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Infectious Disease [ALERT]

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

SPECIAL FEATURE

Superbugs Keep Coming, but New Antibiotics Do Not

By Stan Deresinski, MD, FACP, FIDSA
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The headlines once again warn of a new superbug threatening mankind. Having apparently grown weary of MRSA and *Clostridium difficile*, the media has apparently moved on to NDM-1. In an example of synecdoche, NDM-1, or New Delhi carbapenemase-1, is taken in these reports to refer to organisms that produce this metallocarbapenemase, which are most prevalent in south Asia but have now appeared in many parts of the world, including the United States, having been brought initially to these regions by colonized or infected travelers. While the first cases all had had contact with medical care in south Asia, some recent cases have had no such contact.

In addition to being resistant to β-lactam antibiotics, including carbapenems, NDM-1-producing organisms carry genes encoding additional resistant mechanisms, including a 16sRNA methylase that renders them resistant to all available aminoglycosides, though to date, they remain susceptible to colistin and tigecycline.

NDM-1 has reached the popular press as a result of a new publication reporting the finding that organisms carrying this resistance mechanism have been identified not only in environmental water, but also in tap water in New Delhi.[1] Furthermore, it has been identified for the first time in 11 additional species in which it had not previously

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Infectious Disease [ALERT]

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been detected, including *Shigella boydii* and *Vibrio cholerae*.

The overall problem of antibiotic resistance is extensive in many parts of the world, including areas within the United States and Europe, as well as regions of Africa, Latin America, and Asia. The problem in Asia was extensively highlighted at the 8th International Symposium on Antimicrobial Agents and Resistance held in Seoul, Korea, in early April 2011. A Chinese national surveillance program (CHINET) found that 56% of *Escherichia coli* and 41% of *Klebsiella pneumonia* were ESBL-producers, mostly of CTX-M, while approximately 60% of *E. coli* are resistant to ciprofloxacin. In addition, approximately 50% of *Acinetobacter baumanii* are resistant to carbapenems, although less than 25% of *Pseudomonas aeruginosa* are. The proportion of *A. baumanii* resistant to all antibiotics tested except tigecycline and colistin (which are not available in China) increased from 2.8% in 2007 to 17% in 2009. In India, 90% of *A. baumanii* are resistant to carbapenems. In addition, 23% of *K. pneumoniae* isolated from patients with intra-abdominal infections in the Asia/Pacific region in 2009 were ESBL+ and, in the SMART study, 45%-50% of *E. coli* from intra-abdominal infections were resistant to levofloxacin and ciprofloxacin.

These data provide a vision into what may be facing us all — a global post-antibiotic era. As a consequence of a perceived lack of sufficient financial incentive, large pharmaceutical companies currently show little or no interest in developing novel antibiotics active against these multidrug resistant (MDR) Gram-negative rod (GNR) pathogens. Antibiotics, of course, are administered for relatively short periods of time, in contrast to antihypertensives, for example, and, relative to cancer chemotherapeutic agents, are generally low cost. Furthermore, if a dramatic breakthrough in the development of a novel antibiotic for treatment of MDR GNR infections were to occur, as responsible stewards, we would discourage its use in order to "save it." Factors such as this appear to make solution of the problem of lack of new advances in antibiotic therapy almost impossible.

We can, however, extend the usefulness of antibiotics by responsible stewardship. The continued introduction of rapid point of care diagnostic testing, as well as susceptibility testing, will help in this endeavor, as will the use of biomarkers to assist in decisions regarding the timely discontinuation of antibiotic therapy.

However, antimicrobial stewardship programs in the United States are largely centered around acute care hospitals, while many more antibiotic doses are administered in chronic care facilities and the community at large. Furthermore, antibiotic resistance, as demonstrated by the data from Asia described above, is a global problem. Antibiotic resistance is a huge problem in the lesser developed world, where circumstances generally do not allow for sophisticated stewardship programs and where antibiotics are generally readily available to patients in the absence of a prescription.

Infectious Disease Society of America (IDSA) has stated that "Current data document the impending disaster due to the confluence of decreasing investment in antibacterial drug research and development concomitant with the documented rapid increase in the level of resistance to currently licensed drugs."[2] The problem is huge, is extremely complicated, and requires urgent action. Think of the potential consequences to cancer chemotherapy and organ transplantation in a world in which infections due to organisms for which there is no effective therapy become increasingly common! In their "10 by '20" effort, the IDSA has called for the development to of 10 new antibiotics by 2020, calling for a global commitment. This commitment would require active participation by governments, the pharmaceutical and diagnostics industry, health

care providers, policy and legal communities, universities, philanthropic organizations, and patient advocacy groups.[2]

The goal of the IDSA may prove to be "a bridge too far," but we will face a very different world of medicine from that which most of us currently occupy if a major effort is not made in antibiotic development. And we will all have to become brave in that new world. ■

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2. IDSA. The 10 x '20 initiative: Pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clin Infect Dis 2010;50:1081-1083.

ABSTRACT & COMMENTARY

Impact of Prebiopsy Antibiotics on Pathogen Recovery in Vertebral Osteomyelitis

By Dean L. Winslow, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;
Clinical Professor, Stanford University School of Medicine
Dr. Winslow is a speaker for Cubist pharmaceuticals and GSK, and is a consultant for Siemens Diagnostic.

SYNOPSIS: Ninety-two patients with hematogenous vertebral osteomyelitis underwent biopsy. Pathogens were recovered in 61 patients (66%). Open biopsy yielded a pathogen in 91% of cases and needle biopsy in 53%. Open biopsy predicted positive biopsy culture results, but there was no association with prebiopsy antibiotic administration.

SOURCE: Marschall J, et al. The impact of prebiopsy antibiotics on pathogen recovery in hematogenous vertebral osteomyelitis. CID 2011; 52:867-872.

Of 150 patients with hematogenous vertebral osteomyelitis, 92 (61%) underwent biopsy — 60 (65%) needle and 32 (35%) open. Imaging studies revealed discitis in 75%, vertebral osteomyelitis in 70%, and epidural abscess in 44% of patients. Patients undergoing open biopsy were more likely to have neurologic symptoms and signs (29% vs. 10%) and epidural abscess on imaging studies, but were less likely to have a positive blood culture (30% vs. 52%). Sixty patients (65% of the patients undergoing biopsy) received antibiotics ≤ 14 days before the procedure (median, 4 days). Of the 92 patients who underwent biopsy, 34% of samples were culture-negative, 28% grew MSSA, 25% MRSA, 15% coagulase-negative staphylococci, and 7% *E. coli*. Open biopsy predicted positive biopsy culture results (91% positive on open biopsy vs. 53% on needle biopsy), but there was no association with prebiopsy antibiotic administration.

■ COMMENTARY

One of the pet peeves of most Infectious Diseases consultants is the rush of inexperienced clinicians to administer empiric antibiotics to clinically stable patients with chronic or subacute infections (particularly infective endocarditis and osteomyelitis) prior to obtaining appropriate cultures. A common scenario involves a well-meaning ER doctor or Internal Medicine house officer making an appropriate diagnosis of one of these conditions and then initiating empiric therapy (generally with "VoSyn" as one of our excellent Stanford ID Fellows refers to the commonly prescribed combination of vancomycin plus piperacillin/tazobactam) prior to obtaining appropriate material for culture to determine the exact pathogens involved. Often this results in committing the patient to 6 or more weeks of excessively broad spectrum or multiple empiric antibiotics given intravenously by PICC (with all of the attendant potential complications of prolonged broad-spectrum intravenous antibiotic therapy). If a highly sensitive pathogen were obtained prior to antibiotic administration, a narrow spectrum, and possibly oral, antibiotic regimen could have been used.

This study has a number of limitations including the following:

1. The study was retrospective and relatively small in size.
2. Epidural abscess was disproportionately represented in the open biopsy group and would be expected to yield a pathogen more often than uncomplicated discitis with or without prior antibiotic administration, so the conclusion that open biopsy is more sensitive than needle biopsy is questionable.
3. Since 65% of patients from the combined open and needle biopsy groups received antibiotics prior to biopsy, it is likely that highly antibiotic-sensitive pathogens such as streptococci may have been missed in both groups of patients.
4. The study only looked at vertebral osteomyelitis and the results may or may not be generalizable to chronic osteomyelitis of the extremities, diabetic foot infections, and orthopedic device/prosthetic joint infections.

I believe the only way this study will alter my own practice is that I will push a little harder for biopsy (either by a surgeon or by interventional radiology) in patients who have received prior antibiotics, rather than just throwing up my hands and recommending broad spectrum antibiotics. While reassuring that it is still possible to obtain a pathogen by culture of a bone biopsy specimen in about two-thirds of cases after the patient has received several days of antibiotics, this does not mean that this is optimal practice. In most cases, culture of a bone biopsy specimen should still be obtained prior to starting antibiotics in clinically stable patients. ■

ABSTRACT & COMMENTARY

Molecular Diagnosis for Pediatric Parapneumonic Empyema

By Hal B. Jenson, MD, FAAP

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Dr. Jenson reports no financial relationship to this field of study.

SYNOPSIS: PCR testing of pleural fluid significantly increased bacterial identification compared to culture of blood and pleural fluid (84% vs. 35%; P < 0.001). PCR was particularly more sensitive for detection of Streptococcus pneumoniae (71% vs. 24%; P < 0.001). Dual infections were identified by PCR in 10% of cases.

SOURCE: Blaschke AJ, et al. Molecular analysis improves pathogen identification and epidemiologic study of pediatric parapneumonic empyema. Pediatr Infect Dis J 2011;30:289-294.

A study compared culture- and PCR-based bacterial identification methods among 85 children hospitalized at a single medical center with parapneumonic effusion in 2009. Pleural fluid specimens for multi-species PCR testing were available from 63 of 85 (74%) hospitalized children. The median length of illness prior to presentation was 6 days (range, 1-16 days) and 86% had been treated with antibiotics prior to pleural fluid sampling.

By culture, pathogens were isolated from the blood and/or pleural fluid of 22 of the 63 children (35%). *Streptococcus pneumoniae* was isolated in 15 of 63 (24%), *Streptococcus pyogenes* in three (5%), and *Staphylococcus aureus* in four (6%; all MRSA). Pleural fluid culture identified a pathogen in 15 of 63 (24%) cases. Blood cultures were the only positive specimen in seven of 22 children (32%) in whom a pathogen was identified by culture.

By PCR, 59 pathogens were identified in the pleural fluid of 53 of the 63 children (84%). *S. pneumoniae* was isolated in 45 of 63 (71%), *S. pyogenes* in seven (11%), *S. aureus* in five (8%; two MSSA and three MRSA), *Haemophilus influenzae* in one (2%), and *Mycoplasma pneumoniae* in one (2%). Pleural fluid PCR identified a pathogen in 53 of the 63 cases (84%). PCR was positive in all cases in which a pathogen was identified by pleural fluid culture. Two bacterial pathogens were identified by PCR in six pleural fluid samples (10%).

Of the 41 of 63 patients (65%) with no pathogen identified by culture of either pleural fluid or

blood, 32 (78%) had a pathogen identified by pleural fluid PCR.

Of the 45 samples positive for *S. pneumoniae* by culture and/or PCR, serotyping using molecular methods could be performed in 78% of cases, which showed only four serotypes: 1, 3, 7F, and 19A. Serotype 7F was the most frequently detected serotype by both culture and PCR, representing eight of 15 (53%) *S. pneumoniae* culture isolates and 21 of 45 (47%) *S. pneumoniae* isolates identified by culture and/or PCR.

■ COMMENTARY

Microbiologic diagnosis and effective management of parapneumonic effusion in children is hampered greatly by the high rate of sterile bacterial cultures of pleural fluid and blood. In this series, a pathogen was identified by culture in only 35% of cases, which is typical. One major factor contributing to the high rate of culture-negative cases is the frequency of prior antibiotic treatment before pleural fluid sampling (86% in this study). Using PCR, pathogens were identified in 84% of cases. *S. pneumoniae* was the most frequent pathogen identified by PCR in culture-negative cases. This study demonstrates the usefulness of molecular diagnostic testing and evaluation for parapneumonic effusions and other serious infections. It also shows that dual infections appear to be more frequent (10%) in parapneumonic effusions than commonly appreciated. In this single-center study, the rate of MRSA as a cause of parapneumonic effusion was very low. It is possible that this may vary regionally.

The study was conducted just prior to the introduction of PCV-13 vaccine. The four *S. pneumoniae* serotypes found in the study are contained in the PCV-13 vaccine. One concern to monitor in the future is the likelihood of replacement disease caused by non-vaccine *S. pneumoniae* serotypes. ■

ABSTRACT & COMMENTARY

Last Doubts Resolved: Artesunate Is Superior to Quinine for the Treatment of Severe Falciparum Malaria

By Brian G. Blackburn, MD

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Dr. Blackburn reports no financial relationship to this field of study.

SYNOPSIS: African children with severe falciparum malaria were randomized to receive either intravenous artesunate or intravenous quinine. Those who received artesunate died significantly less frequently than those who received quinine. These data, taken together with previous trials, strongly suggest that intravenous artesunate should replace intravenous quinine as the treatment of choice for severe falciparum malaria worldwide.

SOURCE: Dondorp AM, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): An open-label, randomised trial. Lancet 2010;376:1647-1657.

Despite the recent gains achieved by multidisciplinary control programs, malaria still kills nearly 1 million people and causes almost 300 million symptomatic illnesses globally each year, with most of this burden borne by sub-Saharan Africa. Severe malaria, usually caused by *Plasmodium falciparum*, is defined in part by respiratory distress, renal failure, altered mental status/seizures, metabolic acidosis/hypoglycemia, and hyperparasitemia. The mortality rate of severe malaria, even with appropriate treatment, is as high as 15%-20% in some series, and the disease is nearly universally fatal if untreated.

The standard treatment worldwide for severe

malaria has been intravenous quinine for many years (given the unavailability of intravenous quinine in the United States, quinidine is used instead, a drug with similar efficacy but more toxicity). Although effective, the mortality rate of severe malaria treated with quinine remains high, and quinine/quinidine are toxic, sometimes causing infusion-related hypotension, cinchonism, blindness, deafness, and hypoglycemia; quinidine adds to these adverse effects an even higher risk of arrhythmias than seen with quinine.

Artemisinins, the most rapidly acting antimalarials available, are potent and well-tolerated, providing a theoretical advantage for this drug class over the quinine derivatives. A major clinical trial performed recently in Southeast Asia showed that the mortality rate in patients with severe falciparum malaria was 22% in patients treated with intravenous quinine, and 15% in those treated with intravenous artesunate.[1] Because few children were included in this trial, the generalizability of these results to children with severe malaria was questioned.[1] In addition, the applicability of these results to malaria acquired in Africa was also unclear. The authors therefore undertook a clinical trial comparing the intravenous formulations of quinine and artesunate in children with severe falciparum malaria in Africa.

More than 5,400 children (age < 15 years) with severe falciparum malaria from nine different sub-Saharan African countries were enrolled in the trial. The median age of enrolled patients was about 3 years. The trial was an open-label, randomized comparison of the standard dosing regimens of intravenous artesunate and intravenous quinine. At trial entry, 30% of patients had severe anemia, about one-third had coma, one-third had seizures, and more than 40% had severe acidosis, with no difference between the study groups. About 6% of those tested (125 of 2,095) were HIV-positive; the case fatality rate was high (28%) in HIV-infected patients, with no significant mortality difference between treatment groups. The primary outcome measure of the trial was in-hospital mortality.

Overall, 8.5% of patients who received artesunate died, compared with 10.9% of patients who received quinine ($P = 0.0022$), a relative mortality reduction of 22.5%. Significantly fewer patients in the artesunate-treated group developed worsening neurological status, coma, or seizures than in the quinine-treated group after trial entry, although the frequency of long-term neurological sequelae did not differ between groups. No serious treatment-related adverse effects were seen, and significantly fewer patients in the artesunate-treated group developed hypoglycemia than in the quinine-treated group after enrollment. The authors also performed a meta-analysis of all severe malaria trials that have compared survival between parenteral artesunate and parenteral quinine. The overall odds ratio for death was 0.69 ($P < 0.00001$) in favor of artesunate, with no significant heterogeneity between results generated in Africa and Asia.

■ COMMENTARY

This large, well-designed trial showed that artesunate significantly reduces mortality among African children with severe falciparum malaria. Despite the findings of the earlier SEAQUAMAT trial in Southeast Asia, which demonstrated a 35% mortality reduction in patients treated with IV artesunate compared to those treated with IV quinine, some questions about the applicability of these results to children or to patients with malaria acquired in Africa were raised.[1] This was in part because of perceived differences in the epidemiology, pathology, and susceptibility of malaria parasites to quinine in Africa, and differences in the natural history of the disease in children as compared to adults. These concerns were not substantiated, based on both the current AQUAMAT trial, and the meta-analysis the authors performed of trials that have compared artesunate to quinine for severe malaria.

It now appears that for all regions and patient populations, artesunate should be the drug of choice for treating severe malaria, given that it is more rapidly acting, better tolerated, and more effective than quinine (and by extension, quinidine). Unfortunately, access to the drug remains problematic, and currently no Good

Manufacturing Process (GMP) formulation of artesunate is commercially available. Because it is not FDA-approved in the United States, artesunate is only available from the Centers for Disease Control and Prevention (CDC) through an investigational new drug (IND) protocol for severe malaria in patients who meet certain criteria.[2] Although the drug is available on an emergency basis through CDC, delay in administration is inevitable with this mechanism, and rapid therapy clearly matters for severe malaria. Given that there is little doubt that this is the superior drug for a disease with a high mortality rate, artesunate should be approved for widespread use in the United States immediately, and wider supplies of this vital drug ensured worldwide. ■

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SPECIAL FEATURE

Linezolid Dosing in Special Populations

By Jessica C. Song, MA, PharmD

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Dr. Song reports no financial relationship to this field of study.

Linezolid is an oxazolidinone agent that has been shown to be effective for the treatment of infections caused by Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).[1] Linezolid exhibits linear pharmacokinetics, since the area under the plasma concentration-time curve (AUC) increases with dosing increments. In addition, this drug displays time-dependent antibacterial activity, since bacterial killing is correlated with the time during which the plasma drug concentration remains above the minimum inhibitory concentration (MIC), along with the ratio between AUC and the MIC (AUC/MIC). Optimal bacterial killing has been shown to occur with an AUC/MIC in excess of 100, along with a T > MIC of 100%.[1]

Linezolid is a moderately lipophilic drug and it primarily undergoes nonrenal clearance (65%). The remaining 35% of the total dose of linezolid appears unchanged in the urine.[2] At present, therapeutic drug monitoring (TDM) of linezolid has not been adopted by institutions worldwide, but may be warranted in some settings. Pea and associates recently reported on their experiences of linezolid TDM at the Institute of Clinical Pharmacology and Toxicology (University of Udine).[2] Findings from this retrospective review were indicative of potential underexposure in 28% of cases.

The purpose of this review is to discuss appropriate dosing of linezolid in renally impaired patients, liver transplant recipients, cystic fibrosis patients, and burn patients.

LINEZOLID DOSING IN PATIENTS WITH RENAL IMPAIRMENT

Renal excretion of linezolid does not appear to be affected by decreases in creatinine clearance, provided that the creatinine clearance remains above 10 mL/min.[2] However, definitive evidence is lacking for dosing recommendations in end stage renal disease (ESRD) patients and in patients requiring continuous renal replacement therapy.

Tsuji et al studied the association of the occurrence of adverse hematologic effects with blood linezolid concentration and $AUC_{0\text{-}24}$ in renally impaired patients who received this agent for MRSA infection.[3] Three cases of linezolid-associated thrombocytopenia were highlighted; the three patients received intravenous linezolid 600 mg dosed every 12 hours for 13-16 days. The patients' estimated glomerular filtration rates (GFR) ranged from 12 mL/min to 39 mL/min. Blood samples were taken from the three patients at 20 time points. Tsuji and associates reported a strong negative correlation between $AUC_{0\text{-}24}$ and hemoglobin level ($r = 0.783$; $P < 0.01$), whereas the correlation between $AUC_{0\text{-}24}$ and platelet count was shown to be weak ($r = 0.593$; $P < 0.01$).

Pea and associates examined the effect of continuous venovenous hemofiltration (CVVH) on the pharmacokinetic profile of linezolid in two patients with severe, postsurgical, intra-abdominal infections.[4] The two patients received pump-driven CVVH (Aquarius, Edwards Lifesciences, Unterschleibheim, Germany), set at a flow rate of 120-130 mL/min, and with a substitution rate of 2000 mL/h. The polysulfone Aquamax PSHF 1200-based hemofilter has an effective surface area of 1.25 m^2. Patient 1 had blood samples taken on day 28 of therapy, with blood draws done 1 hour before dosing and at 0, 0.5, 1, 2, 3, 5, 7, 9, and 11 hours after the morning intravenous infusion of linezolid 600 mg. Patient 2 underwent 10 blood draws (same times as patient 1) on day 4 of therapy.

Patients 1 and 2 exhibited similar hemofiltration clearances (ClCVVH; 0.38 vs. 0.35 mL/min/kg), but Patient 1 showed a higher proportion of clearance through hemofiltration (69% of total linezolid clearance) than patient 2 (29% of total linezolid clearance). Patients 1 and 2 eliminated 314 mg and 160 mg of linezolid, respectively, through hemofiltration during the dosing interval. Linezolid plasma trough concentrations were 21.7 mg/L and 6.5 mg/L for patients 1 and 2, respectively. Both patients had AUC/MIC ratios greater than 100 hours and neither patient required drug withdrawal for linezolid-related toxicity. Pea and associates proposed that the high drug exposure of Patient 1 could have resulted from nonlinear elimination arising from saturation of one of the two major metabolic pathways.

LINEZOLID DOSING IN LIVER TRANSPLANT RECIPIENTS

There are scant data for the dosing of linezolid in hepatically impaired patients. Pea and associates reported on a case of hyperlactacidemia associated with linezolid therapy in a 59-year-old liver transplant recipient who developed bilateral pneumonia 4 days post-surgery.[5] On day 10 of linezolid therapy, multiple blood samples were obtained in order to conduct a pharmacokinetic analysis of linezolid exposure in this patient, since an asymptomatic rise in plasma lactate levels had been noted (peak level, 8.4 mmol/L) since day 4 of linezolid therapy. The pharmacokinetic analysis revealed an $AUC_{0\text{-}12}$ of 412.55 mg × h/L, a maximum concentration of 43.32 mg/L, a trough concentration of 26.99 mg/L, and an elimination half-life of 16.57 hours, clearly indicating plasma overexposure to linezolid.

Within 48 hours of discontinuing linezolid therapy, lactate levels normalized in this patient. The authors stated the possibility that linezolid-associated hyperlactacidemia could be caused by inhibition of mitochondrial protein synthesis, but that the true mechanism of linezolid overexposure had yet to be elucidated. Of note, the patient described in this report received sertraline during linezolid therapy. The authors proposed that linezolid clearance could have been impaired by blockade of p-glycoprotein activity by sertraline.

LINEZOLID DOSING IN CYSTIC FIBROSIS PATIENTS

Cystic fibrosis patients often develop serious and potentially life-threatening respiratory tract infections, so the study of linezolid pharmacokinetics in this population merits particular attention. Bosso and associates conducted a study of 12 cystic fibrosis patients, whose ages ranged from 22 to 39 years.[6] Blood draws occurred immediately before drug infusion and at 0.5, 0.75, 1, 2, 4, 8, and 24 hours after drug infusion. The pharmacokinetic analysis revealed a wide degree of variability in the pharmacokinetic parameters of linezolid observed in the 12 subjects, and the extremes of the pharmacokinetic values were within ranges previously reported for healthy adults. However, when the authors assumed a theoretical value of 4 mg/L for the MIC, none of the subjects achieved $AUC_{0\text{-}\infty}$/MIC ratios of > 80 hours; observed $AUC_{0\text{-}\infty}$/MIC ranged from 16.30 to 52.24 hours.

LINEZOLID DOSING IN BURN PATIENTS

Patients with burn injuries display numerous physiologic alterations affecting organ function and drug metabolism.[7] Patients experiencing large burns may exhibit increased drug volumes of distribution due to changes in fluid volumes of key body compartments, thereby decreasing the concentration when a standard dose is administered. In addition, higher drug clearance and shorter elimination half-lives may be observed in burn patients, due to increased renal blood flow secondary to changes in cardiac output.[7]

Hallam et al reported on the case of a 27-year-old male burn patient (52% body surface area affected) who required an increase in the dosing frequency of linezolid for lobar pneumonia.[7] On hospital day 12, the patient started intravenous linezolid (600 mg twice daily), following a 7-day course of piperacillin-tazobactam and 4 days of meropenem therapy. After 48 hours of linezolid therapy, pharmacokinetic analysis revealed a percentage of dose interval above 4 mg/L of 20% for linezolid (600 mg twice daily). Consequently, the dosing interval was shortened from 12 hours to 8 hours on hospital day 15. The patient became

afebrile and his white count decreased from 36 × 10^9/L to 13.6 × 10^9/L on day 16. Moreover, the percentage of dose interval above 4 mg/L increased to 70% with the every 8-hour dosing regimen. Antibiotic therapy was discontinued on hospital day 19.

CONCLUSION

The standard regimen of linezolid (600 mg twice daily) does not require modification in the majority of patients, including patients with mild renal and hepatic impairment. However, certain patient populations have been shown to achieve insufficient AUC/MIC or T > MIC values, thereby increasing the risk for the development of resistant strains.[2] Conversely, other patient populations with overexposure to linezolid could be at risk for severe toxic effects against target organs (brain, optic nerve, kidney, skeletal muscular tissue).[2] TDM might be warranted in patients with significant burn injuries, in patients with cystic fibrosis or ESRD, and in patients undergoing renal replacement treatment. ■

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ABSTRACT & COMMENTARY

Fever with Thrombocytopenia Associated with a Novel Bunyavirus in China

By Dean L. Winslow, MD, FACP, FIDSA

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Clinical Professor, Stanford University School of Medicine

Dr. Winslow is a speaker for Cubist pharmaceuticals and GSK, and is a consultant for Siemens Diagnostic.

SYNOPSIS: A severe fever with thrombocytopenia syndrome (SFTS) was recognized in China beginning in 2009. A novel virus, SFTS bunyavirus, was isolated from patients meeting the case definition of this syndrome.

SOURCE: Yu Y-J, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med 2011; Epub ahead of print.

Due to heightened surveillance of acute febrile illness in China, a severe illness associated with thrombocytopenia and multi-system organ involvement was recognized beginning in 2009. *Anaplasma phagocytophilium* was originally suggested as a cause but the pathogen was not detected in most patients. Blood samples from patients meeting the case definition were used to inoculate a variety of cells in culture, viral RNA was detected by PCR, and the pathogen was subsequently characterized by electron microscopy and nucleic acid sequencing. Enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay (IFA), and neutralization assays were developed and were used to document seroconversion of patients to the novel pathogen.

A novel virus, designated SFTS bunyavirus, was isolated from 171 patients, ages 39-83 years, from six provinces in China. These patients presented with an illness characterized by fever (100%), abdominal pain (49%), thrombocytopenia (95%), leucopenia (86%), and clinical and laboratory evidence of multi-system organ dysfunction in many cases. Eleven of 81

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Updates

By Carol A. Kemper, MD, FACP

Preparing for Coccidioides Laboratory Exposure

Source: Stevens DA, et al. Expert Opinion: What to do when there is a coccidioides exposure in a laboratory. Clin Infect Dis 2009;49:919-923.

Exposure to coccidioidomycosis in the laboratory can represent a significant hazard, resulting in serious and even fatal infection. In particular, opening culture plates in the lab, without appropriate precautions, can result in the aerosolization of artificially large numbers of arthroconodia. Human coccidioidal infection can occur with inhalation of only 1-10 arthroconidia; therefore, the consequence of such exposure is significant.

Most exposures are inadvertent, and occur when an unsuspecting respiratory sample yields coccidioides in culture in the lab. If *C. immitis* infection is suspected, it is important for the physician to notify the laboratory regarding this possibility when submitting the specimen. However, despite appropriate warning by the ID Fellow on service, who directly phoned the lab ahead of time, and provided a written history on the lab slip ("h/o cocci"), a recent aspirate managed to escape our laboratory's usual precautions. Specimens from a patient with recognized coccidioidomycosis were submitted to the lab for culture. The plates were opened and examined by a pregnant microbiology technician in the presence of a second technician on day 2 (no growth) and day 3. Three colonies of early growth of a fungus were noted on day 3. At that point, the technicians pieced together the history and the possible risk and notified their laboratory supervisor (it is important to note that the terminology "cocci" on the lab request may be misleading and the full name should be indicated). An incident report was written and filed. Only several days later did the employees report to employee health for evaluation. The question was what, if anything, should be done at that point.

This excellent review article highlights the recommended steps for dealing with laboratory exposure, including assessing the risk, environmental measures, and management of exposed personnel. Although pregnancy increased the risk for more severe and disseminated infection, and also precludes the use of prophylactic azole therapy, it was decided the risk of exposure in this case was minimal. Cultures with less than 72 hours of incubation generally do not present a risk, but formation of arthroconidia can occur as early as 96 hours, and large numbers of arthroconidia may be present by 7-10 days of culture. Baseline and follow-up serologic studies were recommended for the two affected employees, but chemoprophylaxis was not provided. If exposure does occur, the administration of either itraconazole or fluconazole orally for 6 weeks is recommended for non-pregnant employees.

Given the increasing number of elderly who travel to cocci-endemic areas such as Arizona and New Mexico for the winter, and who are at risk for coccidioidal infection when they return home months, laboratories, even those in non-cocci-endemic areas, should be prepared for a possible coccidioides exposure. ■

The Benefits of Broader Exposure

Source: Ege MJ, et al. Exposure to environmentalmicroorganismsandchildhoodasthma. N Engl J Med 2011;364:701-709.

It has been speculated that children growing up in an overly clean, suburban environment may experience greater atopy and asthma than children growing up in the inner city or on a farm. These investigators report on the results obtained from two large-scale cross-sectional studies, performed in Europe, comparing the prevalence of atopy and asthma in children. The first study focused on 6,963 children of farmers and school-aged children (ages 6-13 years) growing up in largely rural areas of central Europe; 52% lived on a farm; and 8% had a diagnosis of asthma. Dust from the children's mattresses were collected and DNA extractions were performed. The second study focused on a stratified random sample of 3,668 school-aged children (ages 6-12 years) living in central Europe. Only 16% of these children lived on farms and 11% of these children had a diagnosis of asthma. Airborne dust samples were collected from the children's bedrooms for 2 weeks.

Both studies revealed that the risk of asthma was inversely related to the diversity of microbial exposure in the children's bedroom environment, independent of whether they lived on a farm. In addition, the presence of a more circumscribed range of exposure to a few organisms was also inversely related to an increased risk of asthma. Attempts to create a statistically relevant diversity score, either by a factor

analysis or by summing the total exposure, demonstrated that diversity of flora, however it was measured, was significantly less in children with asthma (but not atopy).

Several "zones" identified in the factor analysis suggested that exposure to groups of bacteria and fungi were associated with a protective effect, although no single organism could be identified as protective. In addition, exposure to fungal taxon eurotium and penicillium seemed to have a protective effect. ■

Chinese Duck Egg-Drop Syndrome

Source: A ProMED post; March 29, 2011; available at: http://www.promedmail.org.

Duck-related foods in China are both a delicacy and a dietary staple, from salted duck eggs to pecking duck. Last spring, farmers in several provinces of eastern China, where duck farming is common, noticed that egg production was decreasing. In some areas, egg production fell by more than 90% — and some ducks became ill, and quickly died of an apparent infection.

Further study has revealed that a novel flavivirus, called BYD virus, is responsible. The virus was isolated from ducks in several areas, is cytopathic in egg embryo tissue culture, and results in a similar disease when administered to healthy ducks. The virus has been identified as an envelope-positive stranded RNA virus that bears similarity to Tembusu virus in nucleotide sequencing. Tembusu is a mosquito-born virus prevalent in Southeast Asia. This places this new virus in the Ntaya serogroup of the flavivirus genus, similar to Israel Turkey Meningoencephalitis virus (ITM), for which a vaccine has been used for many years in Israel. It is still not clear how the virus is spread, and whether mosquitoes are a required vector. Increasing evidence suggests that another flavivirus, West Nile virus, can be transmitted among crows from cloacal shedding and close contact, and may not require a mosquito vector. ■

TB in Captive Elephants in the United States

Source:MurphreeR,etal.Elephant-to-human transmission of tuberculosis, 2009. Emerg Infect Dis 2011;17:366-371.

Animal-to-human transmission of tuberculosis (TB) has been well-documented for a number of mammalian species, including deer, dogs, and even cats (a topic of a recent "Doc Martin" episode). Transmission of TB from circus elephants occurred in the 1990s. Since then, TB has become endemic in captive elephants in the United States, prompting the FDA in 1998 to require annual trunk washings for tuberculosis culture for all captive elephants in the United States. At present, about 270 Asian and 220 African elephants live in the United States, many of them at refuges for the old or infirm. The problem is, no one really knows how to detect latent TB in elephants (imagine the size of the skin test), although interferon-based assays show promise, trunk washings are not sufficiently sensitive.

In 2004, a non-profit reserve in Tennessee, which cares for retired or sick elephants within a 2,700-acre area, received two Asian elephants with a history of active TB. Infection control and treatment protocols were established, and a separate quarantine area for elephants with active infection was created. Sadly, one the elephants died of TB in 2005, but the other was cleared of infection at 1 year of treatment.

The reserve accepted eight more elephants from the same source in 2006 — all of whom had been potentially exposed to TB. The elephants were trained to provide their own truncal washing samples (instill 30-60 cc of saline, lift and lower, lift and lower, and exhale into a plastic bag). In addition, environmental samples from the elephants, their living quarters, and their excrement were cultured. All trunk washing from elephants at the refuge, as well as environmental samples, from 2006 to 2009 were negative, except for one elephant suspected of having active TB, who was quarantined and treated with TB medications (she was poorly tolerant).

Despite these measures, 13 of 46 employees converted their PPD. Five were elephant caregivers, two were maintenance workers, and three were administrative staff who worked in an adjacent two-story building. The two maintenance workers swept hay and sawdust and shoveled excrement on a daily basis, and power washed the barn daily. Smoke tests confirmed that air from the main barn circulated through the administrative building. Although only one caregiver had close contact with the quarantined elephant, employees who worked for > 4 hours in a year in the quarantine area were more likely to convert their skin tests. However, at least five of the employees with skin test conversion had no exposure to the quarantine area.

Employees who converted their skin tests admitted to less rigorous use of N95 mask, in part because trunk washings had been consistently culture-negative from elephants in the main barn, yielding a general laxity regarding IC precautions.

This information suggests that episodic secretion or transmission of TB from elephants believed to be culture-negative by trunk washings is likely. The practice of annual trunk washings for screening should be re-evaluated, and IC practices should be more strictly enforced for employees with contact with high risk elephants. ■

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patients who had adequate clinical data available for study died. The cell line tested, which appeared to have the greatest sensitivity for SFTS virus infection, was DH82 (a canine macrophage cell line). Sequence analysis revealed the novel virus was a member of the genus phlebovirus in the Bunyavirus family.

■ COMMENTARY

This is an interesting report from the world's most populous country and is a testament to the first rate epidemiologic and laboratory research that now exists in China. While this newly described SFTS illness, and the novel bunyavirus that is its etiologic agent, appears to define a distinct syndrome, it is not sufficiently distinctive to exclude other infections in the differential diagnosis. Other infections would potentially include rickettsial infections, anaplasmosis, leptospirosis, and several viral infections such as dengue and various hemorrhagic fever with renal syndromes. The vector for SFTS is not yet known, but most phleboviruses are associated with sandflies. Other phleboviruses are known to be transmitted by ticks and Rift Valley fever is transmitted by *Aedes* species mosquitoes. SFTS RNA has been detected in a small number of *Ixodidae* species ticks and this has been proposed as a candidate vector. ■

CME Questions

1. Which of the following is *correct* with regard to NDM-1 producing organisms?

a. NDM-1 stands for Novel Deletion Mutant type 1.

b. They have only been identified in long-term residents of south Asia.

c. They have been detected in tap water in India.

d. They are highly susceptible to aminoglycoside antibiotics.

2. Which of the following correctly characterizes the use of artesunate for the treatment of severe malaria?

a. Patients treated with IV artesunate have lower mortality rates than those treated with IV quinine.

b. Artesunate is generally better tolerated than quinine.

c. Artesunate belongs to the drug class that contains the most rapidly acting antimalarials available.

d. Artesunate appeared superior to quinine in clinical trials performed on multiple continents, and in multiple patient populations.

e. All of the above

3. Which of the following is *correct* about linezolid?

a. It has linear pharmacokinetics.

b. Renal excretion accounts for 90% of its elimination.

c. Its antibacterial activity most closely correlates with the ratio of its peak serum concentration to the MIC of the infecting pathogen (Cmax/MIC).

d. WIth standard dosing, adequate linezolid exposure has little interindividual variability and is achieved in > 95% of patients.

Answers: 1. c, 2. e, 3. a.

CME Objectives

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

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest 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]

When to start antiretroviral therapy in HIV-infected patients

Vaccination against human papillomavirus and herpes zoster: New indications

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Tiotropium for COPD — The New Standard?

In this issue: Anticholinergic drugs for COPD; pioglitazone for diabetes prevention; insulin degludec in Phase 3 trials; and FDA Actions.

Anticholinergic drugs for COPD

Should anticholinergic drugs be first-line agents for preventing exacerbations in patients with chronic obstructive pulmonary disease (COPD)? The answer may be yes, according to a new study in the *New England Journal of Medicine*. Researchers from Europe compared the anticholinergic drug tiotropium to the beta-agonist salmeterol in more than 7000 patients with moderate-to-very-severe COPD. The study was a randomized, double-blind, double-dummy, parallel-group trial in which tiotropium once a day was compared to salmeterol twice a day. The endpoint was the incidence of moderate or severe exacerbations. Over the 1-year study, tiotropium increased the time to first exacerbation compared to salmeterol (187 days vs 145 days, 17% risk reduction, hazard ratio [HR] 0.83; 95% confidence interval [CI], 0.77 to 0.90; $P < 0.001$). Tiotropium also increased the time to first severe exacerbation ($P < 0.001$), reduced the annual number of moderate or severe exacerbations (0.64 vs 0.72; $P = 0.002$), and reduced the annual number of severe exacerbations (0.09 vs 0.13; $P < 0.001$). Adverse events were similar in both groups. There were 64 deaths in the tiotropium group (1.7%) and 78 in the salmeterol group (2.1%). The authors conclude that in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations (*N Engl J Med* 2011;364:1093-1103). This is the first head-to-head study to show benefit for anticholinergics but it must be pointed out that cardiac patients were excluded from the study, and the annual exacerbation rates were lower than has been seen in other trials. The concomitant use of inhaled corticosteroids was evaluated and did not make a difference in the outcomes. The study was sponsored by Boehringer Ingelheim, the manufacturer of tiotropium (Spiriva). ■

Pioglitazone for diabetes prevention

Pioglitazone reduces the risk of development of diabetes among prediabetic patients, according to a new study. Pioglitazone was compared to placebo in a total of 600 patients with impaired glucose tolerance. After a median follow-up of 2.4 years, the annualized incident rates for type 2 diabetes were 2.1% in the pioglitazone group and 7.6% in the placebo group (HR 0.28, 95% CI, 0.16 to 0.49; $P < 0.001$). Conversion to normal glucose tolerance occurred in nearly half of the pioglitazone group and in 20% of the placebo group ($P < 0.001$) and treatment with pioglitazone was associated with significantly lower fasting glucose levels, 2-hour glucose levels, and hemoglobin A1c levels. Pioglitazone also was associated with a decrease in diastolic blood pressure (2.0 mmHg vs 0.0 placebo), reduced rates of carotid intimal-medial thickening ($P = 0.047$), and an increased level of HDL cholesterol (increase of 7.35 mg/dL vs 4.5 mg/dL; $P =$

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0.008). Pioglitazone caused greater weight gain than placebo (3.9 kg vs 0.77 kg; $P < 0.001$), as well as edema (12.9% vs 6.4%; $P = 0.007$). The authors conclude that pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes but was associated with significant weight gain and edema (*N Engl J Med* 2011;364:1104-1115). Thiazolidinediones have been falling out of favor in recent years for the treatment of type 2 diabetes due to association with edema and heart failure. This new industry-sponsored study suggests that pioglitazone (Actos) is more effective than metformin or lifestyle changes in preventing conversion of prediabetes to diabetes. What is unclear is the effect of these various interventions on long-term diabetic complications. ■

Insulin degludec in Phase 3 trials

Insulin degludec is an ultralong-acting insulin that is currently in Phase 3 trials. It forms soluble multihexamer assemblies after subcutaneous injection, resulting in a very long half-life of up to 40 hours. A new study suggests that it can be used three times a week, achieving blood sugar control equivalent to daily insulin glargine. In a 16-week randomized, open-label, parallel group trial, 245 type 2 diabetics aged 18-75 were randomized to insulin degludec once a day or three times a week, or insulin glargine once a day, all in combination with metformin. At the end of the study, mean hemoglobin A1c levels were similar across the treatment groups at 7.3%, 7.4%, and 7.2%, respectively. The rate of hypoglycemia was low in all three groups. The authors conclude that insulin degludec provides comparable glycemic control to insulin glargine without additional adverse events and may reduce dosing frequency due to its ultra-long action profile (*Lancet* 2011;377:924-931). The study was sponsored by its manufacturer, Novo Nordisk. ■

FDA actions

The FDA has approved the first new drug for lupus (systemic lupus erythematosus) since 1955. Belimumab is a fully human monoclonal antibody the targets human soluble B-lymphocyte receptor stimulator protein. It is indicated for the treatment of adult patients with active, autoantibody-positive lupus who are receiving standard therapy. In two pivotal studies, the drug was found to reduce disease activity compared to placebo plus standard therapy. More deaths and serious infections were reported for belimumab compared to placebo, and it does not appear to be effective in people of African or African American heritage (in whom the disease is three times more common), although more studies are needed to confirm this finding. Belimumab is marketed by GlaxoSmithKline as Benlysta.

The FDA has approved a phosphodiesterase type 4 inhibitor to reduce the number of exacerbations from severe COPD associated with chronic bronchitis. Roflumilast is a once daily oral pill that reduces excess mucus and cough. It does not appear to benefit COPD that involves primarily emphysema. The approval was based on two Phase 3 studies of more than 1500 patients. An accompanying medication guide informs patients of the potential risk of mental health problems including changes in mood, thinking, or behavior, as well as unexplained weight loss. Roflumilast is marketed by Forest Pharmaceuticals as Daliresp.

The FDA has approved a new angiotensin II receptor antagonist, the eighth introduced to the American market. Azilsartan medoxomil is approved for the treatment of hypertension in 40 mg and 80 mg once daily doses. The drug is touted as being more effective in lowering blood pressure than valsartan or olmesartan based on clinical trials. Like other angiotensin II receptor blockers, the drug will carry a box warning regarding pregnancy. Azilsartan is marketed by Takeda Pharmaceuticals as Edarbi.

Zostavax, Merck's vaccine for the prevention of shingles, has been approved for use in individuals ages 50-59. It previously was approved only for those 60 and older. The approval was based on a placebo-controlled trial of more than 20,000 individuals 50-59 years of age. The vaccine reduced the risk of developing shingles in this group by approximately 70%.

The FDA has approved ipilimumab for the treatment of late stage (metastatic) melanoma. The drug is a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen (CTLA-4). The approval was based on a single study of 676 patients with melanoma who had stopped responding to other therapies. When compared to an experimental tumor vaccine, those receiving ipilimumab lived an average of 3.5 months longer (10 months vs 6.5 months). Autoimmune reactions were common including fatigue, diarrhea, rash, endocrine deficiencies, and colitis. Severe to fatal autoimmune reactions were seen in 13% of treated patients. Ipilimumab is manufactured by Bristol-Myers Squibb and marketed as Yervoy. ■