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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Hospital Wards with Higher Rates of Antibiotic Prescribing Are Associated with Increased Risk for *C. difficile* Infection

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins discloses that he has received research support from Forest Pharmaceuticals.

SYNOPSIS: A retrospective observational study found that among hospitalized patients, ward-level antibiotic prescribing was associated with a significantly increased risk for *C. difficile* infection beyond what would be expected with patient-level antibiotic use.

SOURCE: Brown K, et al. Hospital ward prescribing and the risks of *Clostridium difficile* infection. *JAMA Intern Med* 2015;175:626-633.

Clostridium difficile infection (CDI) is a prevalent and challenging disease in clinical practice. Although the incidence of community-acquired CDI is increasing, the majority of cases occur in health care facilities. The main risk factor for CDI is antibiotic exposure, with clindamycin, cephalosporins, and fluoroquinolones associated with greater risk compared with other antibiotic classes. Brown and colleagues aimed to determine the effect of ward antibiotic prescribing on ward CDI incidence and if there are factors that impact the risk of infection beyond the direct effects from the antibiotics.

The study was a retrospective cohort from a single institution that included patients aged 18 years and older during a four-year period. Individual risk factors for CDI were assessed, including age, sex, admission unit (surgical, medical, or oncology), number of previous admissions, use of a feeding tube, and inpatient medications including antibiotics, antacids, and chemotherapy. The

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authors also recorded characteristics of the ward population, including mean age, feeding tube use (tube in situ per 100 patient-days), medication usage (antibiotics, chemotherapy drugs, and antacids) in days of therapy per 100 patient-days, patient density, and hand hygiene adherence. Patients were excluded who received metronidazole, oral vancomycin, or fidaxomicin. Individual antibiotic risk was classified according to whether the patient received a high-risk antibiotic (cephalosporins, carbapenems, fluoroquinolones, or clindamycin), a medium-risk antibiotic (penicillins, sulfonamides, macrolides, or aminoglycosides), or a low-risk antibiotic (tetracyclines). Multivariate models were constructed to examine patient and ward factors that increased the risk for acquiring CDI.

A total of 255 patients developed CDI during the 46-month study period. The individual-level risk factors were found to be age, readmission, antibiotic usage, and use of a feeding tube. Admission to the oncology service led to an increased risk for CDI compared to medicine and surgery services. Receipt of a high-risk antibiotic was associated with the greatest relative risk for developing CDI (2.73, 95% confidence interval [CI], 2.05-3.63). At the ward level, each 10% increase in antibiotic use was associated with an increased incidence of CDI of 2.1 per 10,000 patient-days ($P < .001$). The other ward-level factors were not significantly associated with CDI incidence. Moreover, the multivariate model showed each 10% increase in antibiotic exposure was associated with a 1.34-fold increase in CDI infection risk (95% CI, 1.16-1.57).

■ COMMENTARY

The most interesting result of this study was that each 10% increase in antibiotic prescribing at the ward level was associated with a 34% increase in CDI incidence. This means that antibiotics increase the risk for acquiring CDI for every patient on a particular hospital ward, including those who never receive them. The authors argued that the high prevalence of antibiotic use led to an increase in the number of patients colonized with and shedding *C. difficile*, which subsequently increased environmental contamination. This hypothesis is supported by previous research that showed antibiotic exposure is the main risk factor for *C. difficile* colonization. The finding that hand hygiene compliance, which ranged from 84.6% to 92.9%, was not associated with CDI incidence is surprising. Perhaps the hand hygiene rates were too close to produce meaningful difference or maybe a higher rate (e.g. 95%) would have been significant. Future studies are needed to clarify this issue.

The main clinical implication of the study by Brown and colleagues is that aggregate ward-level antibiotic prescribing should be monitored by infection control and antibiotic stewardship personnel. This strategy might be useful for institutions with CDI rates higher than national and regional averages. However, since the study was conducted at a single institution and might have been influenced by confounding factors, additional multi-center studies are warranted to confirm the findings and to justify the additional expenses that would occur in performing ward-level antibiotic monitoring.

Another limitation to the study is the way the antibiotic risk index was determined, which left out several agents that are frequently used on the wards, such as linezolid, daptomycin, and intravenous vancomycin. These would likely have been put in the medium-risk category. Brown and colleagues' findings add further evidence of the benefits of antibiotic stewardship programs and support expanding their role in health care systems.

Finally, questions also remain about the role of asymptomatic *C. difficile* colonization on admission and how much of a risk it is for the development of CDI. At present, active surveillance testing is not recommended to control CDI. This is another topic that needs to be further elucidated through larger, multi-center studies. ■

ABSTRACT & COMMENTARY

Early, Goal-directed Therapy of Septic Shock

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: One thousand two hundred sixty patients with early septic shock were randomized to early, goal-directed therapy (EGDT) vs. usual care. Hemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome.

SOURCE: Mouncey PR, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015;372:1301-1311.

An integrated pragmatic randomized trial (incorporating cost effectiveness analysis) was conducted in 56 hospitals in the United Kingdom. One thousand two hundred sixty patients (630 per arm) were randomized to early goal-directed therapy (EGDT) vs. usual care. After randomization, the usual care group received monitoring, investigations, and treatment as determined by the treating physicians. The EGDT group started a six-hour resuscitation protocol, which included: supplemental O2 to produce SpO2 >= 93%, placement of a central catheter capable of ScvO2 continuous measurement within the first hour, placement of arterial line, using 500 mL fluid boluses every 30 minutes to maintain CVP >= 8 mm, use of vasopressors to maintain MAP and SBP if needed, and use of transfusion of packed red blood cells (RBCs), dobutamine, and mechanical ventilation to maintain ScvO2 >= 70%. The primary clinical outcome was all-cause mortality at 90 days.

By 90 days, 29.5% of patients in the EGDT group and 29.2% of patients in the usual-care group had died. Increased treatment intensity in the EGDT group was evidenced by increased volume of IV fluids, vasoactive drugs, and pRBC transfusions administered. The EGDT group experienced worse organ failure scores, more days receiving advanced cardiovascular support, and longer stays in the intensive care unit (ICU). EGDT also increased costs.

■ COMMENTARY

Since 2002, the Surviving Sepsis Campaign (SSC) has promoted "best practices" in management of sepsis, and has undoubtedly raised awareness of the importance of early recognition and treatment of sepsis, including source control and prompt administration of antibiotics. The resuscitation guidance (EGDT) is largely based on the 2001 single-center study by Rivers et al.[1] Three harmonized studies (ProCESS—U.S., ARISE—Australia, and ProMISe—UK) were initiated to specifically evaluate the effectiveness of EGDT. The two published studies (ProCESS and ARISE) did not show a benefit of EGDT; however, both studies reported lower than anticipated mortality in both EGDT and control arms, so the potential for a 20% reduction in 90-day mortality could not be excluded. The sample size calculations for ProMISe were estimated to be able to demonstrate a 20% relative risk reduction.

My personal take on this study is that the overall management of sepsis has improved dramatically during the past 13 years, making it difficult to isolate/demonstrate the benefit of a small subset of interventions. Rather than interpreting this study as "EGDT is worthless," my interpretation is that we have done such a good job recognizing and treating sepsis early that strict adherence to every element of the Rivers EGDT resuscitation protocol is not necessary and (in the absence of exercise of good clinical judgment) may even result in excess administration of crystalloid, and use of vasopressors and blood products (which may have adverse effects). I do believe we have come a long way since the turn of this century with now more routine early recognition of sepsis, early institution of volume expansion, and administration of appropriate antibiotics. While the results of this study should not make clinicians complacent about looking for areas to improve our management of sepsis, I feel strongly we need to work harder to prevent sepsis, especially to resist the use of central lines and urinary catheters in patients who do not absolutely need them, and of course limit the unnecessary use of antibiotics — which makes sepsis harder to treat when it does occur. ■

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ABSTRACT & COMMENTARY

Early Benefits of HPV Vaccination

By Hal B. Jenson, MD, FAAP

Dr. Jenson is Professor of Pediatric and Adolescent Medicine, and Dean, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, Michigan.

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

SYNOPSIS: A large study of HPV vaccination among girls 13-14 years of age demonstrated significant reduction of cervical dysplasia that was detectable by 17 years of age, providing justification for not delaying HPV vaccination in girls until older adolescence.

SOURCE: Smith LM, Strumpf EC, Kaufman JS, et al. The early benefits of human papillomavirus vaccination on cervical dysplasia and anogenital warts. *Pediatrics* 2015;135:e1131-e1140.

Using health databases in Ontario, Canada, researchers performed a population-based retrospective study comparing one cohort of all girls in grade 8 in 2007/2008 and 2008/2009 who were eligible for publicly funded quadrivalent human papillomavirus (HPV) vaccine, and a second cohort of girls in grade 8 in 2005/2006 and 2006/2007 who did not receive the vaccine. HPV vaccine was licensed in Canada in 2006.

Vaccine exposure was determined for girls in grades 8-9, with outcomes of cervical dysplasia and anogenital warts determined in grades 10-12. A quasi-experimental approach, regression discontinuity, was used to estimate absolute risk difference (RD), relative risk (RR), and the 95% confidence interval (CI) attributable to vaccination and intention-to-treat analysis. Observational studies of vaccine effects are vulnerable to confounding bias because individuals who choose vaccination tend to have different health histories and preventive behaviors than those who do not, and these characteristics are difficult to identify and quantify. Regression discontinuity evaluates the causal effects of interventions in a way that accounts for observed and unobserved confounding, thus facilitating reliable causal inference. Both cohorts were similar for vaccinations other than HPV.

In a total of 260,493 girls, including 131,781 vaccine-ineligible girls and 128,712 vaccine-eligible girls, there were 2,436 cases of cervical dysplasia and 400 cases of anogenital warts. HPV vaccination significantly reduced the incidence of cervical dysplasia with an RD of 5.70/1000 girls (95% CI 9.91 to 1.50), corresponding to a relative reduction of 44% (RR 0.56; 95% CI 0.36 to 0.87). There was a trend attributable to HPV vaccination to decrease anogenital warts (RD 0.83/1000 girls, 95% CI 2.54 to 0.88; RR 0.57, 95% CI 0.20 to 1.58).

COMMENTARY

The quadrivalent HPV vaccine provides protection against four types of HPV that cause 70% of cases of cervical cancer and at least 90% of cases of anogenital warts. The clinical benefit of HPV vaccination for young girls in preventing cervical dysplasia and cancer is generally thought to be observable only during adulthood and later life. This study of a real world population before and after routine HPV vaccination demonstrated that quadrivalent HPV vaccination of girls 13-14 years of age is highly efficacious in preventing vaccine-type cervical dysplasia and anogenital warts even by 17 years of age. Thus, the cost-benefit analysis of HPV vaccination may be even more favorable than previously thought.

Demonstration of benefits of HPV vaccination that are detectable even during late adolescence, before graduation from high school, is solid evidence of the benefits of HPV vaccination in young girls and provides strong justification for not delaying HPV vaccination until girls are older. Girls should be vaccinated at 9-13 years of age before the onset of sexual activity and the associated risk of exposure to HPV.

Some parents have delayed vaccination for their daughters until late adolescence, based on their perceptions of their daughter's low likelihood of sexual activity. Delay of vaccination based on parent's preferences is a flawed approach because parents underestimate their child's sexual experiences. Delayed vaccination will result in missed opportunities for cancer prevention. Universal HPV vaccination of all girls at 9-13 years of age provides the best opportunity for reducing the incidence of cervical dysplasia and, hence, cervical cancer. ■

ABSTRACT & COMMENTARY

Lung Ultrasound to Diagnose Pneumonia in Children

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

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

SYNOPSIS: Whether based on history, tachypnea, or X-ray findings, the diagnosis of pneumonia in children is incompletely accurate. Ultrasound is a reasonable alternative tool for the diagnosis of childhood pneumonia.

SOURCE: Pereda MA, Chavez MA, Hooper-Miele CC, Gilman RH, Steinhoff MC, Ellington LE, Gross M, Price C, Tielsch JM, Checkley W. Lung ultrasound for the diagnosis of pneumonia in children: A meta-analysis. *Pediatrics* 2015;135:714-722.

Pneumonia accounts for more pre-school-aged deaths worldwide than do tuberculosis, HIV, and malaria combined. Chest radiographs give risks of ionizing radiation and are not always available in resource-limited areas. Seeking an available, accurate, attractive alternative means of diagnosing lung infections, Pereda and colleagues reviewed studies of the diagnostic accuracy of lung ultrasound for pediatric pneumonia.

Eight studies were deemed adequate for inclusion in the meta-analysis. Study sites had been emergency departments (3), hospital wards (2), a pediatric intensive care unit (1), and neonatal intensive care units (2) in China, Egypt, Italy, and the United States. Combined, the eight studies included 765 children with a mean age of 5 years (range 0-17). The degree of ultrasound training varied between the studies. Compared to chest radiography, ultrasound had a sensitivity of 96% and a specificity of 84% in diagnosing pneumonia. Specificity was higher in inpatient settings than in emergency departments, and specificity was higher with more extensively trained physicians performing the ultrasounds.

The authors point out that ultrasound would only detect consolidations reaching the pleura and that atelectasis appears similar to consolidation on ultrasound. They also report that while extensive training improves specificity, there are data showing that a pediatric resident with seven hours of training can reach high sensitivity (98%) and specificity (95%).

COMMENTARY

Worldwide, pneumonia kills nearly one million children each year.[1] Only a third of children with pneumonia receive appropriate antibiotic treatment.[1] Global efforts have included improved diagnostic education so that affected children are adequately identified as having pneumonia.

In resource-limited areas, at least, "pneumonia" is typically defined as an acute febrile illness with cough and tachypnea (respiratory rate more than 50 breaths per minute between 2 and 12 months of age and more than 40 between 12 and 60 months of age).[2] Focusing on tachypnea as a key diagnostic finding has helped prevent overuse of antibiotics in children with viral respiratory infections while increasing the use of antibiotics for children who actually have bacterial pneumonia. This has been especially useful when laboratory and radiologic support for a pneumonia diagnosis is not available.

Using X-ray as a "gold standard" for the diagnosis of pneumonia, however, several studies have found that tachypnea is neither adequately sensitive nor specific enough to be the main criterion to diagnose pneumonia (and, thus, determine that antibiotic treatment is needed).[3,4,5] Ultrasound is increasingly available and affordable at points-of-care where lab testing and X-ray imaging take too long and cost too much to be used. The meta-analysis by Pereda and colleagues gives added support to reliance on ultrasound in diagnosing pediatric pneumonia.

Will ultrasound become widely used to diagnose lower respiratory infection in children? In 2013, a European journal included an article suggesting that lung ultrasound might be "internationally officialized in a near future" to diagnose pediatric pneumonia,[6] and an American journal carried an article suggesting that it was "prime time for routine use."[7] Now in 2015, ultrasound is still not routinely used. As Pereda and colleagues suggest, training of the people caring for children will be needed if this tool is to become

useful in varied clinical settings.

At the same time, studies of pneumonia diagnosis are hampered by the lack of a true "gold standard" that proves the diagnosis.[8] Studies of the validity of ultrasound in diagnosing pediatric pneumonia typically use chest radiographs as the "gold standard" by which the sensitivity and specificity of ultrasound are judged. Ultrasound compares more favorably than does the identification of tachypnea. But, is X-ray truly a gold standard for the diagnosis of pneumonia? Nearly two decades ago, good pediatric radiologists at a major children's hospital independently read and re-read 40 infant chest films without knowledge of clinical information; the kappa statistic of agreement as to whether or not there was "consolidation" was only 0.91 when the same radiologist saw the same X-ray twice, and only 0.79 for agreement between radiologists.[9] Interpretation of X-ray findings is not completely reliable.[10]

What's a clinician to do? We should still get good history information and pay attention to vital signs as part of our physical exam. We should be concerned that acutely ill, coughing, febrile children with tachypnea might need antibiotic treatment. And, we should consider learning how to use ultrasound at the bedside to help in diagnosing consolidating lung disease in children. ■

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ABSTRACT & COMMENTARY

Initial Antiretroviral Regimens — New Recommendations

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Professor of Medicine, Stanford University.

Dr. Deresinski reports that he has served as a one-time consultant for Cubist and Bayer.

SYNOPSIS: Four of the five recommended initial antiretroviral regimens in treatment-naïve adolescents and adults are based on integrase strand transfer inhibitors.

SOURCE: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

The invaluable guidelines on antiretroviral therapy (ART) of adolescents and adults produced by the CDC, NIH, and HIVMA were updated on April 8, 2015. The following is a summary of some of

the significant changes to the previous guidelines in recommendations regarding the choice of an initial antiretroviral regimen in treatment-naïve patients.

The continued development of new antiretroviral agents has led to changes in recommendations for initial ART in treatment-naïve patients. They now include four distinct regimens based on an integrase strand transfer inhibitor together with one ritonavir-boosted protease inhibitor-based regimen; each recommendation is graded AI. The recommended regimens are:
- Dolutegravir/abacavir/lamivudine (only if HLA-B*5701-negative;
- Dolutegravir/tenofovir fumarate/emtricitabine;
- Elvitegravir/cobicistat/tenofovir fumarate/emtricitabine (only if CrCl > 70 mL/min);
- Raltegravir/tenofovir fumarate/emtricitabine;
- Darunavir/ritonavir/tenofovir fumarate/emtricitabine.

The following previously recommended regimens are now listed only as alternatives, with each recommendation graded BI:
- Efavirenz/tenofovir fumarate/emtricitabine;
- Atazanavir/ritonavir/tenofovir fumarate/emtricitabine.

Both these regimens were "demoted" because of toxicity. In the case of the efavirenz-based regimen, this involves adverse central nervous system reactions, including possible increased suicidality. The following three regimens that were previously listed as recommended for individuals with a baseline plasma RNA concentration < 100,000 copies/mL or > 200 CD4+ T cells per mm^3 are now considered **alternatives**:
- Atazanavir/ritonavir/abacavir/lamivudine;
- Efavirenz/abacavir/lamivudine;
- Rilpivirine/tenofovir fumarate/lamivudine. ■

Nasal Screening for MRSA: The New Basis for De-escalation of Empiric Antibiotics?

By Kathryn Radigan, MD, MSc

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

This article originally appeared in the May 2015 issue of **Critical Care Alert.**

SYNOPSIS: The high negative predictive value of a negative nasal screen for methicillin-resistant *Staphylococcus aureus* suggests these patients do not have lower respiratory tract infections caused by the organism.

SOURCE: Tilahun B, et al. Nasal colonization and lower respiratory tract infections with methicillin-resistant *Staphylococcus aureus*. *Am J Crit Care* 2015;24:8-12.

Although nasal screening for methicillin-resistant *Staphylococcus aureus* (MRSA) is a widely accepted method for infection control, the relationship between nasal carriage and development of MRSA lower respiratory tract infection (LRTI) is not well studied. Tilahun and colleagues sought to determine the association between MRSA nasal swab results and MRSA LRTI in a medical ICU. In this single-site, retrospective cohort study, 165 patients were diagnosed with pneumonia and had both nasal swabbing and culturing of respiratory specimens within 24 hours of admission.

Among the 28 patients who had a nasal swab positive for MRSA, eight (4.8%) patients had respiratory specimens positive for MRSA. Of the 165 patients who were involved in the study, only two (1.2%) had negative nasal swabs but positive MRSA respiratory cultures. The sensitivity and specificity for nasal MRSA colonization for subsequent infection were 80% and 87.1% and the positive and negative predictive values were 28.6% and 98.5%, respectively.

■ COMMENTARY

It has long been recognized that treating our critically ill patients with early and appropriate antibiotics is a critical determinant of survival in septic shock.[1] The Surviving Sepsis Campaign suggests that IV antimicrobials should be given within the first hour of recognition of septic shock and severe sepsis without septic shock.[2] The guidelines for the choice of antibiotics are complicated and based on the individual patient and the identity and susceptibility pattern of the bacteria isolated on the individual

unit. With good intention, antibiotics are often overprescribed with failure of timely de-escalation, leading to unintended adverse consequences including patient morbidity and mortality, increasing health care costs, and antimicrobial resistance. Prescribing antibiotics to cover MRSA empirically is one of the biggest culprits.[3] This manuscript examined whether a correlation exists between MRSA nasal swab results and MRSA LRTI in a medical ICU. Even though researchers found that positive MRSA nasal swabs were not as helpful in guiding antibiotic therapy, they did conclude that the high predictive value of a negative nasal swab may be helpful with de-escalation of empiric antimicrobial therapy.

Although the overall message of this manuscript may be helpful, a word of caution should be exercised with these recommendations in regard to the type of specimen collected for respiratory tract culture. As described within the manuscript, only 5% of the specimens were collected by bronchoalveolar lavage; 65% of the specimens were tracheal aspirate or sputum collected by suctioning, 13% were from expectorated sputum, and 16% were collected from induced sputum. Since the majority of the specimens were not collected through bronchoalveolar lavage, the ability to differentiate upper respiratory tract colonization from lower tract pathogens is less accurate. Furthermore, the rate of pathogen detection for sputum samples can be quite poor, especially if standards of quality control for sputum culture are not followed. Taking into account these limitations, a negative nasal screen for MRSA should be an additional, but not the only, consideration to be included among a number of other important factors when deciding to de-escalate antibiotic therapy in our critically ill patients. ■

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ABSTRACT & COMMENTARY

Treatment of Invasive Aspergillosis: Are Two Drugs Better Than One?

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Professor of Medicine, Stanford University.

Dr. Deresinski reports that he has served as a one-time consultant for Cubist and Bayer.

SYNOPSIS: Although potential benefit may have been detected in a post hoc subset analysis, the addition of anidulafungin in the initial phase of primary treatment of suspected or documented invasive aspergillosis was not associated with a significant improvement in survival.

SOURCE: Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: A randomized trial. *Ann Intern Med.* 2015;162:81-89.

The use of antifungals in combination in the primary treatment of invasive aspergillosis has been increasing despite the fact that the available data supporting this practice is, at best, contradictory.[1] This issue has now been addressed in a large clinical trial.

Marr and colleagues at 93 international sites randomly assigned 454 patients — the intent-to-treat (ITT) population — with underlying hematologic malignancy or hematopoietic stem cell transplantation with suspected or documented invasive aspergillosis (IA) to blindly receive either anidulafungin or placebo, each together with voriconazole. Voriconazole was administered intravenously for the first week, after which it could be given by mouth, while anidulafungin or placebo was administered intravenously for 2-4 weeks. The primary efficacy endpoint was mortality at 6 weeks in the 277 patients in whom the diagnosis of IA was confirmed to be either possible, probable, or proven — who comprised the modified intent-to-treat (mITT) population. Secondary pre-specified end points were 6- and 12-week mortality in 6 subgroups believed to have prognostic import.

In addition to consistent radiographic findings, the diagnosis was proven in only 1.4% of patients, and was probable based on a galactomannan index > 0.5 in serum or bronchoalveolar lavage (BAL) specimen in 77.5% and on positive histopathology, culture, and/or cytology in 21.1%. Combination treatment (voriconazole and anidulafungin or placebo) was administered for a median of 14 days (range, 1 to 29) while the median duration of voriconazole administration was 42 days (range, 1 to 48). Voriconazole serum concentrations did not differ between treatment groups in the subset in which it was measured.

Six-week mortality in the ITT population was 20.6% (47 of 228) in the combination therapy group and 23.5% (53 of 226) in those receiving monotherapy. In the mITT population, mortality rates at 6 weeks were 19.5% (26 of 135) and 27.8% (26 of 135), respectively (95% CI of the difference, -19.0 to 1.5; 2-siede P=0.087). A successful global response was achieved at 6 weeks in 44 (32.6%) of combination therapy patients and in 61 (43.0%) of those given monotherapy (95% CI for the difference, -21.6 to 1.2). The frequency of hepatobiliary adverse events was higher in the combination group than in those receiving monotherapy (12.7% vs. 8.4%).

A post hoc analysis identified low Karnofsky score, low platelet count, and high maximum baseline galactomannan as independent prognostic factors for 6-week mortality. Not having found their desired outcome, the investigators subsequently searched for apparent differences in outcome between subgroups in addition to the multiple ones they had pre-specified — and they found one. A further post hoc analysis examined outcomes in patients with elevated serum or BAL and found that the all-cause mortality was 15.7% (17 of 108) in the combination therapy group compared with 27.3% (30 of 110) in the monotherapy group (difference, –11.6 percentage points [CI, –22.7 to –0.4]; P = 0.037). This apparent difference, however, appears to be largely limited to individuals with galactomannan indices in the range of > 0.5–1.5, with no significant difference between treatment groups in those with higher indices.

■ COMMENTARY

One issue not addressed in this study that could have affected results is the emergence of resistance to voriconazole in Europe, where many of the study centers were located.

This ambitious study failed to identify a survival advantage from the addition of anidulafungin to voriconazole in the initial portion of primary treatment in selected patients with suspected or documented aspergillosis. On further digging into the results, however, they concluded:

- From the Discussion: "We conclude that treatment of IA with the combination of voriconazole and anidulafungin was associated with a nonsignificant but clinically meaningful survival benefit in patients with HM or HCT."
- From the Abstract: "Compared with voriconazole monotherapy, combination therapy with anidulafungin led to higher survival in subgroups of patients with IA. Limitations in power preclude definitive conclusions about superiority."
- From the Editors' Notes: "Mortality was lower with combination therapy in a subgroup of patients whose IA diagnosis was established by radiographic findings and galactomannan positivity."

Thus, despite the lack of support from the results of the predetermined primary outcome, the authors (and editors) make a strong pitch for combination therapy, based on an exploratory post hoc subset analysis that appears to apply only to individuals with a modest range of galactomannan elevation. The validity of such a subgroup analysis deserves examination.

Sun and colleagues have listed four criteria for the assessment of subgroup analyses within individual studies and systematic reviews:[2]

- Can chance explain the apparent subgroup effect?
The examination of multiple subgroups, along with a P value = 0.39 raises the question of a chance effect.
- Is the effect consistent across studies?
There are no randomized trials with which to compare.
- Was the subgroup hypothesis one of a small number of hypotheses developed a priori with direction specified?
No.
- Is there strong preexisting biological support?
The result is not biologically implausible.

Thus, the reader should approach the conclusions of the authors with caution in making their therapeutic decisions. ■

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Updates

By Carol A. Kemper, MD, FACP

Surprise! My Kid Has Chlamydia

Various news alerts, May 2-5, 2015

Crane Independent School District has alerted parents to an outbreak of chlamydia in their school system. School officials became aware of a problem after Texas public health authorities noted 20 cases of chlamydia in school-aged kids residing in Crane and adjacent Upton County. This figure represents about 1 in 15 students at Crane High School. Chlamydia is a reportable disease in Texas.

The school district felt compelled to notify the parents of all junior high and high school students, although only high schoolers are known to be affected. The letter lists facts about chlamydia, including that it is a sexually transmitted disease and that most infections are asymptomatic. What the kids have been told is not clear from news reports.

According to the Crane Independent School District Student Handbook for 2014-2015, the district "does not offer a curriculum in human sexuality." In 2012, the district's School Health Advisory Committee had recommended Scott & White's "Worth the Wait" Abstinence Plus curriculum.

Texas state law requires any sex-education course to spend more attention on abstinence than on other behavior. And students must be taught that abstinence until marriage is the best way to prevent sexually transmitted diseases.

According to KOSA-TV, Crane High School does offer three days of sexual education during the fall semester. The district's Schools Health Advisory Committee was planning to meet to discuss how to deal with the chlamydia outbreak, and present their recommendations to the school board.

According to the National Campaign to Reduce Teen and Unplanned Pregnancy 2013 data, Texas rates 46th highest in teen births within the United States, and 47th highest in teen pregnancy rate (approximately 41 babies were born to 1000 Texas teens in 2013).

More on *C. diff.* Transmission

Eyre DW, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. *N Engl J Med* 2015;369(13):1195-1205.

Transmission of *Clostridium difficile* (CD) from a specific source is difficult to pinpoint, as genotyping or ribotyping is not sufficiently sensitive to distinguish between isolates. In an effort to establish genetic relatedness and specific sources for human infection, these authors went to great lengths to perform whole genome sequencing of all clinically significant isolates from symptomatic patients in the Oxfordshire area from 2007 to 2011. A total of 1250 CD cases yielded 1223 successfully sequenced isolates. Of these, 957 isolates obtained from 2008 to 2011 were compared to isolates from September 2007 onward. Transmission was presumed to occur when at least two isolates shared two or fewer single nucleotide variants (SNVs), consistent with genetic-relatedness, less than 124 days apart.

Epidemiologic investigation helped to define the nature of the potential exposure, using hospital data to fill in the blanks: Ward contact within a hospital was defined as transmission between two or more patients on the same hospital unit if infection occurred one week before or eight weeks after diagnosis of another case, and within an incubation period of 12 weeks. Hospital contact was defined similarly if within the same hospital but not the same unit, within 28 days of discharge (or infectivity). Community contact was defined as residing within the same postal address or within the same medical practice.

A total of 333 (35%) of the isolates were genetically related to at least one earlier case. Of these, 126 (38%) had ward contact, 29 (9%) had hospital-wide exposure, and 21 (6%) had both. In addition, 5 (2%) cases were genetically related to another hospital patient, but occurred following discharge of the case-patient, believed to be related to hospital exposure. Interestingly, only two or a few cases appeared to be genetically related, indicating that secondary transmission, even within hospitals, is limited. There were no large clusters or outbreaks of a single genetic strain.

Of the remaining 152 patients who shared a genetically similar isolate, no hospital link could be established. But 15 (10%) of these patients shared a common medical practice and 17 (11%) shared the same postal address. A good third had no obvious connection to another genetically similar case of CD infection. Even when the time frames for hospital exposure were broadened, at least 20% of the cases had no obvious link. Some of these patients (27%) were suspected of having been in close contact with an intermediate contact who had contact with a symptomatic CD patient. However, in examining all 190 date-based pairs of CD patients with ward contact, at least 54 (28%) had strains with more than 10 SNVs. In other words, a similar number of the date-based hospital CD cases had no genetic relatedness compared with those who did have related strains, suggesting a certain randomness to the process.

A total of 428 (45%) isolates were genetically distinct with more than 10 SNVs compared with other isolates — indicating a large number of varied sources for infection, even within their own community. (The authors believed that travel outside the area was not a likely risk factor for exposure, since the average age of the patients was 78 years [many of whom were ill]). Controlling exposures would therefore require identification of a larger number of diverse sources within any community — whether food, pets or other animals, etc.

An encouraging finding from this article was the gradual but statistically significant reduction in hospital-related cases from 2007 to 2011, indicating a change in hospital practices and improved source control in hospitals. One potential source for CD transmission in our area in Northern California, not mentioned in this article, is nursing homes or other long-term care facilities for the elderly. Routine surveillance screening of higher risk admissions at our hospital has found about 10% of long-term care facilities admissions are colonized with CD.

Staph. aureus Carriage and Moustaches

Soylu E, et al. Effect of a moustache on nasal *Staphylococcus aureus* colonization and nasal cytology results in men. *J Laryngology and Otol* 2015;129:155-158.

Some jobs, such as police, airlines, or the food industry, require men to be regularly clean shaven, which may have social and religious implications for some men. While not a health issue, Disney does not allow facial hair except for moustaches. But, presumably for many jobs, there is concern that moustaches may retain food or drink and be prone to colonization with bacteria. There may be some truth to this assertion: Moustaches do form a good mop and can absorb up to 20% of their weight in liquid. And, one of those odd little Internet tidbits, a man with a moustache touches his moustache an average of 760 times per day. Since nose picking is a risk factor for nasal carriage of *S. aureus*, does moustache hair affect nasal carriage of bacteria such as *S. aureus*?

In this study from Medipol University Hospital in Turkey, nasal colonization with *S. aureus* was examined in men with or without moustache hair. A total of 118 men who had worn a moustache for at least one year were compared to a control group of 123 men who had shaved this area daily for at least one year. Using a nasal speculum, specimens were collected from the right nasal cavity for cytology and from the left nasal cavity for culture. The swabs were soaked in saline and rotated within each nostril 5 times. The mean age of participants was 34 years. None of the men were smokers, had URI, or had chronic underlying disease or immune deficiency.

S. aureus nasal colonization was detected in 48 (20%) of the study participants. There was no difference in the frequency of MSSA or MRSA nasal carriage observed between the two groups of men. Twenty-three (19.5%) men with a moustache and 25 (20.3%) men without a moustache had a positive nares swab culture for *S. aureus*. Only two men with a moustache and three without had MRSA. These data are similar to other data for rates of *Staph. aureus* nasal carriage for the general population.

An interesting observation, however, was a greater frequency of eosinophils present in the nostrils of men with a moustache compared to those without. Nearly half (49%) of men with a moustache had nasal eosinophils on cytology, compared with 38% of men without a moustache, and 20% of moustached men had rich clusters of eosinophils compared with 7% of the control group ($p = .012$). Moustached men were also more likely to have nasal mast cells than their clean-shaven counterparts (17% vs 9%, $p = .06$).

Eosinophils and mast cells are believed to play an important role in allergic vs non-allergic rhinitis. Individuals with 20% or greater nasal eosinophilia but without evidence of atopy on allergy testing can develop chronic nasal inflammation and nasal polyposis, and they appear to be at greater risk for obstructive sleep apnea. In ENT speak, this is called nonallergic rhinitis with eosinophilia or NARES syndrome, and may contribute to episodes of sneezing, profuse watery rhinorrhea, and itchy noses. Maybe that's why men with moustaches frequently touch their facial hair. Or maybe they just like to look thoughtful. ■

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. Scan the QR code to the right, or log on to **AHCMedia.com** to take a post-test; tests can be taken after each issue. 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.
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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Ultrasound, when used to diagnose pediatric pneumonia, is:

A. sensitive and specific as compared with chest radiography

B. highly sensitive but not specific as compared with chest radiography

C. worthless since pulmonary air blocks the transmission of ultrasound waves

D. the current standard of care in resource-limited regions of the world

2. Which of the following is correct with regard to the study of *C. difficile* infections (CDI) on hospital wards?

A. Each 10% increase in antibiotic use was associated with a 1.34-fold increase in CDI infection risk.

B. The effect of antibiotic use on the occurrence of CDI at the ward level was undetectable in this study.

C. Antibiotic use on the ward only affected the occurrence of CDI in recipients of that therapy.

D. Monitoring of aggregate, as opposed to individual antibiotic use, is of no value.

3. Which of the following antiretroviral regimens is listed as "recommended" in the April 8, 2015, updated guideline?

A. Efavirenz/tenofovir fumarate/emtricitabine

B. Atazanavir/ritonavir/ tenofovir fumarate/ emtricitabine

C. Efavirenz/abacavir/ lamivudine

D. Dolutegravir/tenofovir fumarate/emtricitabine

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 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