

Example Needs Statement from: Infectious Disease Case Conference

Infectious diseases kill more people worldwide than any other single cause. TB ranks second to HIV among infectious diseases killers worldwide, claiming nearly two million lives annually. The disease is evolving faster than therapies with the emergence in recent years of strains that are resistant to every last one of the antibiotic defenses. About 36,000 people per year in the US die from influenza. In the US, about 930,000 people are living with HIV or AIDS. Infectious diseases are in constant evolution therefore it is vital that physicians in this specialty stay abreast of the latest techniques for testing, current vaccines and the most effective treatment for this disease.

The use of rapid influenza tests can help to reduce unnecessary diagnostic testing, to facilitate antiviral treatment, to decrease inappropriate antibiotic use, and to reduce the duration of treatment in the emergency department or hospitalization. Rapid influenza tests also are used for public health purpose to investigate suspected influenza outbreaks. Identification of influenza virus infection by rapid tests can facilitate prompt implementation of control measures before confirmatory test results are available from shell viral culture, or RT-PCR (link #1, literature review, Low sensitivity of rapid diagnostic test for influenza).

According to researchers at Emory University, there is a new and faster method of rapidly producing highly targeted monoclonal antibodies for use in diagnostic tests as well as a temporary therapy to stave off infectious diseases such as the H1N1 (swine flu) virus. The monoclonal antibody technology allows researchers to quickly generate human antibodies against a pandemic flu strain as a stopgap therapy or to protect people from infection. The new method is quicker and less cumbersome and can be applied to almost any infectious disease (link #2, new technique, New, faster way to diagnose, fight flu).

Current tools for monitoring tuberculosis in preclinical studies are costly and time consuming. A new novel tool for non-invasive assessment of M. tuberculosis in liver experimentally-infected animals has been developed. This tool will allow real-time pathogenesis studies in animal models of TB and has the potential to simplify preclinical studies and accelerate TB research (link #3, recent research, Bacterial thymidine kinase as a non-invasive imaging reporter for Mycobacterium TB in live animals).

Experts at JH have evidence from a four-year series of experiments in mice that anti-inflammatory drugs could eventually prove effective in treating the highly contagious lung disease, TB, adding to current antibiotic therapies. The scientists say their findings are believed to be the first and most detailed explanation of how the invading bacterium evades the immune system and instead is protected by it, thus fostering infection (link #4, recent research, Fighting TB with anti-inflammatory drugs shown possible in animal studies).

A new TB vaccine called AdAg85A has been developed and based on pre-clinical studies, this vaccine appears likely to offer better protection against the potentially fatal disease (see attachment 5 recent research, TB vaccine developed, clinical trial starting).

A systematic review was performed to determine the effectiveness of different approaches for eradicating methicillin-resistant Staphylococcus aureus carriage. The most effective result from the review is a short term (4-7 days in duration) topical nasal application of mupirocin for eradicating MRSA, with an estimated success probability of ~90% 1 week after treatment and ~60% after a longer follow-up

period, ranging from 14 days through 365 days in different studies (link #6, literature review, Eradication of Methicillin-Resistant *Staphylococcus aureus*).

Example Needs Statement from: State of the Art Management of Blood Stream Infections and Sepsis

Bacteremia represents a failure of innate and adaptive immunity that often progresses to septic shock and significant mortality. Multiple portals exist for entry of bacteria into the bloodstream. One common mechanism is by breaching the skin barrier, for example, iatrogenically by vascular catheter or in abusers of intravenous drugs. Alternately, bacteremia can result from a local focus of infection, such as a skin and soft tissue infection, pneumonia, genitourinary tract infection or hepatobiliary tract infection. With or without associated bacteremia, such infections can trigger systemic inflammatory responses. Data collected from 198 intensive care units from 24 European countries indicated that the mortality rate for patients with severe sepsis was 32% and when septic shock was present the rate was 54%. (link #1, literature review, Zambon).

As the leading cause of bacteremia, *S. aureus* poses particular clinical challenges. *S. aureus* bacteremia is frequently

associated with endocarditis and spread of infection to other parts of the body including septic pulmonary emboli,

cerebral emboli, osteomyelitis and vertebral diskitis. Determining if *S. aureus* bacteremia is complicated by such metastatic spread influences treatment decisions and can justify routine use of transesophageal echocardiography to judge whether endocarditis is present. For methicillin-sensitive *S. aureus*, beta-lactam agents are the therapy of choice since they have superior outcomes compared to vancomycin. For MRSA, vancomycin remains first line therapy.

Importantly, a series of important but thorny issues continue to be debated regarding *S. aureus*, including persistent bacteremia, relapsing infection and vancomycin MIC creep—especially regarding what are the indications to change antibiotic therapy (link #2, data from public health source, IDSA Prevention of Endocarditis).

While *S. aureus* causes a significant portion of endocarditis cases, other important pathogens include Streptococcal species, gram-negative pathogens such as *Pseudomonas*, and less commonly, the HACEK group organisms. Clinicians ought to recognize that fever and constitutional symptoms, especially in combination with embolic phenomenon or newly arising heart failure, should prompt properly spaced and drawn blood cultures prior to antibiotic initiation.

Echocardiography is an important method to secure a diagnosis of endocarditis although occasionally serologic tests will be needed for the especially challenging cases of culture-negative endocarditis. Empiric antibiotic therapy should be narrowed according to susceptibility reports from the microbiology laboratory in conjunction with AHA/IDSA guideline recommendations on the type and the duration of antibiotic therapy (link #3, data from public health source – IDSA Endocarditis Management). If needed, proper timing of cardiac valve surgery often remains a part of the elusive to define mix of clinical judgment from infectious disease specialists, cardiologists and cardiac surgeons. If enterococci are offending organisms or prosthetic cardiac valves are infected, combination antimicrobial therapy is

often advocated by guideline statements, although evidence for this approach remains slender in the clinical literature. Furthermore, AHA/IDSA guidelines for endocarditis prophylaxis have recently been significantly changed, trimming the kinds of patients as well as procedure indications deemed necessary to receive antibiotics (link #2, data from public health source - IDSA Prevention of Endocarditis).

With an associated crude mortality of more than 25%, nosocomial bloodstream infections are most often associated with intravascular devices. Numerous interventions, ranging from improved sterile insertion techniques to antibiotic-impregnated catheters have been shown to reduce the number of catheter-associated infections. Management of bacteremia associated with a catheter requires management of both the infection and the catheter. Catheter removal is generally recommended, but catheter salvage is attempted in some situations, and so called “antibiotic-lock” therapy can be an important adjunctive measure for durable success. Final antimicrobial choice is dictated by the causative pathogen as well as any patient factors such as allergies, et cetera. A notable rising proportion of nosocomial bacteremia is due to more antibiotic-resistant organisms in US hospitals.

Bacteremia or other infectious processes can promote a systemic inflammatory response, defined by unstable hemodynamic parameters, fever and abnormal white blood cell count. Severe sepsis and shock are associated with end organ dysfunction. Only ruptured abdominal aortic aneurysm has a higher percent mortality rate than sepsis (link #4, recent research, Rubulotta). Empiric antimicrobial therapy given within one hour of presentation is now a standard recommendation based upon beneficial impact on mortality. Clinicians do need to take some care at crafting an initial antibiotic program to cover all usually suspected pathogens as well as additional factors that may be gleaned from clinical history and presentation. Sepsis results from interaction between the infectious pathogen and host immune responses, including inflammatory and coagulation pathways. In addition to antimicrobials, optimal management includes a series of supportive and pharmacologic measures to intervene on this septic pathophysiology. Early goal directed therapy is geared to optimize hemodynamic and oxygenation. Other treatment interventions such as “sepsis bundles” (link #1, literature review, Zambon), corticosteroids, activated protein C and tight glucose control have had their positive studies and advocates, although now more recent data have sullied these routine measures.

Example Needs Statement from: Today’s patient with Non-Small Cell Lung Cancer: Does History Make a Difference?

In the United States, lung cancer remains the leading cause of cancer mortality in both men and women, with more than half of patients presenting with locally advanced, inoperable, or metastatic disease.

NSCLC accounts for 85% of all lung cancers, and comprises mainly adenocarcinoma, squamous cell carcinoma, and large cell carcinoma subtypes. (link #1, literature review - Smith). Despite advances in therapeutic options, only 15% of lung cancer patients survive beyond 5 years. (link #2, recent research, Jackson). Even with the numerous therapeutic options available, only 15% of lung cancer patients survive beyond 5 years from diagnosis. (link #3, literature review - Stafford).

The identification of histological markers may lead towards personalized therapy for patients with NSCLC, where treatment regimens can be selected based on tumor histology. Recent data presented at ASCO suggest limiting first-line chemotherapy to 4 cycles, as randomized trials failed to show a benefit with extended therapy. Paul Bunn, MD, Director of the University of Colorado and past president of

ASCO, said these trials raise the issue of whether we should be giving a better drug up front, not waiting for disease progression. Therefore, a full review of the appropriate sequencing and scheduling of various regimens must be part of an educational program to maximize treatment of NSCLC patients based on their histology. (link #4, expert opinion).

The current research is prolific and ongoing, and in order to provide the best treatments possible and to make the best informed decision possible, clinicians managing patients with NSCLC need to be updated on the latest clinical evidence and treatment options for this disease. Data presented in recent years on the combination of bevacizumab and chemotherapy stirred interest in the idea that certain drugs may produce improved outcomes when targeted to a specific histological subtype: in the case of bevacizumab, the nonsquamous subtype.², (link #5, recent research, Solvoski).

Our in-depth analysis indicates that oncologists and hematologists have significant knowledge gaps in tumor and cell biology and in the clinical trial data necessary to help them optimize treatment and management of patients with certain subtypes of NSCLC. In fact, approximately 50% respondents from a Johns Hopkins School of Medicine survey to oncologists indicated they were somewhat or less than somewhat knowledgeable about tumor and cell biology. In addition, 88% indicated they would like an educational activity to cover treatment options. (link #6, physician survey).