not mean that you have escaped inducing resistance. To the contrary, it is very likely that after exposure to antibiotics, somewhere in the patient's body, strains of normal flora that are resistant to the antibiotics used have been enriched. Those strains can cause future infections, or spread to others in communities or hospitals.

Myth 5: Cidal Antibiotics Result in Superior Clinical Outcomes and Less Risk for Emergence of Resistance Than Do Static Antibiotics

This is another widespread clinical belief that is based on no evidence. First, contrary to common belief, bacteriostatic ("static") antibiotics do kill bacteria; they just require a higher concentration to achieve specific thresholds of bacterial reduction. The formal definition of a bactericidal ("cidal") antibiotic is one for which the minimum bactericidal concentration (MBC) of the drug is fourfold or more above the minimum inhibitory concentration (MIC) of the drug.[9]

The MBC is the concentration of the drug that results in a 1000-fold reduction in bacterial density at 24 hours of growth. The MIC is the concentration that inhibits visible growth at 24 hours of growth. These definitions are arbitrary: Why should it be that MBC requires a 1000-fold reduction in bacterial density as opposed to a 100-, 500-, 5000-, or 10,000-fold reduction? Why 24 hours? Why must the MBC not be more than fourfold above the MIC, as

opposed to twofold, or 16-fold, or 23-fold?

Finally, an antibiotic that achieves a > 1000-fold reduction in bacterial density but does so at a concentration that is eightfold above the MIC of the drug is considered static, even though it clearly kills the bacteria.

Given that these terms have been defined by accepted convention and are not based on specific scientific principles, perhaps it is not surprising that there is no clinical evidence of benefit of cidal agents over static agents. A systematic literature review identified 28 randomized controlled trials that compared the efficacy of static vs cidal antibiotics, head to head, for patients with invasive bacterial infection (Table).

Table. Randomized Controlled Trials Comparing Cidal vs Static Therapy

Disease	Drugs	Efficacy
Typhoid fever[10-13]	Chloramphenicol (static) or azithromycin (static) vs levofloxacin (cidal) or cefixime (cidal)	No significant difference
Cellulitis[14]	Doxycycline (static) vs TMP/SMX (cidal)	No significant difference
Chlamydia (genital)[15]	Azithromycin (static) vs rifalazil (cidal)	No significant difference
Meningococcal meningitis[16]	Chloramphenicol (static) vs ceftriaxone (cidal)	No significant difference
Febrile neutropenia[17]	Linezolid (static) vs vancomycin (cidal)	No significant difference
MRSA infections[18] (across infection sites)	Linezolid (static) vs TMP/SMX + rifampin (cidal)	No significant difference
Gram-positive infections in children[19]	Linezolid (static) vs vancomycin (cidal)	No significant difference
Skin infections[20]	Linezolid (static) vs vancomycin (cidal)	No significant difference
Gram-positive catheter-associated bloodstream infection and skin infections[21]	Linezolid (static) vs vancomycin (cidal)	No significant difference
Pediatric severe community-acquired pneumonia[22,23]	Chloramphenicol (static) vs beta lactam + gentamicin (cidal)	No significant difference
Community-acquired pneumonia[24-26]	Doxycycline (static) vs beta lactam or fluoroquinolone (cidal)	No significant difference
Aspiration pneumonia[27-29]	Clindamycin (static for anaerobes) vs beta-lactam (cidal)	No significant difference
Nosocomial pneumonia[30]	Linezolid (static) vs vancomycin (cidal)	No significant difference
Ventilator- associated pneumonia[31]	Tigecycline (static) vs imipenem (cidal)	No significant difference

Cellulitis[32-34]	Linezolid (static) vs vancomycin (cidal)	Linezolid (static) superior
Streptococcus pneumoniae community pneumonia[35]	Linezolid (static) vs cephalosporin (cidal)	Linezolid (static) superior
MRSA nosocomial pneumonia[36]	Linezolid (static) vs vancomycin (cidal)	Linezolid (static) superior
Ventilator-associated pneumonia[37]	Tigecycline (static) vs imipenem (cidal)	Imipenem (cidal) superior

MRSA = methicillin-resistant Staphylococcus aureus; *TMP/SMX = trimethoprim/sulfamethoxazole*

Almost no trials found a significant difference in efficacy between static vs cidal antibiotics. The exceptions? Three studies found the static agent linezolid to be superior in efficacy to the cidal agent vancomycin for the treatment of complicated skin infections,[32-34] and one trended toward superiority of linezolid (*P* =.057).[20] A trial found that linezolid was superior in efficacy to vancomycin for the treatment of MRSA pneumonia,[36] and another found linezolid to be superior in efficacy to cephalosporins for pneumococcal pneumonia.[35]

In contrast, only one trial found a cidal antibiotic to be superior in efficacy to a static agent. That trial compared tigecycline vs imipenem for the treatment of ventilator-associated pneumonia, and found that tigecycline was inferior.[37] However, pharmacologic analysis determined that the tigecycline dose used in the trial was too low, resulting in inadequate drug levels compared with the susceptibility of bacteria causing the infections[38]; when a subsequent trial was done with double the dose of tigecycline, tigecycline was similar in efficacy to imipenem for the same disease.[31]

Thus, there is no evidence that cidal antibiotics are more clinically effective than static antibiotics. To the contrary, more studies have found a static agent to be superior in efficacy to a cidal agent than the reverse!

Implications of busting this myth. Although clinicians continue to prefer cidal antibiotics, there is no evidence that these result in superior clinical outcomes than static agents, nor that cidal drugs more effectively prevent the emergence of resistance. Whether an antibiotic is static or cidal should not be a factor in determining antibiotic therapy for patients.

What Are the Take-Home Messages for Clinicians?

There is no end to our struggle with bacteria; we will never "win a war" against them, and no "gorilla-cillin" will ever come along to save us from emergence of antibiotic resistance. Resistance is inevitable.

Thus, it is critical that we not waste antibiotics. They must not be prescribed to patients who do not have bacterial infections. When appropriate, prescribe the narrowest-spectrum agent and the shortest duration possible to treat bacterial infections.

Do not instruct patients to take every dose prescribed even after they feel better. Rather, focus on evidenced-based, short-course regimens, and if the patient's symptoms resolve before completing the course of therapy, ask that they call you to discuss whether they should stop the antibiotic course early. Encourage them to stop early when their symptoms resolve.

Do not be falsely reassured by the lack of emergence of resistance at the site of infection. When you prescribe an antibiotic, you are selecting for resistance in the patient's microbiome. The resistant bacteria colonize the patient and can cause future antibiotic-resistant infections.

When choosing an antibiotic regimen, cidal vs static is largely irrelevant.

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