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Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

Fecal Transplants Promising for *C. difficile* Infection, Endless Poop Puns a Side Effect

From 'poopsickle' to 'rePOOPulating the gut'

By Ellen Jo Baron, Ph.D., D(ABMM)

Professor Emerita, Stanford University School of Medicine, Director of Medical Affairs, Cepheid, Sunnyvale, CA, Associate Editor of Infectious Disease Alert.

Dr. Baron is a stockholder for Cepheid, and Immunogenetics, is Director of Medical Affairs for Cepheid, and is on the Scientific Advisory Board for OpGen, Immunogenetics, and NanoMR. She is co-founder of the Diagnostic Microbiology development Program (www.dmdp.org), a non-profit organization that does laboratory capacity building in the developing world.

SOURCE: van Nood, E., et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013;368:407-15.

The distress felt by patients with recurring bouts of *Clostridium difficile* diarrhea is so acute that they welcome the opportunity to accept another's feces to bring them back to baseline. There have been more than 30 publications on the topic since it was first introduced in 1958[1], most of them in the last 10 years. The recent resurgence of severe *C. difficile* infection (CDI), precipitated in part by the rapid expansion of the highly virulent NAP1/027/BI strain[2], has left physicians grasping for effective therapies. Metronidazole, vancomycin, and the newest FDA-cleared option, fidaxomycin, all work, but a significant subset of patients fail to achieve a sustainable cure.[3] These are the candidates for the fecal transplant.

The form of this unique therapeutic approach ranges from pooled donor feces (residents and fellows?) to individual donor feces, usually from a family member, reluctantly screened for viruses and other pathogens by the local microbiology diagnostic laboratory with no standard protocol for guidance. There are hints that the FDA may assume regulatory responsibility for this therapeutic, moving it from

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Infectious Disease [ALERT]

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"food" to "drug" status. In the current situation of multiple disparate donors for feces for transplantation, regulation could prove very difficult. When the majority of patients received their donations via enema, it would have been more difficult to classify the material as food, but nowadays most infusions are via the nasogastric route, which patients seem to tolerate better.[4]

Excitement has been generated anew by the recently published research of van Nood, E., et al. This Dutch group studied three series of patients randomized to receive vancomycin (500 mg orally, 4x/day for 14 days), vancomycin (same dose) followed by bowel lavage, or the same dosage of vancomycin for 4 days followed by bowel lavage and fecal transplant via a nasoduodenal infusion. All patients were followed for relapse over 10 weeks. The study was stopped after the results of the first 41 patients were assessed. One single donor fecal infusion cured 13 of 16 patients, and a second fecal transplant from a different donor cured 2 of the remaining 3 patients (94%). The 12 vancomycin-only patients had a 31% cure rate and the 13 patients in the vancomycin plus bowel lavage arm had a 23% cure rate. Adverse events were similar for each group.

One aspect of these studies, increasingly utilized by the most progressive groups, is analysis of the diversity and composition of the bacterial content of the patients' feces before and after treatments, using highly complex molecular methods. In this case, the authors used a human intestinal tract chip-based microarray method to assess the fecal microbiota. Previous studies have shown that patients with CDI display a much reduced diversity of fecal organisms, related primarily to a reduction in the Bacteroidetes group of anaerobes.[5] Not surprisingly, patients' feces after therapy appeared more diverse, reverting toward normal.

Another group is working with a synthetic form of feces comprised of the major microbiota grown independently in the laboratory. Known by the more aesthetically acceptable name, Microbial Ecosystems Therapeutics (MET), the synthetic fecal product may have a better chance of long-term success if the FDA truly does decide to regulate this practice. This Canadian group isolated 62 species from normal stool from one healthy donor and checked the isolates for antibiotic resistance. They ultimately chose 33 susceptible strains for their synthetic fecal mixture, most of them with beautiful and unfamiliar names ranging from *Dorea longicatena* to *Roseburia faecalis*.[6] (Unfamiliar, that is at least to me, proving that past expertise in anaerobic bacteria does not last very long in this age of molecular microbial characterization.) Two initial patients were treated with the mixture and results mirrored those of normal feces based on extensive deep sequencing and sophisticated statistical tools.[7] They call the process "rePOOPulating the gut."

The Fecal Microbiota Transplantation (FMT) Working Group reported their findings in 2011.[8] They coined the term fecal microbiota transplant (FMT) for their definition of the therapeutic agent, which they suggested was less repugnant than "feces." The extensive publication defines the range of pathogens to search for in the donors and the donors' feces, including various parasites, viruses, stool pathogens (especially *C. difficile* itself), and other diseases (syphilis, HIV, and hepatitis, for example); and goes into detail on the various administration methods. The FMT Working Group paper can serve as a source for clinical laboratories being asked to prepare donor feces for transfer in the absence of any other standardized protocol. The same group, working in northern Minnesota, summarized results from 74 patients treated over the last 9 years. Initial therapy resulted in resolution of diarrhea for 79% of patients and 9 of the 16 relapsed patients were cured with a course of vancomycin.[9] Once you have a mixture tested, preferably one from a mix of non-related donors, it is possible to freeze it for future patients. Hamilton and colleagues presented such an approach, testing it on 43 patients, some of whom had inflammatory bowel disease and not CDI.[10] The IBD patients also seemed to respond favorably to the "poopsickle" approach. In short, the

time for coprophagy in the human species seems to have arrived.[11]

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ABSTRACT & COMMENTARY

Carbapenem-Resistant Enterobacteriaceae an Increasing Threat in the United States

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Hospital Epidemiologist, Sequoia Hospital, Redwood City, CA, Editor of Infectious Disease Alert.

SYNOPSIS: The frequency of isolation of carbapenem-resistant enterobacteriaceae is increasing in the U.S., with the highest prevalence in the northeastern region.

SOURCE: Centers for Disease Control and Prevention. Vital signs: carbapenem-resistant Enterobacteriaceae. *MMWR* 2013;62:165-70.

The emergence of resistance in Enterobacteriaceae to ertapenem, imipenem, meropenem, and doripenem due to the production of a carbapenemase is occurring in two primary enzyme groups. One group, also classified within Ambler Class B, is called metalo — lactamases because of a requirement for zinc for their catalytic activity. These metalloenzymes remain rare in the U.S., but are prevalent in a number of other countries -- the New Delhi metallocarbapenemase (NDM) is a recently emerged example. Another group of carbapenemases, termed serine proteases because of the presence of this amino acid within their catalytic site, belong to Ambler Classes A, C, and D. One of these, KPC, first emerged in *Klebsiella pneunoniae* (hence the name, standing for *K. pneumoniae* carbapenemase), but has since spread via plasmids to other members of the Enterobacteriaceae. KPC-producing bacteria first emerged in the U.S. and are becoming increasingly prevalent both here and in other countries in which it has appeared.

■ COMMENTARY

The CDC has now assessed the extent of the problem of carbapenem-resistant Enterobacteriaceae (CRE) in the U.S. Among almost 4000 acute care hospitals that performed surveillance for either catheter-associated urinary tract infections or central line-associated blood stream infections during the first 6 months of 2012, 181 (4.6%) reported at least one CRE infection. This represented an approximate 4-fold increase in the last 10 years. CRE were reported by 3.9% of short-stay and 17.8% of long-term acute-care hospitals. The prevalence ranged from 3.2%-3.6% in the Midwest, South and West to 9.6% of hospitals in the Northeast. *Klebsiella* species were most frequently affected, followed by Enterobacter species and by *Escherichia coli*. In 2011, 4.2% of Enterobacteriaceae were carbapenem-resistant.

As pointed out in the CDC document, invasive infections, such as blood stream infection are associated with high mortality. Furthermore, CRE often contain multiple resistance mechanisms in addition to carbapenemases, making treatment of infections due to them highly problematic. They may rapidly spread within hospitals, where they are most prevalent.

The CDC has published extensive recommendations for control of CRE, including 8 core measures.[1] These are:

- Hand hygiene adherence with monitoring and feedback
- Contact precautions
- Healthcare personnel education
- Minimization of device (e.g., vascular access devices, endotracheal tubes, urinary catheters) utilization
- Patient and staff cohorting
- Procedures for rapid notification of appropriate personnel by the laboratory
- Antimicrobial stewardship
- Screening for CRE colonization

For hospitals that rarely or have never previously identified a CRE[2], they recommend contact isolation in a single room, reinforcement of hand hygiene, and education of staff about prevention measures. They further recommend screening of epidemiologically-linked patient contacts with, at a minimum, stool, rectal or perirectal cultures. Consideration may be given to a point-prevalence study of the affected unit, as well as to preemptive contact precautions. If additional colonizations/infections are detected, consideration may be given to cohorting patients and staff.

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2. CDC. 2012 CRE Toolkit- Guidance for Control of Carbapenem-Resistant Enterobacteriaceae (CRE). Appendix B: General Approach to Carbapenem-resistant Enterobacteriaceae (CRE) Control in Facilities that Rarely or Have Not Identified CRE. http://www.cdc.gov/hai/organisms/cre/cre-toolkit/rCREprevention-AppendixB.html ■

High-Dose Flu Vaccine has Increased Immunogenicity in HIV Patients

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH.

Dr. Watkins reports no financial relationships in this field of study.

SYNOPSIS: A single-center, parallel, double-blind, randomized trial that included HIV patients 18 years and older compared the rate of seroprotection between standard dose and high dose influenza trivalent vaccine. The seroprotection rate was greater in the high-dose group for H1N1 (96% vs. 87%), H3N2 (96% vs. 92%), and influenza B (91% vs. 80%). It is unclear whether these findings correlate with preventing clinical influenza.

SOURCE: McKittrick N, et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV-infected persons. *Annals Intern Med* 2013;158:19-26.

Seasonal influenza is a major worldwide threat to human health. Vaccination against influenza is an important intervention to prevent disease especially in vulnerable populations, such as the elderly and immunocompromised individuals. In particular, HIV-infected patients are at increased risk for complications from influenza including hospitalization, prolonged illness, and death. Unfortunately, antibody responses after influenza immunization are lower in HIV-infected patients than in the general population. It is believed that lower CD4 counts and the presence of HIV viremia contribute to lower immunogenicity in this group. Elderly patients have similarly reduced immune responses to influenza vaccination and increased doses of antigen can lead to higher antibody titers. A previous study that used two double doses (30 mcg/strain) of influenza vaccine in HIV-infected patients found no improvement in immunogenicity.[1]

McKittrick and colleagues sought to determine if high dose (HD) trivalent vaccine (60 mcg/strain, four times the standard dose of 15 mcg) would result in improved immunogenicity in their HIV-infected patients compared to the standard dose (SD) trivalent vaccine. The primary outcome of the study was the proportion of patients with seroprotective antibody levels at 21 to 28 days after vaccination. The primary safety endpoint was the frequency and intensity of adverse events up to 28 days post-vaccination. Secondary endpoints included the seroconversion rate and the geometric mean titers before and after receiving the vaccine. Of 195 participants enrolled, 192 completed the second visit. Ninety-seven received the HD vaccine and 93 the standard dose. Participants were mostly men, African-American, receiving HAART, and had undetectable HIV RNA viral loads. Approximately 10% had current CD4 counts less than 0.200 X 10^9 cells/L. For study purposes the authors defined seroconversion as a 4-fold increase in antibody titer from baseline or an increase in titer from ≤ 1:10 to 1:40 and seroprotection

as an antibody titer ≥ 1:40.
The percentage of patients that achieved seroprotective antibody titers was greater for those who received the HD vaccine, with significant ($P < 0.05$) increases for the H1N1 and influenza B strains. For the H1N1 strain, 96% of the HD group vs 87% of the SD group developed protective antibodies ($P = 0.029$); for H3N2, 96% of the HD group vs the 92% of the SD group developed protective antibodies ($P = 0.32$); and for influenza B, 91% of the HD group vs 80% of the SD group developed protective antibodies ($P = 0.03$).

Furthermore, seroconversion rates were greater in the HD group than in the SD group for H1N1 (75% vs. 59%), H3N2 (78% vs. 74%), and influenza B (56% vs. 34%) strains. Participants with CD4 counts less than 0.200 X 10^9 cells/L were less responsive to both the HD and SD vaccines, with fewer achieving seroprotective levels compared to participants with higher counts. Logistic regression models revealed that baseline antibody titer for the corresponding strain and randomization to the HD group always resulted in seroconversion. Both vaccines were well-tolerated with no significant differences in local or systemic reactions and no serious adverse events occurred with either one.

■ COMMENTARY

This study suggests it is possible to increase protective antibody titers for influenza in HIV-infected patients through the use of high dose seasonal influenza trivalent vaccine. If further randomized trials confirm these data, it will be an important advancement for preventing the sequelae of influenza in HIV-infected patients. One limitation of the study was the finding that half of the patients had evidence of protective titers at baseline. This likely resulted in a higher seroprotection rate at the end of the study than would have been normally expected. Another limitation was that the authors did not measure the incidence of clinical influenza. While it seems logical that higher seroconversion and seroprotection would result in lower risk for clinical disease, this assumption is speculative and unproven based on the study.

The overall clinical effectiveness of the HD vaccine remains uncertain. While investigators demonstrated improved immune response in elderly patients,[2] outcome data showing significantly improved protection against influenza is not yet available. Results from clinical trials on vaccine efficacy are not expected for another 2 to 3 years. Indeed, neither the CDC nor the ACIP have recommended one influenza dose over the other. The HD vaccine costs approximately double the SD vaccine, although Medicare will pay for either one. Another potential drawback for the HD vaccine seems to be more side effects, such as myalgias, headaches and pain at the injection site although there was no difference between the HD and SD doses in the present study. The theoretical benefits of the HD vaccine in HIV-infected individuals seem to justify its use with little downside, although it is certainly reasonable for clinicians to wait until results of further clinical trials are known.

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ABSTRACT & COMMENTARY

Topical Paromomycin for Cutaneous Leishmaniasis

By Dean L. Winslow, MD, FACP, FIDSA

Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine, Associate Editor of Infectious Disease Alert.

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: 375 patients with cutaneous leishmaniasis (CL) were randomized to receiving topical paromomycin (PM) with or without gentamicin (GM) vs. vehicle control. Creams were applied once daily for 20 days. The cure rate for PM+GM was 81%, PM alone 82% and 58% for vehicle control.

SOURCE: Ben Salah A, et al. Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. *New Eng J Med* 2013;368:524-32.

A randomized vehicle-controlled phase 3 trial of topical PM 15% vs. PM 15% + GM 0.5% vs. vehicle control was conducted in Tunisian patients with CL due to Leishmania major. 375 patients were randomized. Patients had from 1-5 lesions each. Lesions were treated daily for 20 days. Cure was defined as at least 50% reduction in size of the index lesion by day 42 and complete re-epithelialization by 98 days and absence of relapse by 168 days. Cure of the index lesion was 81% in the PM-GM group, 82% in the PM-only group, and 58% for the vehicle control. Mild-moderate application site reactions (erythema) were more frequent in the active PM groups than in the vehicle control but did not require treatment discontinuation. No evidence of systemic aminoglycoside toxicity was observed.

■ COMMENTARY

Cutaneous leishmaniasis is a common clinical problem in North Africa and the Middle East. In fact, one of my colleagues who did his medical training in Iran told me that infection with CL is almost universal in children from this part of the world who grow up outside of urban areas. However it is almost always a self-limited infection, is generally not treated, but can leave a scar (which if in an area like the face is of significant cosmetic concern).

The "gold standard" treatment for CL is still pentavalent antimonial compounds such as stibogluconate (Pentostam) given parenterally daily for 20 days. This compound is painful when given IM, is difficult to give IV, and is associated with some toxicity (headache, nausea, myalgias, neutropenia, thrombocytopenia, electrolyte abnormalities, renal and hepatic toxicity). This is what we used to treat most of the U.S. Army 3rd Infantry Division soldiers who acquired this infection in southern Iraq in the spring and summer of 2003 during the early phase of OPERATION Iraqi Freedom and most of these otherwise healthy young men tolerated treatment well. More recently, miltefosine has shown efficacy for CL but this drug is not available in the U.S.

Probably the most effective systemic treatment for CL (as well as mucocutaneous leishmaniasis and visceral leishmaniasis) is liposomal amphotericin B. Very abbreviated courses of liposomal amphotericin B is now the treatment preferred by the U.S. military infectious diseases community for treatment of CL acquired by our troops in Southwest Asia. When I was Commander of the USAF EMEDS in Baghdad during the "surge" a few years ago I personally used short courses of liposomal amphotericin B for the treatment of CL in Coalition forces and in detainees in Iraq with dramatic success. These abbreviated courses are well-tolerated but liposomal amphotericin B remains incredibly expensive and the cost is prohibitive for the treatment of CL in most patients in the developing world. Oral antifungal triazoles (fluconazole) have also shown some limited efficacy in CL due to *L. major* but many patients in the one randomized trial which showed efficacy were lost to follow up. The antifungal triazoles are also not effective in CL or mucocutaneous leishmaniasis acquired in the Americas.

This study shows that topical paromomycin applied daily for 20 days in patients with cutaneous leishmaniasis due *L. major* appears to be safe and effective. I am looking forward to the next patient I see with this infection so I can give it a try.

ABSTRACT & COMMENTARY

Novel Coronavirus — It Hasn't Gone Away

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Hospital Epidemiologist, Sequoia Hospital, Redwood City, CA, Editor of Infectious Disease Alert.

SYNOPSIS: Another case of novel coronavirus infection, for which person-to-person transmission has been demonstrated, has been reported.

SOURCE: WHO. Novel coronavirus infection – update. http://www.who.int/csr/don/2013_03_12/en/index.html

In the January 2013 issue of *Infectious Disease Alert* the initial reports of a novel coronavirus were reviewed.[1] These included 5 cases (including 3 deaths) from Saudi Arabia, two cases from Qatar and two cases (both fatal) from Jordan. Unfortunately, this potentially lethal virus has not disappeared, as the SARS coronavirus appears to have done, and a 15th case has been reported.

On 12 March 2013, the WHO reported that they

had been informed by the Ministry of Health in Saudi Arabia of a new confirmed case of infection with the novel coronavirus (nCoV). A 39-year-old man became ill on 24 February 2013 and died on 2 March, several days after hospitalization. While the epidemiological investigation is incomplete, no link to previously reported cases had been identified. This patient was the 15th known case of nCoV infection; 9 have died.

COMMENTARY

No cases of nCoV infection have yet been reported in the U.S. but 3 cases within one family in the U.K. have been confirmed. The index family in that cluster had traveled to Pakistan and Saudi Arabia. Investigation indicated person-to-person transmission within the family.

The Centers for Disease Control and Prevention recommends reporting the following to your health department:[2,3]

- A person with an acute respiratory infection, which may include fever and cough, AND
- Suspicion of pulmonary parenchymal disease (such as pneumonia or acute respiratory distress syndrome based on clinical or radiological evidence of consolidation, AND
- History of travel from the Arabian Peninsula or neighboring countries within 10 days, AND
- Not already explained by any other infection or etiology, including all clinically indicated tests for community-acquired pneumonia* according to local management guidelines, AND
- Persons who develop severe acute lower respiratory illness of known etiology within 10 days after traveling from the Arabian Peninsula or neighboring countries* but who do not respond to appropriate therapy, OR

Persons who develop severe lower respiratory illness who are close contacts of a symptomatic traveler who developed fever and acute respiratory illness within 10 days of traveling from the Arabian Peninsula or neighboring countries.

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ABSTRACT & COMMENTARY

Should Aerosolized Antibiotics be Used to Treat Gram-Negative, Multidrug-Resistant, Ventilator-Associated Pneumonia?

By Richard H. Kallet, MS, RRT, FAARC, FCCM

Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital

Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: This prospective, single-center, comparative observational study found aerosolized colistin to be effective in treating ventilator-associated pneumonia caused by multidrug-resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

SOURCE: Lu Q, et al. Efficacy of high-dose nebulized coilstin in ventilator-associated pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acincetobacter baumannii*. *Anesthesiology* 2012;117:1335-1347.

Lu et al prospectively studied 165 patients with culture-confirmed (bronchoalveolar lavage samples), ventilator-associated pneumonia (VAP) caused by either *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. Antibiotic therapy was based on antibiotic sensitivity. A cohort of 122 patients had strains that were susceptible to beta-lactam antibiotics; these patients were treated with a 14-day course of systemic beta-lactam antibiotics, supplemented with a 3-day course of either an aminoglycoside or a quinolone. The remaining 43 patients had multidrug-resistant (MDR) strains and were treated for up to 14 days (or until extubation) with high-dose (400 mg) aerosolized colistin every 8 hours. A state-of-the-art vibrating-mesh nebulizer (Aeroneb™), in conjunction with a comprehensive ventilator and sedation protocol, was used to maximize lower respiratory tract antibiotic deposition.

Twenty-eight patients (65%) in the MDR cohort received antibiotic monotherapy, whereas the managing physicians chose to supplement therapy with a 3-day systemic course with an aminoglycoside in the remaining 15 patients.

The average duration of aerosolized antibiotic therapy in the MDR cohort was 12 days with a reported cure rate of 67%, compared to 66% in the beta-lactam susceptible cohort who received systemic antibiotic therapy. Also, there was no difference in the cure rate between those who received aerosolized antibiotic monotherapy (68%) and those who also received supplemental systemic antibiotic therapy (67%). In the MDR cohort, there was a nonsignificant trend toward a higher incidence of both persistent VAP at day 14 (31% vs 19%, $P = 0.12$) and recurrent VAP after day 14 (26% vs 10%; $P = 0.16$), as compared to the beta-lactam susceptible cohort. Only two patients (4.7%) receiving aerosolized colistin showed evidence of acquired antibiotic resistance. All-cause ICU mortality also was not different between cohorts.

■ COMMENTARY

VAP is the leading cause of death among critically ill patients with hospital-acquired infection and accounts for more than 50% of antibiotic use in some ICUs. Pulmonary infections caused by *Pseudomonas aeruginosa* are particularly problematic as they are characterized by both recurrent infection and a high tendency toward antibiotic resistance despite appropriate antibiotic management.[1] The difficulty in achieving a pulmonary drug concentration capable of eradicating bacterial reservoirs residing within thick secretions and biofilm limits the effectiveness of systemic antibiotic therapy. Moreover, systemic antibiotic therapy requires drug dosages that increase the likelihood of systemic toxicity, as well as eliminate the normal flora of the gastrointestinal tract that paradoxically promotes the selection of MDR organisms.

For several decades, aerosolized antibiotics have been used successfully to treat both cystic fibrosis and *Pneumocystis jiroveci* pneumonia. The recent advent of high-efficiency, vibrating-mesh nebulizer technology represents an important advance in aerosolized antibiotic therapy. The current study by Lu and colleagues adds to a growing body of literature suggesting that the administration of aerosolized antibiotics may be a more effective strategy to treat VAP, particularly in cases caused by MDR microorganisms. Particular attention should be focused on ventilator settings, circuit conditions, and patient-ventilator synchrony, as described by Lu and colleagues. This underscores what is needed to maximize lower respiratory tract drug deposition and largely determines whether aerosolized antibiotic therapy can be effective in treating VAP.

Unfortunately, most available studies on this topic have been either relatively small randomized, controlled trials or uncontrolled studies, some with methodological concerns. Therefore, lacking a sufficiently large Phase III randomized, controlled trial, aerosolized antibiotics cannot be advocated for general use in the treatment of VAP. However, it is reasonable to consider using aerosolized antibiotics in highly selected individual cases of VAP caused by MDR microorganisms that are unresponsive to traditional intravenous antibiotic therapy, or when avoiding renal toxicity is of paramount importance.

Reference

1. Rello J, et al. Recurrent *Pseudomonas aeruginosa* pneumonia in ventilated patients: Relapse or reinfection? *Am J Respir Crit Care Med* 1998;157: 912-916. ■

Vaccination Considerations for Chemotherapy Patients

By William B. Ershler, MD

INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC

Dr. Ersheler reports no financial relationships in this field of study.

Patients with cancer in general, but particularly those with hematologic malignancies, are at increased risk for infectious diseases, some of which are preventable by vaccination. Risk for infection is heightened by the immunosuppressive effects of chemotherapy, with some agents, such as rituximab being particularly powerful at diminishing vaccine response.[1]

Although immunization appears to be an obvious way to prevent infection, many patients with impaired immunity are unable to mount a protective immune response to active vaccination. Furthermore, studies demonstrating efficacy of vaccines in patients with cancer are insufficient to provide formal evidence-based guidelines for the prevention of vaccine-preventable infections in oncology patients

(excluding those who undergo hematopoietic cell transplantation). Nonetheless, immunization recommendations for immunocompromised patients in the United States have been developed by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC). In general, immunocompromised patients, such as those with cancer, should receive only inactivated vaccines (such as influenza and pneumococcal vaccines) and not live virus vaccines, such as the zoster vaccine.[2]

Influenza vaccine. Influenza-related hospitalization is 3-5 times higher in cancer patients than the general population and the mortality rate is 9% (relative risk 4, compared with the general population).3 Accordingly, annual vaccination is strongly recommended for those with cancer.4 Furthermore, antiviral prophylaxis should be considered for those undergoing the most intense chemotherapy under certain circumstances, such as following an exposure. As mentioned, certain systemic anticancer agents have profound effects on immunity. A recent study to determine whether lymphoma patients receiving rituximab-containing treatment regimens during or within the prior 6 months were able to mount protective antibody responses to the influenza A (H1N1) 2009 virus. The investigators found that contrary to age-matched controls without lymphoma in whom 82% responded adequately to the vaccine, none of the 67 patients achieved protective antibody titers.[1] In earlier studies, the same group reported adequate influenza vaccine responses among non-Hodgkin lymphoma patients receiving combination chemotherapy without rituximab.[5,6] Thus, rituximab appears particularly suppressive with regard to vaccine response — an observation that warrants recognition by clinicians in formulating vaccine schedules and considering use of antivirals.

It makes sense that the optimal time to receive a vaccine is before the initiation of chemotherapy. However, due to the seasonal nature of influenza vaccination programs, such timing often is not feasible. The optimal time for vaccination in patients already receiving chemotherapy is not established. In a recent report of breast cancer patients receiving FEC (5-fluorouracil, epirubicin, and cyclophosphamide)-containing chemotherapy regimens, patients were randomized to receive influenza vaccine early in the cycle (day 4) or at mid-cycle (day 16). As expected, the overall patient group had significantly lower responses to the vaccine compared with healthy controls. However, patients vaccinated at day 4 tended to have higher antibody titers compared to patients vaccinated at day 16. Thus, at least for breast cancer patients on combination chemotherapy, vaccination early during the chemotherapy cycle induces better responses than does vaccination at day 16. Whether this finding can be generalized to patients receiving other chemotherapies for other tumors remains to be studied.

Pneumococcal vaccine. Infections due to *Streptococcus pneumoniae* are an important cause of morbidity and mortality in oncology patients. Cancer patients are known to respond variably to the 23-valent pneumococcal polysaccharide vaccine, although responses are almost comparable to age-matched controls if the vaccine is given prior to chemotherapy.7 However, responses after chemotherapy, even years later, have been shown to be suboptimal.8 Although a novel protein conjugated pneumococcal vaccine (Prevnar-13) currently has been approved for use in the United States, its efficacy in patients who are immunocompromised has yet to be established. It is expected that vaccine schedules including both the conjugate and polysaccharide vaccines will be developed for immunocompromised patients, but these have yet to be provided.

Zoster vaccine. Although patients with malignancy are at increased risk for shingles, the zoster vaccine (Zostavax) is a live-attenuated virus and its use is contraindicated in cancer patients. Nonetheless, the CDC suggests that patients with hematological cancers in remission and off chemotherapy (and radiotherapy) for 3 or more months may receive zoster vaccine.[4]

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Updates

By Carol A. Kemper, MD, FACP

The economics of HIV treatment

Walensky RP, et al. Economic savings versus health losses: The cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med* 2013;158: 84-92.

Atripla ® is a branded, combination once-daily tablet recommended as first-line anti-retroviral therapy (ART) for HIV in the United States (containing tenofovir-emtricitabine-efavirenz). However, as of January 2012, some similar drugs are now available as generics in the U.S. Therefore, a combination of generic lamivudine, generic efavirenz, and branded Tenofovir, which is a similar, if not quite as effective, combination as Atripla, could be used in the treatment of HIV infection, and would significantly reduce the cost of HIV treatment in the U.S.

Walensky and colleagues compared the relative Quality-Adjusted Life-Year (QALY) and cost-effectiveness of the branded ART combination pill vs the 3-drug generic combination therapy. Estimates of the difference in effectiveness of the 3-drug regimen compared with Atripla were factored into the assessment. The authors do allow however, that the compliance of patients on a 3-pill a day vs one-pill a day regimen may also be reduced, also reducing the potential effectiveness of the combination regimen. Branded Atripla per person per year costs approximately $19,870 wholesale. Assuming standard wholesale discounting for all drugs, the annual per person treatment for Atripla vs the generic combination regimen is $15,300 vs $9200 per person per year, respectively.

The discounted per person QALY, from age 43 years, was 4.05 for no ART, 12.08 for the 3-drug generic combination regimen, and 12.45 yrs for the branded ART. The estimated per person cost, factoring in costs of routine clinical care and laboratory monitoring, was $131,200 for no ART, $300,300 for generic combination ART, and $342,800 for branded ART.

When factoring in estimates of efficacy and failure, the incremental cost effectiveness ratio (ICER) per QALY was significantly greater for branded Atripla compared with generic drug combination (an ICER of $114,800/QALY). The deeper the discount for generic medications, the greater the difference in ICER between the two regimens. Even modest price reductions in the generic medications had a sizeable impact on the relative ICER. The authors estimate that $920 million dollars would be saved annually if all eligible U.S. patients started or were switched to the 3-drug generic combination treatment. ■

Honeybees and tetracycline resistance

Tian B, et al. Long-term exposure to antibiotics has caused accumulation of resistance determinants in the gut microbiota of honeybees. mBIO 3(6):3000377-12.http://dx.doi.org/10/1128/mbio. (and accompanying editorial)_.

In the United States, tetracyclines (e.g., oxytetracycline) are commonly used in the domestic honeybee industry to prevent bacterial super-infections. These authors examined the microflora of the honeybee gut for evidence of tetracycline resistance, and surprisingly found that the relatively tiny gut of the honeybee has a diverse set of tetracycline resistance genes (8 different genes!). Most of the honeybee gut flora is comprised of gram negative organisms, but resistance genes were found in both gram positives and in gram negatives. Most of the bacteria harboring the resistance genes were considered commensals and not pathogens. PCN/Ampicillin resistance was also detected in some bees, although neither agent was used in the tested hives. This suggests that extensive use of a single antibiotic can place sufficient selective pressure on organisms to promote mechanisms of resistance leading to multi-drug resistance, as has been demonstrated in other species (e.g., chickens and humans). By comparison, European bees, where tetracyclines are not commonly used by beekeepers, do not harbor tetracycline resistance genes. Since the fly has been demonstrated to pass resistant strains of *E. coli* among farm animals, the honeybee, which forages up to 2-3 miles away from the hive, could be a ready disseminator for antibiotic resistance in the greater ecosystem. ■

Catching the flu

1. Catching the Flu: NIOSH research on Airborne Influenza transmission (Http://blogs.cdc.gov/niosh-science-blog/2013/01/catchingth-eflu);

2. Blachere FM, et al. Measurement of airborne influenza virus in a hospital emergency department. *Clin Infect Dis* 2009; 48: 438-40.

Our Emergency Department had a recent spate of Influenza illness in employees (despite prior annual influenza vaccination) – two of whom came to work despite fever and cough. Employee Health promptly instituted screening procedures for all ED employees prior to the start of their shift (temperature and symptom assessment). In total 12 employees went out ill. It's good to remember that the typical incubation period for the flu is 1-4 days (average, 2 days), and adults may shed Influenza virus one day prior to symptom onset and up to 5-6 days after symptom onset. Children can shed virus for 10 or more days after symptom onset, and immunocompromised patients with Influenza can shed virus for up to weeks or months.

Influenza is primarily transmitted by large-particle respiratory droplet transmission, e.g., when infected people cough, sneeze or talk. Large droplets settle to the ground almost immediately (> 50 micrometers in diam.), but intermediate droplets (10-50 micrometers in diam.) may take several minutes. Smaller droplets (<10 micrometers in diam.) and what they call evaporated droplet nuclei, which are larger particles that have lost water, may take hours to settle to the ground. Virus may also be spread through contact (and fomites) as well as airborne transmission. The relative significance of these routes of transmission to health care workers is not known.

In order to test how well different personal protective equipment works to protect health care workers from large droplets and small aerosols, NIOSH has designed a custom-built coughing machine that can cough an aerosol much like a patient – and a breathing machine that simulates a person taking a breath.[1] The multi-hospital NIOSH investigation will also measure the amount of virus on gloves, face masks, respirators and equipment and furniture. Researchers are also attempting to develop better methods for measuring viable virus in samples.

Blachere and colleagues tested aerosolized particles for Influenza virus in an emergency room setting using a two-stage cyclone aerosol sampler (which samples particles of varying size). The equipement was set up in various sites within the ED on 6 afternoons and collected 74 aerosol samples. Seven physicians wore personal aerosol samplers for 3-4 hours each. Real-time PCR was used to assess the presence of Influenza A matrix gene (M1). Eight of the aerosol samples were positive for Influenza A, all of which were found in the waiting room or triage. More than half of the particles detected (53%) were of a size that could readily be inhaled into the deep respiratory tract. Three of 7 of physician samples (43%) were also positive for influenza virus.

Influenza virus is indeed freely floating about the ED during the influenza season; presumably at least some of this is viable virus. I'll remember this as I wander thru the ED on my way home at night ! ■

Rapid detection of Plague

DePalma A. "Reliving nightmare of Plague, 10 years on", *The New York Times*, Science Times section. 2013;D5-D6.

Each year, the WHO reports 1000-2000 world-wide cases of plague, most of which occurs in Africa (mostly Madagascar). The disease is, however, present at low levels in the United States, mostly in New Mexico, Arizona, Texas, California (where it subsists in low levels in rodents and the prairie dog population in the Southwest, and rodents and Jack Rabbits in California), with rare cases in Nevada, Oregon, Idaho and Wyoming. Larger carnivores and domestic cats and dogs can acquire infection from infected fleas and rodents, especially during the warmer summer months, and spread it to humans. An average of 7 human cases occur annually in the U.S (range, 1-17 cases per year); no human cases were reported in California in 2011 and 2012, but two cases in New Mexico and in Oregon in 2012 occurred as the result of contact with infected domestic cats.

Despite the availability of cheap and effective antibiotic therapy, the disease remains frequently fatal (11%-38% of the time), often within days, in large part because of the delay in recognition and laboratory confirmation of infection. Even in the United States, it can take days for the lab to get back a positive culture or a serology; and the problem is even worse in clinics or rural areas in Africa.

A simple "dipstick" test-kit has been developed to rapidly detect the presence of Yersinia pestis–specific F1-capsular antigen. The test is based on a simple immunochromatographic dipstick (much like a pregnancy test), provides rapid results (much like a pregnancy test), and is 100% sensitive and specific for both bubonic and pneumonic forms of the disease. In field tests, it worked better than the standard ELIZA test or cultures, and allows physicians or clinicians in more remote or rural locations to quickly confirm infection and start appropriate antibiotics.

Although the *NY Times* indicates the tests costs less than $1 per dipstick, I found the BADD Plague Detection kit for $245 for a box of 10. It has a shelf life of 2 years, does not require refrigeration, and functions in hot weather up to 120 degrees F. ■

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CME QUESTIONS

1. Which of the following was the best therapy in the study of treatment of Clostridium difficile infections by van Nood and colleagues?

A. Oral vancomycin (14 days) alone.

B. Oral vancomycin (14 days) followed by bowel lavage.

C. Oral vancomycin (4 days) followed by bowel lavage and fecal transplant via colonoscopy.

D. Oral vancomycin (4 days) followed by bowel lavage and fecal transplant via nasoduodenal infusion.

2. Which of the following is correct?

A. KPCs are the most frequently identified type of carbapenemase in the U.S.

B. Metallo-carbapenemases are the most frequently identified type of carbapenemase in the U.S.

C. KPCs and metallo-carbapenemases only occur in Klebsiella pneumoniae.

D. Metallo-carbapenemases are so-named because of the presence of a serine moiety in the catalytic site.

3. Which of the following is correct regarding the recently described novel coronavirus (nCoV)?

A. Infection with nCoV is associated with a 100% mortality rate.

B. Person-to-person transmission has been identified.

C. Cases have been acquired in the United States.

D. It causes a hemorrhagic fever syndrome with predominant renal manifestations.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latent information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies

[IN FUTURE ISSUES]

A Large Multicenter Study of Methicillin-Susceptible and Methicillin-Resistant *Staphylococcus aureus* Prosthetic Joint Infections Managed With Implant Retention

Extended-Spectrum β-Lactamase-Producing *Escherichia coli* in the United States: Time to Rethink Empirical Treatment for Suspected *E. coli* Infections?

Human Rabies Infection Following Organ Transplant

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Is This the End of the Road for Calcium Supplementation?

In this issue: Calcium supplementation in women; type 2 diabetes treatments and pancreatitis risk; treating chronic idiopathic urticaria; rivaroxaban and VTE; and FDA actions.

High calcium intakes in women

Another study suggests that calcium supplementation may lead to excess all-cause mortality and cardiovascular disease in otherwise healthy women. Researchers studied more than 61,000 Swedish women for 19 years. Diet and calcium intake, including calcium supplementation, were assessed with the primary outcome being death from all causes and cause-specific cardiovascular disease, ischemic heart disease, and stroke. Higher *dietary* intake of calcium (> 1400 mg/day) was associated with a higher death rate from all causes compared to intake between 600-1000 mg/day (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.17-1.67). Higher calcium intake was also linked to increased risk of cardiovascular disease (HR, 1.49; CI, 1.09-2.02) and ischemic heart disease (HR, 2.14; CI, 1.48-3.09). There was no higher risk of stroke. Intake of calcium in tablet form > 1400 mg/day was associated with 2.5 times greater risk of death from all causes (HR, 2.57; CI, 1.19-5.55). The authors conclude that higher intakes of calcium in women are associated with higher death rates from all causes as well as increased rates of cardiovascular disease but not stroke (*BMJ* published online Feb. 13, 2013. DOI: org/10.1136/bmj.f228). Previous studies have focused more on stroke risk associated with calcium showing mixed results. This well-done study, along with previously published data from the Women's Health Initiative, provides ample evidence to rethink calcium supplementation for the 60% of middle-aged and older American women who are regular users of calcium supplements. The U.S. Preventive Services Task Force came to the same conclusion (even before this study was published) with publication of updated guidelines in February stating that "current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplements for the primary prevention of fractures in postmenopausal women or men." They further state there is no evidence to support use of more than 1000 mg of calcium and 400 mcg of vitamin D per day and recommends against using doses lower than 1000 mg of calcium and 400 mcg of vitamin D. Their rationale is that supplementation does not reduce fracture risk but does increase the risk of renal stones in otherwise healthy women. This does not apply to women with osteoporosis or vitamin D deficiency (*Ann Intern Med*, published online Feb. 26, 2013). ■

Diabetes therapies and pancreatitis risk

Glucagonlike peptide 1 (GLP-1) mimetics (e.g., analogs of GLP-1 and dipeptidyl peptidase IV inhibitors) used for the treatment of type 2 diabetes might increase the risk of pancreatitis, according to a recent population-based, case-control study. Using a large population database of

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

type 2 diabetics, 1269 cases of acute pancreatitis were identified and those patients were matched with 1269 controls with similar risk factors (age, sex, diabetes mellitus complications, etc). After adjusting for available confounders, current use of GLP-1 based therapies (exenatide [Byetta] and sitagliptin [Januvia]) more than doubled the risk for acute pancreatitis (adjusted odds ratio 2.24, 95% CI, 1.36-3.68). The authors state that "Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus" (*JAMA Intern Med* published online Feb. 25, 2013. DOI: 10.1001/jamainternmed.2013.2720). Both drugs already carry a boxed warning regarding pancreatitis. ■

Omalizumab for idiopathic urticaria

Chronic idiopathic urticaria is one of the most frustrating entities to treat as many patients do not respond to antihistamines, even in high doses. Now, a new study suggests that omalizumab (Xolair), an IgE monoclonal antibody used to treat asthma, may be effective in these patients. Patients with moderate-to-severe chronic idiopathic urticaria (n = 323) were randomized to SQ injections of omalizumab every 4 weeks for three total injections at doses of 75 mg, 150 mg, 300 mg, or placebo. The primary outcome was itch-severity score. The 75 mg dose was no better than placebo, but the two higher doses showed significant reductions in itching, with the 300 mg dose being the most effective. The higher dose was also associated with the highest risk of side effects, however, at about 6%. The authors conclude that omalizumab was effective in these patients who were previously symptomatic despite antihistamines. The study was sponsored by the drug manufacturers Genentech and Novartis Pharma (*N Engl J Med* published online Feb. 24, 2013. DOI: 10.1056/NEJMoa1215372). ■

Rivaroxaban for VTE prevention

Rivaroxaban, the oral Xa inhibitor, is as effective as enoxaparin in preventing venous thromboembolism (VTE) in patients with acute medical illnesses, but with a higher risk of bleeding, according to a new study. More than 8100 acutely ill hospitalized patients were randomized to 10 days of enoxaparin 40 mg SQ daily or 35 days of rivaroxaban 40 mg orally with matching placebos. The primary outcome of asymptomatic or symptomatic VTE occurred in 2.7% of patients in both groups by day 10. By day 35, the rates were 4.4% for rivaroxaban and 5.7% for enoxaparin ($P = 0.02$). However, the bleeding rate was more than double in the rivaroxaban group at day 10 (2.8% vs 1.2%, $P < 0.001$) and even higher at day 35 (4.1% vs 1.7%, $P < 0.001$). The authors conclude that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days) and reduced the risk of VTE at 35 days with an increased risk of bleeding (*N Engl J Med* 2013;368:513-523). ■

FDA actions

A new selective estrogen receptor modulator (SERM) has been approved for the treatment of dyspareunia due to vulvar and vaginal atrophy in postmenopausal women. Ospemifene appears to benefit vaginal epithelium without significant effect on the endometrium. The drug's safety and efficacy was established in three clinical trials of nearly 1900 postmenopausal women with vulvar and vaginal atrophy who were randomly assigned to ospemifene or placebo. After 12 weeks, the first two trials showed statistically significant improvement in dyspareunia while the third trial supported the long-term safety of the drug. The drug is contraindicated in women with genital bleeding, estrogen-dependent cancer, or thromboembolic disease. The risk of stroke and VTE was higher than baseline but lower than the rates seen with estrogen replacement therapy. Ospemifene comes with a boxed warning regarding endometrial hyperplasia and abnormal vaginal bleeding. Common side effects include hot flashes, vaginal discharge, muscle spasms, and sweating. It will be marketed by Shionogi Inc. as Osphena.

The FDA has approved ado-trastuzumab emtansine for use as a single agent in patients with late-stage, HER2-positive breast cancer. The drug is approved for patients who have already been treated with trastuzumab and taxane separately or in combination. Approval was based on a study of nearly 1000 women with metastatic breast cancer in which progression-free survival was about 3 months longer with the drug compared to lapatinib plus capecitabine, and overall survival was about 6 months longer. Ado-trastuzumab emtansine is marketed by Genentech as Kadcyla. ■