



# "I Think I Need a Different Prescription..."



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## Harry's Case

Harry, a 64-year-old man, returns to the ED five days after starting a course of clarithromycin for community-acquired pneumonia. Although he is no longer febrile and his vital signs are within normal limits, he complains of continued cough, and is still very weak. He has mild COPD and is being treated for hypertension, but is otherwise healthy. He would like to try a different antibiotic.

Read on for more on Harry.

## Questions and Answers

### 1. When should we consider that we are dealing with 'failure' of antimicrobial therapy?

Most definitions of antibiotic failure in the literature are for the purposes of evaluating therapy in clinical trials; several specific definitions are: the need for specialist consultation, hospital admission, mechanical ventilation, a change in antibiotics or a surgical procedure (*e.g.*, incision and debridement), depending on the disease process being treated. These definitions are not that helpful in a busy ED; for the purposes of this article we will refer to antibiotic failure as: "failure of the patient's clinical condition to improve to a satisfactory extent following an adequate dose and duration of therapy with an antimicrobial agent."

### 2. Why do some patients fail to improve on antibiotics?

The reason for lack of response to antibiotics depends on a number of factors (Table 1), and this apparent lack of response is an opportunity to re-evaluate the clinical situation, in the light of apparent non-response or progression of symptoms. Although the most common reason for non-response is that the original illness did not indicate antibiotic therapy, another common reason is unrealistic expectations of both patient and provider. Antibiotics (with a few exceptions) do not treat the non-infective aspects of disease, they just kill bacteria. Much of the symptomatology of infectious disease results from the inflammation that the infection initiates. Clinical and radiologic response will frequently lag behind bacterial eradication, especially in older patients. Patients should always be warned at the start of therapy that infections cannot be "switched off" like an electric light; for example, symptoms of pneumonia in young, otherwise healthy people are often still present a month after starting treatment, and older patients with the disease should expect to wait six months before returning to baseline. However, they should also be warned that progression of symptoms is an indication for a re-assessment.

**Table 1**  
**Factors to Consider When Faced with Antibiotic Failure**

Non-response Reason	Examples
Initial misdiagnosis	<ul style="list-style-type: none"> <li>• Non-bacterial infection (viral, fungal, mycobacterial)</li> <li>• Non-infective illness (e.g., vasculitis, auto-immune process, allergic, ischemic, venous thromboembolism)</li> </ul>
Inadequate spectrum of coverage	<ul style="list-style-type: none"> <li>• Different class of organism (gram-negative, anaerobe)</li> <li>• Resistant organism (e.g., MRSA, PRSP)</li> </ul>
Improper pharmacokinetics	<ul style="list-style-type: none"> <li>• Concentration-dependent drug at inadequate dosage</li> <li>• Time-dependent drug at inadequate dosing interval</li> <li>• Inadequate dosage at site (e.g., blood versus urine)</li> <li>• Augmented renal clearance</li> </ul>
Illness-specific issues	<ul style="list-style-type: none"> <li>• Severe inflammatory response to infection</li> </ul>
Complication of original problem	<ul style="list-style-type: none"> <li>• Re-infection after initial response</li> <li>• Co-infection of unsuspected organism</li> <li>• Superinfection of a new organism</li> </ul>
Inadequate source control	<ul style="list-style-type: none"> <li>• Retained products of conception</li> <li>• Abscess/pus</li> <li>• Foreign body</li> </ul>
Drug-related issue	<ul style="list-style-type: none"> <li>• Drug fever</li> </ul>
Lab error/inappropriate use of tests	<ul style="list-style-type: none"> <li>• Contaminant or false positive microbiology test suggesting inappropriate agent</li> </ul>
Patient expectations	<ul style="list-style-type: none"> <li>• Impatience</li> <li>• Unrealistic expectations</li> </ul>

### 3. When should we consider a change of therapy?

It has been said that “the most common mistake made with apparent antibiotic failure, is to change or add additional antibiotics.”<sup>1</sup> The same author goes on to say that “the most important strategy is to analyze the cause of the antibiotic failure by careful evaluation and use of appropriate diagnostic tests to avoid needless, expensive, and potentially dangerous antimicrobial therapy.”<sup>1</sup>

Carefully reconsidering the original diagnosis is the most important step at this stage. Presuming that after this, you are still convinced

of a bacterial cause, the next question is whether the apparent non-response is simply due to inadequate healing time. In these cases, the vital signs generally will have returned to normal, and the symptoms will not be worse (the margin of cellulitis may actually increase in the first 48 hours of treatment, but fever will generally settle rapidly).

If the patient’s condition is deteriorating, the next step depends on the perceived cause of non-response. A thorough history of how the patient became infected may suggest a less common organism. For example, infections of wounds sustained in lakes, the ocean or from animal bites will often not respond to first-generation cephalosporins; instead they require antibiotics with coverage against unique pathogens. A table of antimicrobial sensitivities (antibiogram) in your area or hospital may be available from your microbiology laboratory, and, along with an idea of local resistance patterns, may guide you to a different antibiotic. If the patient was recently in another geographical area, it is a good idea to find out resistance patterns from that area.

Patients are most likely to carry bacteria that are resistant to any antibiotic that they have received in the previous three months, so prescribing a different class of antibiotic is a good approach.<sup>2</sup> Writing another prescription for the current drug, to which they have not adequately responded, should only be considered if there has been partial but inadequate response in patients who are difficult to clear of infection (e.g., lymphedema). Precipitants of infection, such as smoking, urinary obstruction or athlete’s foot, should be addressed. In skin and soft

Table 2

## Patient Conditions Associated with Slow Response to Antibiotics

Patient Factors	Examples
Chronic co-morbidity affecting healing	<ul style="list-style-type: none"> <li>• Circulation issues</li> <li>• Immune suppression</li> <li>• Lymphedema</li> <li>• Obesity</li> </ul>
Condition that precipitated infection	<ul style="list-style-type: none"> <li>• Obstructing tumour</li> <li>• Foreign body</li> <li>• Athlete's foot</li> <li>• Dry dermatoses</li> <li>• Infection (scabies, bed bugs)</li> </ul>
Patient behavioural issues	<ul style="list-style-type: none"> <li>• Patient compliance with prescription</li> <li>• Compliance with instructions (elevation)</li> <li>• Smoking</li> <li>• Munchausen's syndrome (or by proxy)</li> </ul>


tissue infection, the possibility of occult pus should be aggressively pursued, by ultrasound or aspiration, if indicated.

Contemporary recommendations for antibiotic treatment often indicate shorter courses; however, certain patients, such as those with peripheral vascular disease, lymphedema or a history of requiring prolonged treatment, may well need extended courses or a higher dose of medication. These patients are often better served by referral to an infectious disease specialist.

## Back To Harry

After re-examination, Harry does not seem to be significantly worse than on his initial visit. He is reassured that the symptoms of pneumonia will take several weeks to resolve, and that repeating his X-ray or blood tests will not likely change treatment. He is prescribed symptomatic therapy and told to return if his fever reappears or if he becomes more short of breath.

The advantages of intravenous administration over oral administration have yet to be proven; however, in critically ill patients, those who have previously required long-term intravenous antibiotics, or in cases of suspected malabsorption or bacteremia, intravenous administration is prudent.

Inappropriate antibiotic use is not benign; it adds an unnecessary expense, may delay correct diagnosis, and may cause toxicity, allergy, and the selection of resistant organisms in patients. Perhaps most important is the issue of “antibiotic pollution” in our environment, which threatens our therapeutic armamentarium against multiply-resistant organisms. 

### References

1. Cunha BA, Ortega AM. Antibiotic Failure. *Med Clin North Am.* 1995;79(3):663-72.
2. Vanderkooi OG, Low DE, Green K, et al. Predicting Antimicrobial Resistance in Invasive Pneumococcal Infections. *Clin Infect Dis* 2005;40(9):1288-97.

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Publication Mail Agreement No.: 40063348  
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