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Infectious Disease [ALERT]

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

ABSTRACT & COMMENTARY

Continuous Infusion of Beta-lactams for Sepsis Improves Outcomes

By Richard R. Watkins, MD, MS, FACP

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

SOURCE: Dulhunty JM et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis* 2013;56:236-244.

Despite notable advances in critical care medicine, mortality from severe sepsis remains unacceptably high. With current therapeutic strategies, nothing has proven more crucial than early and effective antibiotics. Among the most commonly utilized antibiotics in intensive care units (ICUs) are beta-lactams, such as piperacillin-tazobactam and meropenem. These agents are usually administered by intermittent bolus dosing. However, pharmocodynamic data have shown that continuous infusion administration results in greater blood and fluid exposure with more time above the minimum inhibitory concentration (MIC) compared to intermittent dosing. Dulhunty and colleagues sought to determine the clinical and pharmacokinetic differences between continuous and intermittent bolus dosing of beta-lactam antibiotics in patients with severe sepsis.

The study was a prospective, double-blind, randomized controlled trial conducted at several hospitals in Australia and Hong Kong between

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April 2010 and November 2011. Patient inclusion criteria included > 18 years of age, severe sepsis in the preceding 24 hours, treatment within the previous 24 hours with ticarcillin-clavulanate, piperacillin-tazobactam or meropenem, and expected or actual ICU stay greater than 24 hours. Patients were excluded if they were on continuous renal replacement therapy, lacked a central access catheter with at least 3 lumens, or received the study drug for > 24 hours. They were randomized to receive active infusion and placebo boluses (intervention group), or placebo infusion and active boluses (control group). On days 3 and 4 blood samples were taken to ascertain plasma trough levels. The primary endpoint was the time that antibiotic concentraton was above the MIC. Secondary endpoints were clinical response at days 7 to 14 after study drug cessation, time to clinical resolution, status at ICU and hospital discharge, and number of days alive and free of ICU admission in the first 28 days post-randomization. Sixty patients were enrolled, 30 in the continuous infusion group and 30 in the intermittent bolus group. The most common source of infection in both groups was lung, followed by blood, intra-abdominal, skin or skin structure, urinary tract, and central nervous system.

The patients who received continuous infusion compared to intermittent bolus administration achieved higher times above the MIC (82% vs. 29%, P = .001) and higher clinical cure (76.7% vs. 50%, P = .032). Moreover, there was less time to clinical resolution (11 days vs. 16.5 days, P = .14), lower ICU length of stay (7.5 days vs. 9 days, P = .50), better hospital survival (90% vs 80%, P = .47), and higher ICU survival (93.3% vs. 86.7%, P = .67) in the continuous infusion group, but these did not reach statistical significance. Plasma antibiotic concentration of meropenem was greater than the MIC in 100% of patients who received continuous infusion compared to 22% in the intermittent bolus group. Piperacillin-tazobactam and ticarcillin-clavulanate continuous infusions resulted in concentrations above the MIC 75% and 50% of the time, respectively. The corresponding intermittent bolus administration achieved concentrations above the MIC 36% and 0% of the time with piperacillin-tazobactam and ticarcillin-clavulanate.

■ COMMENTARY

Patients with severe sepsis are a challenge to treat, especially those with multi-drug resistant pathogens. This unfortunate situation is unlikely to improve in the near future given the lack of promising new antibiotics. One potential solution is to find innovative ways to use currently available agents. For example, maximizing the pharmacokinetic and pharmacodynamics properties of beta-lactams has been investigated in several animal studies and in a limited number of human ones. The present study exemplifies an unconventional approach that resulted in improved clinical outcomes. It is the largest prospective ICU trial of continuous vs. intermittent bolus administration of beta-lactams, as well as the first to be conducted in a blinded fashion with allocation concealment. Of the three beta-lactams studied, meropenem seems to be the best candidate for continuous infusion as it achieved the highest success for concentration above the MIC (100%). There were a few limitations, one being different patient characteristics (younger age, more males, more comorbidities, higher proportion of pre-ICU infections) in the intervention group compared to the control group. Another was the potential confounding effect of concurrently administered antibiotics (e.g. vancomycin, antifungals). Moreover, the study was likely underpowered which led to many endpoints not reaching statistical significance. No adverse events occurred to any of the patients as a result of the study drug or intervention. While this may have resulted from optimized dosing and judicious monitoring of renal

function, equally plausible is that it was due to the relatively small number of patients in the two groups.

This study represents an important advancement in treating patients with severe sepsis. Indeed, the continuous administration of beta-lactams seems to be most helpful for infections caused by high MIC organisms, which are often found in ICUs. However, it may be advisable to wait for the results from a larger phase II randomized controlled multicenter trial with additional data on clinical outcomes, length of stay, and mortality before implementing a change to continuous infusion therapy. Hopefully these data will elucidate the types of infections (e.g. pneumonia, bacteremia) for which continuous infusion therapy will be most beneficial ■

ABSTRACT & COMMENTARY

Antibiotics for Severe Acute Malnutrition

By Hal B. Jenson, MD, FAAP

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

SYNOPSIS: In a large study of children with uncomplicated severe acute malnutrition in Malawi, the addition of amoxicillin or cefdinir to therapeutic food regimens was associated with significant improvement in recovery and mortality rates.

SOURCE: Trehan I, et al: Antibiotics as part of the management of severe acute malnutrition. *N Engl J Med* 2013;368:425-435.

A randomized, double-blind, placebo-controlled clinical trial was conducted from December 2009 through January 2011 at 18 feeding sites in Malawi. This region of oral sub-Saharan Africa has a subsistence farming population with an estimated 11% of adults infected with the human immunodeficiency virus (HIV).

Children 6 to 59 months of age with severe acute malnutrition were randomized to receive amoxicillin (80-90 mg/kg/day in two divided doses), cefdinir (14 mg/kg/day in two divided doses), or placebo (twice daily) for seven days. Providers reported excellent adherence. All children received standardized counseling and ready-to-use therapeutic food.

A total of 2,767 children with severe acute malnutrition were enrolled. The overall study recovery rate was 88.3%. Children with treatment failure were significantly younger and less likely to have their father alive and still in the home. Symptoms of acute infections and poor appetite at enrollment and at the first follow-up visit were also associated with increased risk of treatment failure.

The recovery rates were 88.7% for treatment with amoxicillin, 90.9% for cefdinir, and 85.1% for placebo. The relative risk of treatment failure with placebo versus amoxicillin was 1.32 (95% CI, 1.04 to 1.68), and with placebo versus cefdinir was 1.64 (95% CI, 1.27 to 2.11). The mortality rates were 4.8% (amoxicillin), 4.1% (cefdinir), and 7.4% (placebo). The relative risk of death with placebo versus amoxicillin was 1.55 (95% CI, 1.07 to 2.24), and with placebo versus cefdinir was 1.80 (95% CI, 1.22 to 2.64). The rate of weight gain was increased among children receiving antibiotics compared to children receiving placebo. No interaction was observed between interventions and the type of severe acute malnutrition. The rates of common adverse effects, such as diarrhea, were lower among children receiving antibiotics than among children receiving placebo. No cases of severe allergy or anaphylaxis were identified.

The cost of amoxicillin was $2.67 per child, and the cost of cefdinir was $7.85 per child. The cost of ready-to-use therapeutic food was approximately $50 per child.

■ COMMENTARY

It is estimated that more than 20 million children worldwide have severe wasting and

that more than 1 million children annually still die from malnutrition. Even with international consensus guidelines and availability of ready-to-use therapeutic food regimens for children with severe acute malnutrition, approximately 10-15% of children do not recover. Many studies have shown a high prevalence of clinically significant infections among children with severe acute malnutrition, leading to treatment guidelines recommending the use of antibiotics routinely for these children. This is the first prospective study of the routine administration of oral antibiotics as part of the management of severe acute malnutrition to improve nutritional and mortality outcomes.

In this prospective study, amoxicillin was associated with a 24.4% reduction in the treatment-failure rate, and cefdinir was associated with a 38.9% reduction. Secondary outcomes were also consistent with these findings.

The mechanism of the benefits of antibiotics for malnutrition remains speculative. The lower rates of diarrhea among children receiving antibiotics may suggest that this is via reduction of dehydrating diarrhea. Alternatively, antibiotics may decreasing the rate of concomitant infections, including even subclinical infections, such as bacterial pneumonia.

There is always concern about the adverse impact of widespread use of broad-spectrum antibiotics among a large population of children. Changes in the balance and resistance patterns of intestinal flora do occur with only a few days of antibiotic treatment. The resulting changes in the individual child's microbiome, and also in the community, in this setting have not been clarified, let alone defining the clinical significance of the changes. These concerns should always be weighed against the proven benefits of antibiotics. Based on the benefits observed in this study of nutritional recovery and reduced risk of death, the authors advocate for the serious consideration of routine use of antibiotics for specific populations of high-risk children with severe acute malnutrition. ■

Malaria Continues to Take Staggering Toll as Relief Efforts Plateau

By Stan Deresinski, MD, FACP, FIDSA

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

SOURCE: World Malaria Report 2012. Summary and Key Points. World Health Organization. http://ow.ly/hlj0n

It is estimated that there were approximately 219 million cases of malaria in the world in 2010 and 680,000 or these cases were fatal. The majority of deaths occur in children, most in Africa — with one dying every minute. Fourteen countries are estimated to account for 80% of deaths, with the Democratic Republic of the Congo and Nigeria accounting for 40% of total global malaria deaths. These startling statistics exist despite elimination efforts of this preventable disease by WHO and other organizations which have been associated with a reduction in malaria mortality rates which have diminished since 2000 by >25% worldwide and by 33% in the WHO African Region. Those efforts appear, however, to be leveling off, despite great continued need. Worldwide disbursements for malaria control increased from less than US$ 100 million in 2011 to US$ 1.66 billion in 2011 and US$ 1.84 billion in 2012. This amount appears to be plateauing and falls well short of the US$ 5.1 billion judged to be necessary to achieve universal implementation of malaria interventions.

Among the supported preventive measures is the use of insecticide-treated nets (ITN) for use while sleeping. It is estimated that

the proportion of households in sub-Saharan Africa owning at least one ITN increased from 3% in 2000 to 53% in 2011, but with no change in the following year. Survey data indicates that 9 of 10 ITNs are actually used. The proportion of the population sleeping under an ITN increased from 2% in 2000 to 33% in both 2011 and 2012. Another important control measure is mosquito control. In the African Region, the percentage of households protected by indoor residual spraying (IRS) rose from <5% in 2005 to 11% (77 million individuals) in 2010 with no further increase in 2011. Globally, 153 million people were protected by IRS. However, resistance of mosquitoes to at least one pesticide has been detected in 64 countries. As of 2011, 77 countries had a policy for monitoring of insecticide resistance.

Many studies have found a lack of accuracy of microscopic diagnosis in many endemic regions as well as the frequent empiric administration of antimalarials in febrile individuals without diagnostic testing. In 2005, 68% of suspected cases globally received a parasitological test, a proportion that increased to 77% in 2011, an increase of only 1% from 2010. In the public sector in the African region, this value increased from 20% in 2005 to 47% in 2011, with most of the increase due to the use of rapid diagnostic tests.

Artemesinin combination therapy (ACT) is the recommended therapy for infections due to Plasmodium falciparum, as well as for Plasmodium vivax infections acquired in regions where this parasite is resistant to chloroquine. In 2011 the total number of tests performed was less than half the number of ACT distributed, indicating that they are given to many patients in the absence of confirmatory testing. It is estimated, however, that, despite their inappropriate use without a laboratory diagnosis, only 52% of patients managed in the public sector in the African Region received ACT in 2011. Because of a concern about the development of resistance, WHO has officially recommended since 2007 that oral artemesinin monotherapies be progressively removed from the market and replaced by ACTs. The number of countries that continue to allow single agent artemesinin oral products decreased from 55 in 2008 to 16 in 2012, with 8 of the 16 being in the African Region. Unfortunately, resistance to artemisinins has been detected in 4 countries of the South-East Asia Region — Cambodia, Thailand, Myanmar, and Viet Nam. ACT is still often effective as long as the parasite is susceptible to the partner drug. However, resistance to both components of multiple ACTs is present in the Palin province in western Cambodia near the border with Thailand.

Another important measure is the following: "Intermittent preventive treatment (IPT) is recommended for population groups in areas of high transmission who are particularly vulnerable to Plasmodium infection and its consequences, particularly pregnant women and infants." With IPT, a curative dose of an effective antimalarial drug is administered to all pregnant women at each routine antenatal care visit beginning in the second trimester whether or not they are Plasmodium-infected. Thirty-six of 45 countries of sub-Saharan Africa, where 32 million pregnant women and a large proportion of the estimated 28 million infants born each year could benefit, had adopted this policy by 2011. Primarily due to low coverage in Nigeria and the Republic of Congo, only an average of 22% of pregnant women had received 2 doses of IPT (the recommendation at the time) in the 16 African countries for which household survey data was available.

Seasonal malaria chemoprevention, recently recommended by WHO, could benefit 25 million children in the region.

In assessing these statistics, it must be realized that only 58 of 99 countries with ongoing malaria transmission reported adequate data to WHO in 2011. The countries that did report accounted for only 15% of the estimated worldwide burden of malaria.

An important concern is the leveling off of international financial support and, consequently, of control and treatment activities. An example is the procurement of ITNs, 66 million of which were obtained in 2012 represents a decrease from the 145 million in 2010 and 92 million in 2010. Given the estimated mean useful life of ITNs of 2-3 years, ITN coverage appears to be headed for a decline in the absence of a massive increase in procurement in 2013. While there has been progress, there is a long distance to go and it is no time to slow down in efforts to control malaria. ■

Burden of Human Metapneumovirus Infection in Young Children

By Joseph F John, Jr., MD, FACP, FIDSA, FSHEA

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Dr. John reports no financial relationships with this field of study.

SYNOPSIS: Over a period of six years, three sites studied the prevalence of Human metapneumovirus (HMPV) in children less than 5 years old. Over the course of the study 12,363 symptomatic children were enrolled. Of 3,490 hospitalized children, 200 had evidence of HMPV infection, with the majority of these children being previously healthy.

SOURCE: Edwards KM, et al. Burden of human metapneumovirus infection in young children. *New Eng J Med* 2013 368:633-43.

Human metapneumovirus (HMPV) was only discovered about a decade ago and until this study the extent of the disease — particularly in the young — was not known. Over a six year period, three sites (Cincinnati, Nashville, Rochester, NY) studied the prevalence in children less than 5 years old. At the three sites symptomatic and non-symptomatic control children had nasal and throat swabs analyzed by RT-PCR that amplified a piece of the HMPV. Over the course of the study 12,363 symptomatic children were enrolled. Of 3490 hospitalized children, 200 had evidence of HMPV infection, with the majority of these children being previously healthy. That translates to about 20,000 children a year who are hospitalized with this virus.

HMPV as compared to non-HMPV disease acted like many of the viruses that produce severe respiratory infection in children and in adults. However, in this study HMPV was more likely to produce a disease that required ICU stay, had a diagnosis of pneumonia or asthma, and needed oxygen supplementation. Other outcomes like hospital length of stay were the same for HMPV and other respiratory viruses. Both boys and girls had the same rate of hospitalization. The actual rate of hospitalization was 1 per 1000 children for HMPV, lower than that for respiratory syncytial virus (RSV) but the same as influenza. The rate of HMPV infection was 55 per 1000 clinic visits. There were no deaths in the study cohort, as well as in those children with influenza or RSV.

■ COMMENTARY

Since 2000 we have seen the emergence of a number of newly recognized pathogens. New coronaviruses after SARS have emerged. New influenza viruses have caused human infection and death. Hantavirus continues to evolve. Since the HMPV discovery a decade ago, we have seen the quilt of HMPV being pieced together: A respiratory pathogen that caused a spectrum of respiratory disease in young children including pneumonia that requires hospitalization. One of the authors of this paper, Carolyn Breeze Hall — in seminal papers published on RSV over 30 years ago — uncovered an RSV story that sounds much like the one of HMPV today. It was first recognized as a new respiratory pathogen capable of causing serious illness and even requiring ICU admission. A sad footnote on this paper was the fact that Dr. Hall is recently deceased, a great loss to our infectious diseases community. Her work with others at the University of Rochester, has allowed us to compare a sizeable RSV epidemiology database to that for emerging HMPV. Specifically in the current paper, HMPV probably causes more frank pneumonia than bronchiolitis. The current study also warns us that HMPV's epidemiology, while resembling RSV of the early days of clinical investigation, looms as an adult pathogen that I predict we will recognize with more study.

Where do we go from here with HMPV? We need more epidemiologic studies from across

the world. We need to know the molecular variation the virus manifests. We need more data of how often other respiratory pathogens act with HMPV to cause disease in children and adults. Finally we need serious, supported funding to find antiviral medications that can limit or cure these infections. Such antiviral agents would not be orphan drugs, but will not garner huge profits for pharmaceutical companies. Still, like the early antibiotics, they will bring true and needed relief from pain and suffering for children and their families due to the severe illness caused by these respiratory viruses. ■

ABSTRACT & COMMENTARY

Doxycycline May Protect Against *Clostridium Difficile* Infection

By Betty Tran, MD, MS

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Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: This retrospective study of hospitalized patients receiving ceftriaxone found that additional treatment with doxycycline compared to other antibiotics was associated with a lower risk of *Clostridium difficile* infection.

SOURCE: Doernberg SB, et al. Does doxycycline protect against development of *Clostridium difficile* infection? *Clin Infect Dis* 2012;55:615-620.

Doernberg and colleagues sought to determine whether receipt of doxycycline was associated with protection from development of *Clostridium difficile* infection (CDI) in hospitalized patients being treated with ceftriaxone, a known high-risk antibiotic for CDI. They retrospectively identified 2734 hospitalizations involving 2305 adult patients at San Francisco General Hospital who received ceftriaxone during their hospitalization. Of these, 1066 (39%) patients also received doxycycline; these patients tended to be older, were more likely to have pneumonia on admission, were less likely to be surgical patients, had higher Charlson Comorbidity Index scores, and received shorter courses of additional antibiotics. The duration of treatment with ceftriaxone, the number of hospital days before development of CDI, and total length of hospital stay, however, were similar between the group that received doxycycline and the group that did not. The primary outcome of interest was development of CDI within 30 days of receiving ceftriaxone.

During the 2005-2010 study period, the overall incidence of CDI was 5.60 per 10,000 patient-days, a rate that is lower than reported in other studies. The incidence of CDI in patients who received doxycycline was 1.67 per 10,000 patient-days compared to 8.11 per 10,000 patient-days in patients who did not receive doxycycline. For each day that a patient received doxycycline, there was a 27% lower risk of CDI compared to a patient who was not receiving doxycycline (95% confidence interval [CI], 0.56-0.96; P = 0.03). When the authors directly compared common therapies for community-acquired pneumonia (CAP), a 5-day course of ceftriaxone plus doxycycline was associated with an 85% lower rate of CDI (95% CI, 0.03-0.77) compared to a 5-day course of ceftriaxone plus a macrolide, and an 87% lower rate of CDI (95% CI, 0.03-0.62) compared to a 5-day course of ceftriaxone plus a fluoroquinolone. Because of the uncertainty of capturing all data on antibiotic exposure and CDI cases after discharge, a sensitivity analysis was performed using only hospital data up until discharge with similar results, according to the authors.

■ COMMENTARY

Given the increasing morbidity and mortality of CDI, especially among hospitalized patients, and the high prevalence with which inpatients receive at least one dose of

antibiotics, this article poses a fascinating question and springboard for further clinical and laboratory investigations.

San Francisco General Hospital, the study site, presented a unique opportunity for investigators as doxycycline was the recommended first-line therapy for CAP in non-ICU inpatients. Current American Thoracic Society and Infectious Diseases Society of America guidelines, however, recommend doxycycline as an alternative to either a macrolide or a fluoroquinolone as part of a treatment regimen for CAP based only on level III evidence. Findings from this study suggest that further research is needed to revisit the use of doxycycline as a preferred antibiotic in CAP treatment. Doxycycline may reduce the burden of CDI in already vulnerable patient populations, but widespread recommendations for its use may be tempered by differences in clinical outcomes of CAP depending on the setting (outpatient vs inpatient vs ICU).

The mechanisms to explain the association between receiving doxycycline and having a lower risk of CDI also need to be explored. The authors posit a few possibilities, including doxycycline's in vitro activity against C. difficile, its attenuation of *C. difficile* toxin production, and its minimal effects on bowel flora due to maximal absorption in the upper gastrointestinal tract. These hypotheses sound plausible, although further data will be informative, especially to ensure that doxycycline use does not result in inadvertent but unwanted outcomes such as the selection of rarer but more virulent strains of *C. difficile*.

Although further data are needed to support the findings reported, this study is encouraging and also highlights an approach to reducing the rate of CDI by using "lower-risk" antibiotics, a method that may prove to be a valuable weapon in the antibiotic stewardship arsenal. ■

ABSTRACT & COMMENTARY

Direct-acting antivirals for hepatitis C show promise

By Dean L. Winslow, MD, FACP, FIDSA
Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine, is Associate Editor for Infectious Disease Alert.

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Gane et al found that sofosbuvir (nucleotide inhibitor of the NS5B HCV RNA-dependent RNA polymerase) plus ribavirin (RBV) showed efficacy in previously untreated patients with HCV genotype 1, 2, or 3 infection. Poordad et al found that ABT-450 (a HCV NS3 protease inhibitor) plus ABT-333 (a non-nucleoside NS5B polymerase inhibitor) showed efficacy in patients with HCV genotype 1 infection.

SOURCES: Gane EJ, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *New Eng Jrl Med* 2013;368:34-44.
Poordad F, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. *New Eng Jrl Med* 2013;368:45-53.

Gane et al conducted a randomized open label trial of 40 patients with HCV genotype 2 or 3 infection which evaluated sofosbuvir 400 mg once daily plus ribavirin (RBV) for 12 weeks. Ten were treated without pegylated interferon (IFN) and 30 received sofusbuvir plus RBV for 12 weeks along with IFN for 4, 8, or 12 weeks. All of these patients had sustained virologic response (SVR) at 24 weeks. In addition, 35 patients with HCV genotype 1 infection were treated sofosbuvir plus RBV as well. There were 21/25 previously untreated patients (84%) and 1/10 (10%) of genotype 1 patients with no response to previous therapy with IFN plus RBV had SVR at 24 weeks. Adverse effects were mild in patients not treated with IFN and appeared to be largely attributable to RBV.

Poordad et al conducted a 12-week phase 2a open label study of HCV genotype 1 infected patients without cirrhosis. All patients received ABT-333 400 mg BID plus RBV 1000-1200 mg daily. Groups 1 and 2 included previously untreated patients with group 1 receiving ABT-450 250 mg plus ritonavir 100 mg. Group 2 received ABT-450 150 mg with ritonavir. Group 3 included patients who had demonstrated either a null or partial response to previous therapy with IFN+RBV and received ABT-450 150 mg plus ritonavir. Overall, 17/19 (89%) group 1 patients had an extended virologic response (undetectable HCV RNA at 12 weeks); 11/14 (79%) group 2 patients and 8/17 (47%) group 3 patients had SVR 12 weeks after completion of therapy. Adverse events included abnormal LFT's, fatigue, nausea, headache, dizziness, insomnia, pruritus, rash, and vomiting. They were generally mild-moderate and did not appear to be dose-related.

■ COMMENTARY

While the use of newer pegylated IFN's plus weight-based RBV has modestly increased the efficacy of treatment for HCV infection, response rates remain low for HCV genotype 1 infection and patients co-infected with HIV. Also, treatment generally needs to be given for 48 weeks and side effects of IFN-based regimens are considerable with many patients unable to complete their planned courses of treatment.

In the past few years several pharmaceutical companies have made steady progress discovering and developing direct-acting antivirals (DAA's) for HCV infection. HCV possesses a serine protease encoded by the NS3-4A region of the HCV genome, and a HCV RNA-dependent RNA polymerase encoded by NS5B. HCV protease has proven to be a somewhat difficult target for which to design inhibitors (compared to the HIV aspartyl protease) but persistence has paid off and now a number of potent, orally bioavailable small molecule HCV PI's are entering late stage clinical trials. Similarly both nucleoside/nucleotide analogue competitive inhibitors and non-nucleoside allosteric inhibitors of the HCV polymerase have reached clinical development. Lastly, inhibitors of the NS5A replication complex have been identified and are in clinical trial (but are not discussed in this review).

The small open-label trials presented here demonstrate that these new DAA's are potent and clinically effective. At least in treatment-naïve patients with HCV, treatment courses consisting of oral small molecule drugs administered for as little as 12 weeks without IFN appear to be close on the horizon. It should be noted that the design of the two trials reported here also used RBV, which likely caused many of the side effects seen. It is conceivable that some combinations of these newer DAA's might someday make cure of HCV possible without IFN or RBV. Stay tuned! ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

How do infection preventionists know what they know?

Saint S, et al, Perceived strength of evidence supporting best practices to prevent health care-associated infection: results from a national survey of infection prevention personnel. *Am J Infect Control* 2013;(41):100-106.

In my experience, the success of a good Infection Control program rests on the shoulders of the IC personnel in your hospital. Infection Control staff are the key to communicating, educating, and enforcing good IC practices in the hospital. But, first, the IC staff must appreciate the validity and worth of any particular measure or recommendation. With so much to do in any given day, including surveillance, ward rounds, education, and policy development, how do IC staff prioritize their activities? How these people perceive the merits of any particular recommendation, and where they place their efforts, may significantly impact health care infections in any one hospital.

These authors conducted a

written survey of IC staff at 478 non-Federal and VA hospitals in 2009. IC personnel at each hospital were asked to rate their perception of the evidence in support of current IC practices on a scale of 1 to 5 (1 being no evidence and 5 being very strong evidence). The rate of response was 68%. The average infection control experience was 9.6 years.

Ninety percent or more of respondents believed the evidence in favor of the following practices was at least strong to very strong: alcohol based hand gel (97%), chlorhexidine gluconate for skin antisepsis, sterile barriers for catheter insertion, avoiding femeral site for catheter insertion, semi-recumbent positioning for the ventilated patient, and aseptic urinary catheter insertion technique. When asked about particular prevention practices for catheter insertion — often included in a "bundle" — 90% believed the supporting evidence for each of the practices/techniques was strong to very strong. In contrast, the perception of strong supporting evidence for ventilator practices was more varied, ranging from the evidence for semi-recumbent posture (97%), to sedation vacation (88%), antiseptic mouth rinse (68%), subglottic secretion drainage (59%), and silver coated endotracheal tubes (16%).

In reality, the recommendation for semi-recumbant posture is considered a "grade B" recommendation whereas the evidence in support of antiseptic mouth rinse is quite good – a "grade A" recommendation. Those practices which may be well supported by clinical data but not presented in the formal guidelines were perceived by IC staff as weakly supported. And, while recent data indicates that silver-coated endotracheal tubes may result in significantly reductions in VAP, this data was published following publication of the CDC guidelines. In other words, most of the IC preventionists responding to this survey appear to be dependent on how the information is "framed" in a standard guideline or bundle, and not the supporting literature or specific clinical data.

My guess is that the Joint Commission and other regulatory bodies may also emphasize certain practices over others, which can also substantially influence what hospitals and IC personnel are doing. For instance the Joint Commission just queried our staff regarding aseptic insertion technique for Foley catheter insertion – although there is little evidence associating this practice with a reduction in catheter-associated UTIs. In contrast, studies demonstrating less Foley use, with automated reminders or stop dates for Foley use, are significantly associated with lower CAUTI rates.

Other regulatory requirements based on meager supporting evidence may actually detract from other more meaningful infection control efforts. For instance, the California Senate has mandated that hospitals screen high risk admissions for MRSA colonization, and provide counseling to positives — although there are zero public health recommendations or guidelines indicating what to do with this information. But IC personnel are forced to busy themselves educating staff about the importance of this practice, and required by law to focus on 100% successful surveillance as a "quality goal."
Infection control personnel with certification in infection control (CIC, provided by the Board of Infection Control and Epidemiology) were generally twice as likely to identify good infection control practices as their colleagues without certification. This is strong support for IC personnel continuing education and training, participation in local APIC meetings, and certification in IC within 2 yrs of practice. It might be a good idea to for educational programs to promote an examination of the literature and an understanding of the clinical evidence for why we do things the way we do — not just adherence to a guideline. ■

Colistin dose and efficacy

Vicari G, et al. Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia. *Clin Infect Dis* 2013;56(3):398-404.

Increasingly, we are faced with gram negative rods with broad resistance to antibacterials (MDRGNR) causing serious infection. These authors retrospectively examined the use of parenterally administered colistin in the treatment of MDRGNR bacteremia. Success of treatment at day 7, defined as clearance of bacteremia and survival, was compared with colistin dose. In addition, survival at

day 28 and the development of acute kidney injury was examined.

A total of 76 patients received colistin; 52 (68%) of these had clearance of bacteremia by day 7. Colistin dosing was significantly associated with treatment success – patients in the microbiologic success group received a mean daily colistin dose of 2.9 mg/kg (range, 1.7 to 3.68 mg/kg) compared with 1.5 mg/kg for patients in the treatment failure group (range, 1.10-2.0 mg/kg), p = .011. However, one-third of patients (36%) developed acute kidney injury during treatment, which was clearly associated with higher colistin dosage (p < .001). No statistically significant difference was observed in mortality between the two groups at day 28. Colistin sensitivity was performed on 58 patient isolates, all but 2 of which had MIC < 2 mg/dL (two isolates with reduced sensitivity were from patients in the treatment success group).

Catheter related infections were responsible for nearly half of the bacteremias in each group, and the catheter was removed in 33 of 34 cases (one patient in the treatment failure group did not have the catheter removed before death). The number of days from the first positive blood culture to initiation of colistin was similar for both groups (approx. 2.8 days). Concomitant antibiotic use was common in both groups (overall, 71% in the treatment success group vs 75% in the treatment failure group). Concurrent use of carbapenems and aminogylcosides was similar, although tigecycline was used more often in the treatment failure group compared with the treatment success group (54% vs 31%). Other patient characteristics, such as gender, age, and comorbidity index were similar. Patients with microbiologic failure had a higher PITT bacteremia score and a higher frequency of pseudomonas infection compared with those with microbiological success (54% vs 37%). None of these differences were significantly different between groups although, in univariate analysis, PITT bacteremia score and the use of tigecycline were independently associated with treatment failure.

Nationwide shortage of isoniazid

CDC. Notes from the field: National shortage of isoniazid 300 mg tablets. *MMWR* 2012; 61(50):1029. (2) Health Alert: Nationwide shortage of isoniazid. County of Santa Clara PHD, January 28, 2013.

Beginning in November 2012, states began reporting difficulties in obtaining adequate supplies of isoniazid 300 mg tablets for the prevention and treatment of tuberculosis (TB). This shortage has now spilled over into most states, and we've recently had an upsurge in phone calls in our office from patients unable to refill their prescriptions. There are 3 suppliers of INH in the United States: Teva, Sandoz, and VersaPharm. According to the FDA.gov/Drugs/DrugSafety/DrugShortage webpage, the shortage has occurred as the result of increased demand. According to the CDC report above (1), Teva is reporting a shortage because of a delay in receiving its shipment and Sandoz is reporting a shortage of the active ingredient from its supplier. In December, all 3 suppliers reported they should be able to fill orders by December or late January. However, as of the update 02/05/13 on the FDA webpage, drug for Teva remains on back order thru March 2013. The webpage states that additional stock from emergency reserves should, however, be available to meet ongoing demand.

Because of the shortage, the CDC is recommending prioritizing the following for patients with active TB:

- Identify a local pharmacy(ies) with an adequate supply of drug for your patients;
- Use INH 100 mg tablets instead of 300 mg tablets
- Use INH liquid formulation instead of tablets

For patients with latent TB infection, recommendations include (2):

- Prioritize INH for those at highest risk for reactivation, such as young children, contacts of known TB cases, documented conversion, HIV+, or immune compromised;
- Consider the use of chemoprophylaxis regimens that use lower amounts of INH, such as weekly INH/rifapentine for 3 months, or twice weekly INH by DOT for 6 months;
- Consider limiting the use of INH to 6 months, instead of 9 months;
- Consider limited use of alternative regimens such as rifampin for 4 months. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is correct with regard to the optimal target for dosing with beta-lactam antibiotics?

A. The ratio of the peak antibiotic concentration to the minimal inhibitory concentration (MIC) of the etiologic organism.
B. The ratio of the peak antibiotic concentration to the minimal bactericidal concentration (MBC) of the etiologic organism.
C. The ratio of the area under the curve (AUC) to the MIC of the etiologic organism.
D. None of the above.

2. Which of the following is correct?

A. The estimated number of deaths from malaria worldwide in 2010 is approximately 680,000.
B. Most malaria deaths occur in the elderly.
C. Fortunately, resistance of mosquitoes to pesticides has not yet been observed.
D. Antimalarial treatment is contraindicated in pregnancy.

3. Based on the benefits of nutritional recovery and reduced risk of death, a study by Trehan I, et al recommended serious consideration of routine use of antibiotics for specific populations of high-risk children with severe acute malnutrition.

A. True
B. False

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]

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Improved Immunogenicity With High-Dose Seasonal Influenza Vaccine in the HIV-Infected

Screening for hepatitis C virus infection in adults: A systematic review for the U.S.

Preventive Services Task Force

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.*

Aspirin Use and Age-Related Macular Degeneration

In this issue: Aspirin use and AMD risk; using NSAIDs and antihypertensive agents; and FDA actions.

Does aspirin cause AMD?

Does regular aspirin use put patients at risk for age-related macular degeneration (AMD)? That is the finding in a highly publicized study from Australia published in *JAMA Internal Medicine* (formerly *Archives of Internal Medicine*). A prospective analysis was conducted from an Australian population-based cohort that included four examinations in 15 years as well as questionnaires regarding aspirin use. Of the 2389 participants with follow-up available, 257 (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular (wet) AMD. Regular aspirin users were more likely to develop neovascular AMD: The 15-year cumulative incidence was 9.3% in aspirin users and 3.7% in non-users. After adjustment for age and multiple cardiovascular risk factors, regular users of aspirin had an odds ratio of neovascular AMD of 2.46 (95% confidence interval [CI], 1.25-4.83). The association showed a dose response effect, with daily users at higher risk. Aspirin was not associated with geographic atrophy (dry AMD). The authors conclude that "regular aspirin use is associated with increased risk of incident neovascular AMD independent of a history of cardiovascular disease and smoking." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.1583). A related editorial points out that age-related AMD is the leading cause of blindness in Western countries, and this study suggests that regular aspirin is associated with an approximate 2.5-fold greater risk in incident AMD. The study is not a randomized trial, and although there is some biological plausibility in the association between aspirin use and development of AMD, this study is "not sufficiently robust to be clinically directive." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.2530.) The take-home message for now is that for patients who are likely to benefit from aspirin (secondary prevention of cardiovascular disease), practice should not change. However, for those patients who take aspirin for indications that are less compelling, we may want to rethink the recommendation until good trials on the relationship between aspirin use and AMD can be assessed. ■

NSAIDs and antihypertensive agents

Mixing certain antihypertensive agents with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal failure, according to a new study. In a retrospective cohort study of nearly 500,000 users of antihypertensive drugs in the United Kingdom, rate ratios of acute kidney injury associated with current use of certain antihypertensive agents with NSAIDs were assessed. After a mean follow-up of 5.9 years, 2215 cases of acute kidney injury were identified. Overall, current use of a single antihypertensive (either diuretics, angiotensin-converting enzyme inhibi-

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tors [ACEIs], or angiotensin receptor blockers [ARBs]), along with an NSAID was not associated with increased rate of acute injury. However, combining a diuretic with either an ACEI or ARB along with an NSAID increased the rate of acute kidney injury significantly (rate ratio 1.31, 95% CI, 1.12-1.53). This 31% increased risk of acute kidney injury was driven by a nearly two-fold increased risk in the first 30 days of use. The authors conclude that triple therapy consisting of diuretics with an ACEI or ARB along with an NSAID was associated with an increased risk of acute kidney injury, especially at the start of treatment (*BMJ* published online January 8, 2013. doi.org/10.1136/bmj.e8713). ■

FDA actions

An advisory committee to the FDA has recommended moving hydrocodone/acetaminophen (Vicodin, Norco) from schedule III to schedule II later this year. The move would put the drug in the same category as morphine and oxycontin, and would require a handwritten, tamper-proof prescription for every prescription and refill. Vicodin — the most widely prescribed drug in this country — is at the center of the controversy regarding prescription drug abuse, which has become "epidemic" in this country, according to the CDC. The United States consumes 99% of all the hydrocodone produced worldwide, and deaths attributable to prescription opioid abuse skyrocketed in the last 2 years, outpacing deaths from illegal opioid drugs, including heroin. The move is supported by some advocacy groups, including an endorsement by the American Academy of Pain Medicine, but not by others. Some physicians are concerned that the schedule change will be a major inconvenience for legitimate pain patients and their physicians, who will be required to write a tamper-proof prescription for each refill of the drug.

The FDA has approved an over-the-counter version of topical oxybutynin for the treatment of overactive bladder in women ages 18 and older. The approval is for women only, with oxybutynin available to men by prescription only. The anticholinergic drug has been used for years by prescription for this indication. In studies of more than 5000 subjects, it was determined that consumers can understand the labeling and "properly select whether the product is right for them." Merck will market the product as a patch that is replaced every 4 days under the trade name Oxytrol for Women.

The FDA has lowered the recommended doses for zolpidem (Ambien) for women. The agency based its recommendation on findings that the popular insomnia drug might impair alertness the next morning if taken at recommended doses. The recommendation is also based on findings that zolpidem stays in the body longer than previously thought, especially in women who process the drug somewhat slower. The new recommended maximal dose for women has been lowered from 10 mg to 5 mg for the immediate-release product, and from 12.5 mg to 6.25 mg for the extended-release (Ambien CR). The FDA further recommends that zolpidem and all insomnia drugs should be used at the lowest dose needed to treat symptoms in both men and woman.

The FDA has approved alogliptin for the treatment of type 2 diabetes. The drug is the fourth dipeptidyl peptidase-4 inhibitor after sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Takeda Pharmaceuticals has been seeking approval for more than 5 years, dealing with the FDA's tighter standards for new diabetes drugs. The approval was based on 14 trials involving about 8500 patients as well as five ongoing postmarketing trials. The agency also approved two additional combinations of alogliptin with metformin and pioglitazone. Alogliptin alone will be marketed as Nesina, alogliptin/metformin will be marketed as Kazano, and alogliptin/pioglitazone will be marketed as Oseni. Both combination products carry boxed warnings (for lactic acidosis associated with metformin and heart failure associated with pioglitazone). All three are distributed by Takeda Pharmaceuticals.

Johnson & Johnson is one step closer to approval of canagliflozin, the first of a new type of diabetes drug. The Endocrionologic and Metabolic Drugs Advisory Committee voted 10 to 5 in favor of approving the drug while still expressing some concern about the cardiovascular safety of the agent. Canagliflozin is an oral inhibitor of the sodium glucose cotransporter 2 (SGLT2) that reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion with a consequent lowering of plasma glucose levels as well as weight loss. If eventually approved by the FDA, it would be the first SGLT2 inhibitor on the U.S. market. The FDA denied a similar drug 1 year ago (dapagliflozin) because of increased risk of bladder and breast cancer. The favorable vote was based on clinical trials of more than 10,000 patients worldwide which showed that the drug improves blood sugar levels and led to modest weight loss as well as reduction in blood pressure. ■