

Diagnostic Gaps in Infectious Diseases: A Proposal for an Interdisciplinary Approach to Develop Mass Spectrometry Methods to Find the Bug and Treat the Host

Speakers:

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Infectious disease testing is traditionally performed under the purview of clinical microbiologists, with the application of Mass Spectrometry in the clinical microbiology laboratory being limited mainly to the identification of microorganisms growing in culture. The development of mass spectrometry applications is, in contrast, generally under the purview of chemists. However, there are a large number of technological gaps in both the diagnosis and management of infections that could potentially make ideal candidates for MS-based solutions. In this panel discussion, three clinical microbiologists will present clinical problems and/or unmet diagnostic needs in the field of clinical microbiology. A panel of experts in MS will then respond to each need presented, weighing in on the potential feasibility of a MS-based analytical solution. The major objective of this session is to foster interdisciplinary collaborations to improve both

the diagnosis and management of infections using novel MS-based assays.

I—Sepsis

Sepsis continues to be a major cause of morbidity and mortality in the United States and worldwide, with increasing mortality observed for each hour of inappropriate antimicrobial therapy. However, assessment of the appropriateness of antimicrobial therapy currently requires growth of the causative microorganism in culture. Even though microorganisms can be directly identified from positive blood cultures and key antimicrobial resistance determinants detected (e.g. methicillin-resistance in *Staphylococcus aureus* –MRSA), the organisms must first be cultured *in vitro*. This requirement results in a delay to assuring optimized, appropriate therapy of >18 hours. Furthermore, patients can remain bacteremic for extended periods (>5 days) despite being on apparently appropriate therapy, raising concerns for the development of future endocarditis. Thus, major diagnostic gaps in the diagnosis and management of sepsis and bloodstream infections include:

- Identification of microbes directly from blood
- Detection of microbial cell death from a blood sample to monitor response to antimicrobial therapy

II—*Clostridium difficile* Infection

Clostridium difficile is one of the most rapidly increasing and feared nosocomial pathogens. *C. difficile* infection (CDI) is a consequence of dysbiosis of the gut, which creates a niche where the organism can flourish and cause a toxin mediated illness. The diagnosis of CDI is difficult. One reason for this is that while *C. difficile* is an important cause of disease, it can be found as a asymptomatic colonizer of the gut. Controversy also exists around the best method for diagnosis of disease. Although nucleic acid detection methods are analytical sensitive, the positive predictive value of these tests can be poor. Alternative methods, like enzyme immunoassays for toxin detection, may lack sensitivity. Thus, the major diagnostic gaps in the diagnosis of CDI that may be reached through optimization of mass spectrometry applications are:

-Differentiation of colonization vs. disease state by proteomic analysis of fecal or blood samples from the host

-Detection and/or quantification of *C. difficile* toxins in fecal specimens

III - Tuberculosis Infection

Tuberculosis is a disease of enormous public health importance: It is estimated that almost one third of the world's population is latently infected with tuberculosis.

Reactivation of infection occurs in 5-10% of latently infected individuals. Although interferon-gamma release assays (IGRA's) are increasingly used in the diagnosis of latent tuberculosis, these assays are not suitable for the diagnosis of active disease. Pulmonary tuberculosis has traditionally been diagnosed using smear microscopy and culture, with nucleic acid detection-based methodologies being increasingly used more recently.

Nevertheless, even with nucleic acid detection, multiple specimens may still be required to rule out infection. Extra-pulmonary tuberculosis can be particularly difficult to diagnose as evidence of concomitant active pulmonary disease may often be lacking.

Thus, major gaps in the tuberculosis diagnostics are:

-Detection of active tuberculosis infection

-Early detection of reactivation