

Personal opinion: Can antifungal sensitivity tests predict clinical treatment outcomes?

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Laboratory tests done with clinical specimens can only ever measure directly the quantity or condition of one or more parameters of the specimen. Responsibility for deciding the meaning of the test result in the clinic lies with the physician attending the patient concerned. The laboratory must, of course, ensure that each test is done with the most stringent possible quality controls to minimize the probability of technical artefacts leading to results that might be misinterpreted in the clinic.

As with all medical laboratory tests, the results of measurement of sensitivity of a fungus to one or more antifungal agents *in vitro* lie on a spectrum between two extremes. At one end are tests (measurements of serum electrolytes are examples) where results that differ from "normal" cannot on their own possibly indicate a precise clinical diagnosis or prognosis. At the other end are tests (many serodiagnostic tests for virus infections are examples) where a positive or negative result has a very high probability of indicating a specific clinical situation. Indeed, it is no accident that serological tests are usually evaluated for their efficacy in terms of statistics that include their "predictive value".

My personal opinion of all antimicrobial sensitivity testing, whether with antibacterials or antifungal agents, is that the results usually have only a low predictive value for the clinician, but that they are far too often interpreted as if their predictive value is high. I believe that microbiologists should work much harder to educate physicians to understand the limitations of sensitivity tests. Such tests provide useful advisory information in determining treatment, but they do not and cannot predict definitively when a particular antimicrobial agent will and will not successfully treat an infected patient.

Over the years, antibacterial testing has developed a mystique close to a dogmatic, almost religious belief. If a bacterium is reported as "sensitive" to a particular agent, then that agent is automatically regarded as a potentially useful treatment for eradication of the bacterium. If a bacterium is reported as "resistant" to an agent, then that agent is usually excluded for use in the infected patient. In reality, this black-and-white interpretation of a sensitivity test result is a massive over-simplification. A sensitivity test predicts only how to treat an infected test tube [1].

There are many reasons why a "sensitive" bacterium may not respond to treatment with an agent that works *in vitro*: they include achievement of inadequate levels of the agent at the site of infection (for reasons that range from the patient failing to take the treatment to inadequate penetration of drug to an infected site) and anti-infective host responses insufficient to eliminate bacteria that have been incapacitated by an agent *in vivo*. There are also many reasons why a bacterium may well respond to treatment with an agent even when it is "resistant" *in vitro*. These include subinhibitory effects of an agent sufficient to allow host defences to eradicate the organisms (a current research growth area) and the possibility that the bacterium tested is not really the microbe causing the infection (a particular possibility when a culture has been made from samples that are not ordinarily sterile).

Those who consider that I am overstating the failure of antibacterial tests to predict clinical outcome should consult the many published papers in which the relation between results *in vitro* and *in vivo* have been assessed with antibacterial agents: chapters 16 and 17 in the current edition of Lorian's "Antibiotics in Laboratory Medicine" [2,3] cite many examples where far fewer than 100% of patients infected with "sensitive" bacteria respond clinically to treatment yet as many as 40-60% of patients infected with "resistant" bacteria do respond to treatment. From these accounts alone it is obvious that the predictive value of "susceptibility" and "resistance" in laboratory tests depends substantially on the nature of the host, the specific site of infection and the pharmacokinetics of the agent in a particular host. It is clearly naive to base the choice of treatment entirely on the results *in vitro*. There are just too many imponderables to permit simplistic extrapolation from the refined simplicity of a lab test to the near-chaotic complexity of an infected human host.

Where antifungal agents are concerned the picture is exactly the same as that with antibacterial agents. A recent publication by Rex *et al.* [4] sets out comprehensively the considerations for determining interpretive breakpoints with two azole antifungal agents in the context of *Candida* infections. At the critical MIC levels selected by Rex and his colleagues [4] as indicating resistance to two triazole antifungal agents *in vitro* it is noteworthy that for both itraconazole and fluconazole, "resistant" strains were associated with a positive clinical response to the agent in 55% of the cases analysed. These figures are directly parallel to those obtained with many analyses of correlations between results *in vitro* and *in vivo* with antibacterial tests and they confirm that it is irresponsible and possibly dangerous to put too much interpretive weight on results of lab tests for antifungal sensitivity. Dangerous, because in life-threatening mycoses a decision not to use

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a particular antifungal agent solely because of a finding of "resistance" *in vitro* might be fatal for a patient. With the relatively limited selection of antifungals currently available for such infections a decision to withhold the use of any particular agent on grounds of fungal resistance should never be taken lightly.

The currently high interest in fungal infections that has been stimulated by a rise in their incidence in immunocompromised hosts has led inevitably to increased interest in antifungal sensitivity testing. More laboratories than ever are seeking to do such tests themselves, and more commercial interests than ever are entering the market for antifungal test kits. This situation is healthy only when the testing and kit development are done in a highly responsible manner. How many labs and kit producers first seek to relate the results of their tests to those obtained with a well-defined antifungal reference method? (The NCCLS method M27A [5] has to be the definitive choice at present). How many labs routinely include defi-

ned reference strains with each test to ensure adequate quality control? How many labs purchase their QC strains directly from a well-regulated, dependable source such as the ATCC or the CBS? How many labs and kit producers make an effort to inform physicians that the results of their tests have only an advisory value in predicting optimal antifungal therapy for a patient?

We should try to be self-critical when we conduct tests in the laboratory. What is the precision of the data? How reproducible are our results? How well do they correlate with results from other laboratories? With antifungal (and most antibacterial) sensitivity tests the published data show that the results are of scientifically proven worth only in a limited set of circumstances [6] and that clinical correlations with MICs are weaker than ideal. We should try to convey that message to physicians along with the results: that way we might ultimately achieve enough clinical interest in the correlation problem to help us devise constructive solutions.

References

1. This is not a novel comment: I first heard it years ago from the mycologist H.B. Levine, and he may well himself have picked it up from someone else before him: such is the nature of pithy remarks.
2. Nicolle LE. Measurement and significance of antibiotic activity in the urine. In: V. Lorian (ed) *Antibiotics in Laboratory Medicine* (4th ed.) Williams & Wilkins, Baltimore, 1996: 793-812.
3. Johnson CC. *in vitro* testing: correlations of bacterial susceptibility, body fluid levels, and effectiveness of antibacterial therapy. In: V. Lorian (ed) *Antibiotics in Laboratory Medicine* (4th ed.) Williams & Wilkins, Baltimore, 1996: 813-834.
4. Rex JH, Pfaller MA, Galgiani JN *et al*. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of *in vitro*—*in vivo* correlation data for fluconazole, itraconazole, and *Candida* infections. *Clin Infect Dis* 1997; 24: 235-247.
5. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved method M27-A. Villanova, Pennsylvania, National Committee for Clinical Laboratory Standards, 1997.
6. Pfaller MA, Rex JH, Rinaldi MG. Antifungal susceptibility testing—technical advances and potential clinical applications. *Clin Infect Dis* 1997; 24: 776-784.