In Vitro Versus In Vivo Culture Sensitivities: An Unchecked Assumption?

Vinay Prasad, MD*
Nancy Ho, MD‡

*Medical Oncology Branch
National Cancer Institute
National Institutes of Health
Bethesda, Maryland.
vinayak.prasad@nih.gov

‡Department of Medicine
University of Maryland

Case Presentation

A patient presents to urgent care with the symptoms of a urinary tract infection (UTI). The urinalysis is consistent with infection, and the urine culture is sent to lab. In the interim, a physician prescribes empiric treatment, and sends the patient home. Two days later, the culture is positive for *E. coli*, resistant to the drug prescribed (Ciprofloxacin, Minimum Inhibitory Concentration (MIC) 64 μg/ml), but attempts to contact the patient (by telephone) are not successful. The patient returns the call two weeks later to say that the infection resolved without sequelae.

Discussion

Many clinicians have the experience of treatment success in the setting of known antibiotic resistance, and, conversely, treatment failure in the setting of known sensitivity. Such anomalies and empiric research described here forces us to revisit assumptions about the relationship between *in vivo* and *in vitro* drug responses.

When it comes to the utility of microbiology cultures, other writers have questioned cost effectiveness and yield (1). Though it is considered a quality measure by some groups in the United States, routine blood cultures seldom change antibiotic choice (3.6%) in patients who present to the emergency room with the clinical and radiographic signs of pneumonia (2)

The objection here is different, but fundamental. Even when culture sensitivities suggest we should change antibiotics, what empirical evidence is there that such changes are warranted? It is by no means a novel doubt. In 1963, at the dawn of *in vitro* sensitivity techniques, one group questioned their utility to predict clinical outcomes:
“Several objections may be raised…. First, local or host defense mechanisms may act in synergism or antagonism with the antibiotic. Second, the concentration of antibiotic in tissue fluids, specifically blood, might bear no relation to the concentration at the site of infection…” (3)

And, while substantial pharmacologic progress has been made to ensure proper tissue concentrations, few empirical studies have sought to address the first concern (4). Recent examples suggest the relationship between in vitro and in vivo outcomes may be questionable.

One study of H. pylori tackled this issue (5). Macrolide and metronidazole resistance were determined in lab, and a urea breath test assessed clinical response. Interestingly, treatment with a clarithromycin regimen failed in 77% of persons with clarithromycin-resistant H. pylori compared with 13% of those with clarithromycin-susceptible isolates (relative risk, 6.2 [CI, 1.9 to 37.1]; P < 0.001). While treatment with metronidazole-based therapy failed in 11% of those with metronidazole-resistant isolates and 38% of those with metronidazole-susceptible isolates (P > 0.25).

These results suggest that metronidazole susceptibility wholly lacks clinical utility, while clarithromycin sensitivity may be useful. To fully prove the utility of clarithromycin sensitivity testing the authors should show a higher cure rate with a different regimen, and then demonstrate that upfront screening is preferable to empiric treatment and observation.

Another study suggests that for some organisms and infections—Acanthamoeba keratitis—there exists no relationship at all between in vitro drug sensitivities and the in vivo response (6).

For some conditions, knowing that a causative organism is susceptible in vitro does in fact predict clinical response. For instance, a large study of gram-negative infections treated with cefotaxime found that as the MIC increased, from <4 μg/ml to 64 μg/ml (in vitro), the rate of clinical response fell from 91% to 50% (4). Thus, nearly all patients with susceptible organisms (low MIC) were successfully treated. But, perhaps, what is most interesting about this study is that even resistant organisms were effectively treated in 50% of patients. This finding is supported by work in urinary tract infections, which similarly found a high percentage of clinical response (>80%), even among patients whose causative organisms were resistant to prescribed agents (7).

Basic studies are required for bacteremia, pneumonia, urinary tract infections, endocarditis, and others. To do this work, we should not use our words interchangeably. Treatment failure must refer to an independent clinical outcome and not defined circularly as antibiotic resistance. As of today, faith that in vitro results predict in vivo outcomes remains an unchecked assumption whose treatment implications remain vast and reaching.
References


