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Bartlett's 2013 Review: Advances in the Highly Kinetic Field of Infectious Diseases

John G. Bartlett, MD | December 05, 2013

Editor's Note:

Medscape asked John G. Bartlett, MD, Professor Emeritus, Johns Hopkins University School of Medicine, to offer his review of the most important and practice changing advances in infectious disease in 2013.

Resistance to Antibiotics

No National Plan

The topic of antibiotic resistance needs no introduction. It is well known and has been declared a crisis by the World Health Organization, the Institute of Medicine (IOM), the Infectious Diseases Society of America, and the US Congress.

The United States has no national plan to deal with antibiotic resistance, despite recognition of the crisis for more than a decade.[1] By contrast, the European Union has been systematically collecting data on antibiotic use and resistance by specific pathogens for 26 countries for 15 years and now has a 12-point plan and budget to address the problem in a coordinated fashion.[2]

India is the source of many resistant microbes that have become global concerns, largely through air travel, including the infamous New Delhi strain of carbapenemase-producing *Klebsiella pneumoniae* (KPC). India has announced plans for a coordinated national attack on this problem, despite incredible economic and health challenges.

To reiterate, it is humbling that the United States has nearly 50% of the global budget for antibiotics, a crisis of abuse, and no plan to deal with what many feel is a looming disaster in modern medical care with the "postantibiotic era."

Resistance Priorities

The Centers for Disease Control and Prevention (CDC) recently published a massive scholarly review[3] (see Antibiotic Resistance: The Big Picture) of antibiotic resistance in the United States and has defined the priorities (but without a plan). The 3 top priorities, which are described as "urgent," may surprise you: carbapenemase-producing Enterobacteriaceae, *Clostridium difficile*, and antibiotic-resistant *Neisseria gonorrhoeae*.

The devastating impact of KPC is well illustrated by the experience at the National Institutes of Health (NIH) Clinical Center, with 18 cases and 6 deaths during a 6-month period.[4] Control was eventually achieved by building a wall to isolate patients with this pathogen, vaporizing rooms with hydrogen peroxide, ripping out plumbing when the agent was found in sinks, obtaining rectal swabs from all patients twice weekly to detect KPC carriage, whole-gene sequencing to determine transmission patterns, banning of cell phones and pagers, standardized handwashing (2 squirts with a 20-second scrub), and antiseptic baths for all patients.[4,5]

The painful messages from these experiences are that once these "bad bugs" become established in a facility, draconian changes in medical care may be necessary at a high cost; referral facilities may reject patient transfers; and the publicity can be very damaging for the facility's image, as well as present liability risks.

Colistin

The problem of resistance and the paucity of new antibiotics has led to the scrambling for a "Hail Mary" to treat nearly pan-resistant gram-negative infections. Many clinicians have been looking to colistin or polymyxin, related drugs that were US Food and Drug Administration (FDA)-approved in 1961. These are the only active

drugs for many highly resistant gram-negative bacteria, but data on their use are modest, dosing recommendations in the package inserts appear to be outdated, there is the perceived need for a companion antibiotic for "heteroresistance," and toxicity is common.[6]

One study reported a 60% rate of nephrotoxicity with currently recommended dosing.[7] This experience highlights the desperate need for new antibiotics.

New Tests, New Pathogens, and MERS-CoV

The New Microbiology Lab

Microbiology is in the process of a veritable sea change, with a shift from methods first used in 1850 -- a culture medium produced from seaweed (agar) -- to molecular methods for pathogen detection that are rapidly being introduced.[8] The FDA has now approved nucleic acid amplification tests (NAATs) for multiple viruses (measles, mumps, human metapneumovirus, rhinovirus, coronavirus, enterovirus, adenovirus, respiratory syncytial virus, influenza, West Nile virus, herpes simplex virus, human papillomavirus, rabies virus, and cytomegalovirus). Bacteria for which NAATs are now approved include *N gonorrhoeae; Chlamydia trachomatis*; *Mycoplasma pneumoniae*; *Legionella* species; *C difficile*; *Coxiella* species; *Borrelia burgdorferi*; *Ehrlichia* species; *Mycobacterium tuberculosis*; and group A, B, C, and G streptococcus. None of these organisms should normally be found, so their presence usually indicates disease.

The bacteria that are most commonly encountered in clinical care, such as pneumococcus and *Escherichia coli*, are far more challenging, because they are so frequently part of the commensal flora. This makes meaningful detection appropriate only with quantitation or recovery from a normally sterile site, such as blood, pleural fluid, or biopsy specimens. This technology is now being used with blood cultures. The great advantage here is rapid detection (1-2 hours instead of the 36-48 hours required with conventional cultures) and the extraordinary sensitivity and specificity of this method. This must be viewed as possibly the biggest advance in microbiology in 150 years, but stewardship and interpretation of results will be critical.

New Pathogens

The field of infectious diseases is somewhat unique in the regular discovery of previously unknown pathogens, such as *Legionella pneumophila* (1978), HIV (1983), *B burgdorferi* (1983), and *Helicobacter pylori* (1986). Some examples of recent new pathogen discoveries include:

• Mimivirus: a giant gram-positive virus that appears to be a rare cause of pneumonia[9];

• *Borrelia miyamotoi*: a tick-borne spirochete that causes a Lyme disease-like illness, found primarily in southern England, detected with serology and treated with doxycycline[10];

• *Emmonsia*: a newly detected dimorphic fungus found to cause disseminated infection with prominent skin lesions in 13 patients with late-stage AIDS in South Africa[11];and

• *Bradyrhizobium enterica*, which causes cord colitis syndrome in stem cell transplant recipients.[12]

The Emergence of MERS-CoV

Middle East respiratory syndrome coronavirus (MERS-CoV) is the newly recognized pathogenic coronavirus that was originally identified in the Middle East and has reportedly infected 138 people and caused 60 deaths (43%).[13] Of importance are the observations that person-to-person transmission has been shown and cases have been detected outside the original epidemic area, including Europe, but not yet in the United States. Nevertheless, there is great concern that this virus, a coronavirus with a bat heritage similar to that of severe acute respiratory syndrome (SARS), will behave like SARS, with global spread.

Thus, warnings have been made for detection, reporting, and isolation of patients who have unexplained severe

respiratory infections and recent travel to the Arabian Peninsula or contact with a patient with this travel history. The CDC has distributed a diagnostic test; there is no effective antiviral therapy.

A major reason for this concern is the experience with SARS (also a coronavirus), which infected more than 8000 people and caused 770 deaths. The history of SARS was that it remained a localized infection in mainland China, until there was the infamous "super-spreader"-- the physician who traveled from Guangdong province to Hong Kong; stayed in room 911 of the Metropole Hotel; and apparently became the source of epidemics in Canada, Vietnam, Singapore, and Hong Kong.[14] Newer thinking discounts the concept of a single person as a "super-spreader," however, and the terminology has been changed to a "super-spreader environment," because the notion that a single patient could produce such devastation is biologically implausible.

Epidemics

A characteristic feature of the infectious diseases discipline is the continuing experience with epidemics. We have learned that they will occur; we just don't know when, where, with what, and how bad they will be. The highlights of 2013 are in 3 categories.

Pediatric Infections

Pediatric infections include measles (which caused 159 cases of a disease that was believed to be eradicated in 2000) and pertussis, with 41,880 reported cases so far in 2013.[15] A big difference between these 2 infections is that most patients with measles are unvaccinated persons, whereas pertussis cases occurred primarily in persons who had received the vaccine, calling attention to the inadequacy of our pertussis vaccine strategy. Despite the noise from antivaccine proponents, vaccination refusal for pediatric patients in 2012-2013 in the United States was only 1.8%, substantially lower than many thought.

Foodborne Outbreaks

Foodborne outbreaks occur regularly and, so far in 2013, have included *Listeria* from contaminated cantaloupes traced to a Colorado farm, which resulted in143 hospitalizations and 33 deaths.[16] There was also an outbreak of *Salmonella enterica* from contaminated turkey, with 278 infected patients and 1 death involving 28 states. This is not surprising, because *Salmonella* is the most common cause of food epidemics,[17] but in this case the implicated strain was resistant to several antibiotics thought to reflect the use or abuse of antibiotics in agriculture -- the "farm to fork" concern in the resistance issue.

The massive geographic spread of foodborne infections from a single source represents the switch from nearby farms as food sources to the massive distribution system that permits exposure to thousands of individuals at distant sites. This could be easily controlled with food irradiation, which is endorsed by the IOM, FDA, CDC, and other reliable sources, but is rejected by consumers because of the perception that irradiation causes cancer.

Fungal Infections

The infamous fungal meningitis outbreak in 2013 that resulted in 741 cases and 55 deaths in 18 states exposed a huge gap in quality assurance policies in the United States.[18] There are 7500 compounding pharmacies in the United States, and these are not subject to requirements for showing safety, efficacy, or even correct dose labeling. At least 3 outbreaks of meningitis have been traced to compounding pharmacies since 2001, so it is clearly time for action.

Influenza

Influenza continues to be a humbling infectious disease, as shown by swine H1N1 influenza. Extensive experience with influenza shows that new epidemic strains come from Asia in the winter, but this influenza virus defied history because it came from the Western Hemisphere during the summer -- a complete surprise to experts in the field. The uniqueness of the strain was detected by molecular analysis of a sample from a child

with flu at a military base in San Diego.

The greatest contemporary influenza concerns are H5N1 and H7N9.[19,20] Recent reports show that H5N1 has been recognized for 16 years; there have been about 733 reported cases, with a mortality rate of 59%. H7N9 reports indicate that about 133 cases have occurred, with a mortality of 28%. Birds are the natural hosts for both agents, but there is a big difference: H5N1 infection is fatal in birds, whereas H7N9 infection is asymptomatic in birds, making elimination of the source virtually impossible.

Influenza will remain a priority health concern for the indefinite future, on the basis of our morbid experience with pandemics and our admittedly suboptimal antiviral medications and vaccines. H5N1 and H7N9 could easily be global epidemics based, in part, on our humbling experience in what we know from swine flu.

The Microbiome

This possibly is the most exciting news story in the field, although now in the nascence of knowledge and practical application. Articles on the microbiome stem from a large, multicenter, NIH-sponsored study using molecular methods (16S ribosomal RNA) to define the flora at 15 anatomical sites in 300 persons.[21-23] This work now has produced 35 billion "reads"(a term that describes counting the number of microbes reported in the NIH network of microbiome centers.) Important principles include the facts that the cellular composition of humans is 90% "them," each anatomical site and individual has unique flora, antibiotics have a major impact on these flora, and certain patterns are associated with different disease states.

At this juncture, it seems clear that study of the microbiome will open new doors to concepts in pathogenesis of common pathologic conditions, such as cardiovascular disease, allergies, obesity, inflammatory bowel disease, cancer, and diabetes. Our understanding of this process will require a departure from the age-old Koch postulates of the single pathogen causing the disease. Instead, the focus will be on communities of communicating organisms.

It now seems clear that this work could change fundamental concepts of common diseases and suggests that antibiotics and probiotics might be used to prevent or treat multiple conditions not considered to be infectious diseases as conventionally defined. For example, studies in rodents show that antibiotics may alter risk for cardiovascular disease, and early studies show promise that this is applicable to humans as well.[22] The use of stool transplants to control relapsing *C difficile* infection (CDI) is a well-established use of this concept, as described below.

Clostridium difficile infection

CDI is listed as 1 of the 3 major microbial threats in the United States in the CDC resistance review[1] as a result of escalating rates, with an estimated 250,000 cases and 14,000 deaths yearly in the United States. Important new developments in the past 2-3 years are:

• The introduction of fidaxomicin[24] as the second FDA-approved drug for treatment, with the significant benefit compared with oral vancomycin of reduced frequency of relapses;

• The fascinating, if impractical, use of a beagle "sniff test" as a near-perfect diagnostic method[25];

• The diverting ileostomy as a new method of surgery for refractory cases, with the advantages of substantial reduction in surgical mortality plus colon preservation[26];

• New epidemiologic data based on whole-gene analysis showing that the major method for prevention favors antibiotic control over infection control[27];and

• The burst of enthusiasm for treatment of relapsing CDI with stool transplants, a practical use of the microbiome, that has been used with good success since 1958.[28]

The stool transplant procedure can be done with delivery of donor stool specimens by nasogastric tube, enema, or colonoscopy, but Dr. Tom Louie recently presented good results with fresh donor specimens delivered in 24-34 oral pellets.[29] Lingering questions are the issue of use of stool as a drug requiring a "treatment IND" (investigational new drug application to the FDA) and stool transplantation as a billable procedure. (Dr. Louie does this without charge in the patient's home.)

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