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Infectious Disease [ALERT]

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

Azithromycin – The Heart of the Matter

By Stan Deresinski, MD, FACP, FIDSA,

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SOURCE: Ray WA, et al. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881-90.

Ray and colleagues examined the risk of cardiovascular death among patients 30 to 74 years of age enrolled in the Tennessee Medicaid program that had been prescribed azithromycin between 1992 and 2006. Individuals with known life-threatening cardiovascular illness, drug abuse, hospitalization in the previous 30 days, or residence in a nursing home in the previous year were excluded. The target patients, who received 347,795 5-day azithromycin prescriptions, were compared to propensity-score- matched individuals who took no antibiotics (1,391,180 control periods), and to patients prescribed amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626), or levofloxacin (193,906).

Compared to "no antibiotic" controls, the hazard ratio for cardiovascular death during 5 days of prescribed azithromycin therapy was 2.88 (95% CI, 1.79 to 4.63; P<0.001) and that of death from any cause was 1.85 (95% CI, 1.25 to 2.75; P=0.002). Azithromycin therapy was also associated with an increased hazard ratio for both cardiovascular and total deaths when compared to amoxicillin therapy, which itself had no increased hazard relative to "no antibiotic" controls. Relative to amoxicillin, azithromycin was associated with an estimated 47 added cardiovascular deaths per 1 million prescriptions. The degree of hazard was, however, strongly associated with the presence of preexisting cardiac risk factors. Those in the lowest deciles of risk (1-5) and those in deciles 6-9 had 9 and 45 excess deaths per 1 million prescriptions respectively, while those in risk decile 10 had 245 excess deaths per million prescriptions. The high-risk decile 10 enrollees accounted for 59% of cardiovascular deaths while receiving azithromycin. Azithromycin recipients also had a significantly greater hazard ratio of sudden death (2.71; 95% CI, 1.58 to 4.54) when compared to amoxicillin recipients.

Azithromycin was also associated with

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increased hazard of death relative to ciprofloxacin but did not significantly differ from levofloxacin. The increased risk associated with azithromycin therapy did not extend beyond the 5 days for which it was prescribed.

■ COMMENTARY

No direct evidence demonstrating the reason for the excess cardiac deaths is provided in this study. The finding, however, that there was an increased risk of sudden cardiac deaths (in addition to other types of cardiovascular deaths) leads to a strong hypothesis that arrhythmias played a significant role. This investigation was in fact prompted, at least in part, by the knowledge that the macrolide antibiotics prolong cardiac repolarization, as measured by the QT interval, and their use has been associated with the development of serious ventricular arrhythmias, especially torsades de pointe. This concern has proven to be well founded with regard to erythromycin and clarithromycin, which also have added potential risk when they are coadministered with drugs that inhibit CYP450, the enzyme responsible for their metabolic clearance (azithromycin is not affected). A previous examination of erythromycin prescriptions in Tennessee Medicaid enrollees found that they were associated with a doubling of the risk of sudden cardiac death and that this risk increased to five-fold in those who concomitantly took medications that inhibited CYP3A.[1] On the other hand, a precise understanding of the pro-arrhythmogenic risk of the azalide, azithromycin, has been lacking. QT prolongation, torsades de pointe, and polymorphic ventricular tachycardias in azithromycin recipients have been reported in only a small number of patients. In addition, the authors indicate that "at least" 20 cases of associated torsades have been reported to the FDA. These numbers must be put into the context of the fact that in 2010 azithromycin was the seventh most frequently prescribed medication in the U.S. with 52.6 million prescriptions.[2]

In the U.S., azithromycin has received FDA approval for use in the treatment of acute bacterial exacerbations of chronic pulmonary disease, acute bacterial sinusitis, community acquired pneumonia, pharyngitis/tonsillitis, uncomplicated skin and skin structure infections, urethritis and cervicitis, and genital ulcer disease. In March of 2012, the FDA issued the following statement:

"Prolongation of the QT interval: Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Although the absolute risk is unknown, it appears to be low with azithromycin likely due to the lack of appreciable drug interactions, and the observation that it is rarely reported as a postmarketing adverse event. However, it would be prudent to avoid use in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval."[3]

In response to the publication by Ray and colleagues, FDA has indicated that they are reviewing its results and will communicate the results of that review when it is completed. In the meantime, they provide the following advice:
"Patients taking azithromycin should not stop taking their medicine without talking to their healthcare professional. Healthcare professionals should be aware of the potential for QT interval prolongation and heart arrhythmias when prescribing or administering macrolides."[4]
The 47 excess cardiovascular deaths per 1 million azithromycin prescriptions in the U.S. together

with the 52.6 million azithromycin prescriptions in 2010 would indicate that there were approximately 2472 deaths attributed to azithromycin that year. This may be compared to a preliminary estimate of 646,421 deaths in individuals 25 – 74 years of age in 2010 [5]. For further comparison, preliminary data for that year indicates that, for all ages, there were 8352 deaths related to HIV infection, 7554 from viral hepatitis, 7284 from *Clostridium difficile* infection, and 569 from tuberculosis.[5]

The fact that more than 50 million azithromycin prescriptions are written in the U.S. in a single year should be surprising but, unfortunately, it is not. The perceptions of azithromycin have been that it is well tolerated, safe, and has few, if any, pharmacokinetic interactions. This view, together with the ease of writing a prescription for it ("Z-Pak" – a brilliant ploy by the marketing department) – has made it easy to make it the antibiotic of choice for many patients, especially those who do not actually need an antibiotic. The report by Ray and colleagues certainly disrupts this view, although it would be quite useful to determine if their results can be duplicated elsewhere, especially since it is likely impossible to totally eliminate all confounders in such an analysis. In the meantime, perhaps the most important result of this study may be to make clinicians think twice about whether their next antibiotic prescription is truly necessary. Clinicians may also wish to examine the extraordinarily long list of other medications, most not antibiotics, that may prolong cardiac repolarization.[6] ■

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ABSTRACT & COMMENTARY

Fatal Outcomes Following Family Transmission of *M. pneumoniae*

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.

SOURCE: Kannan TR, et al. Fatal outcomes in family transmission of *Mycoplasma pneumoniae*. *CID* 2012;54:225-31.

A retrospective study was conducted on members of one family following the deaths of a 15 year old boy and his 13 year old sister. Airway, CSF and serum samples were collected from the two fatal cases. Serum was collected from the three remaining ill siblings and both parents. Autopsy evaluation of sibling 1 showed cerebral edema (consistent with out of hospital cardiorespiratory arrest and anoxic encephalopathy) and pulmonary findings consistent with bronchiolitis obliterans with organizing pneumonia (BOOP) in both. Postmortem examination of sibling 2 revealed lymphoplasmacytic bronchiolitis with intraluminal purulent exudate, BOOP, and pulmonary edema. Detailed examination of lung tissue from sibling 2 confirmed the presence of M.pneumoniae organisms by immunohistochemical and immunoelectron microscopic methods. Mycoplasma was also cultured directly from sibling 2 lung tissue. Autopsy tissue from sibling 2 was positive by immunohistochemical staining for the presence of community-acquired respiratory distress syndrome (CARDS) toxin.

■ COMMENTARY

This report captured my attention for a number of reasons. The first was that at a

human level, I was touched by the tragedy of the sudden deaths of two previously healthy teenagers from what I generally regarded as a seldom-fatal cause of atypical pneumonia. The second was that our Infectious Diseases consult service at our hospital was recently involved in the management of a previously healthy middle-aged woman who had multilobar pneumonia due to *M. pneumoniae* (confirmed by PCR of tracheal aspirate and serology) and despite initial treatment with a macrolide went on to rapidly develop an ARDS picture and respiratory failure requiring prolonged mechanical ventilation. Open lung biopsy in her case also revealed severe bronchiolitis obliterans. She did survive but required heroic levels of care in the ICU including high-frequency ventilation. As in the two fatal cases described in this case series, our patient had developed respiratory symptoms about 2 weeks before she developed respiratory failure, suggesting that the BOOP picture represented a reparative response to the initial infection.

While *M. pneumoniae* is usually thought of as producing a relatively mild community-acquired pneumonia ("walking pneumonia") the fact is that severe and fatal cases have been reported sporadically in the literature over the past 45 years. Since we do not regularly look for evidence of *M. pneumoniae* in cases of BOOP it is likely that many cases of this idiopathic condition may be due to antecedent infection with *M.pneumoniae*. As with all diseases, it is likely that both host factors and pathogenic characteristics of the infecting organism contribute to severe *M. pneumoniae* infections. The same group from San Antonio who reported this tragic case series previously described an adenosine diphosphate-ribosylating and vacuolating cytotoxin (CARDS toxin) which has been shown to be correlated with severe disease in experimentally-infected mice and shares similarities to the toxin of *Bordetella pertussis*.[1] In fact, recombinant CARDS toxin alone elicits airway damage and perivascular cellular inflammation in baboons and mice after experimental inoculation.[2]

This case series is also concerning in light of the recent epidemic of *M. pneumoniae* infection which occurred in two waves in Denmark in 2010 and 2011.[3] While primary macrolide resistance was unusual in the Denmark epidemic (1-3%), rates of macrolide resistance in the Midwestern U.S. were shown to be 8.2% in 2007-2010.[4] Macrolide resistance rates as high as 90% have been reported in China.[5]

It is clear that *M.pneumoniae* should be considered in the differential diagnosis of severe pneumonia complicated by respiratory failure. Due to the significant amount of macrolide resistance now being seen, the use of fluoroquinolones or doxycycline (rather than macrolides) should be considered in patients with severe atypical pneumonia. However, it should be noted that it is unclear what the impact of macrolide resistance (or antibiotic therapy per se) is in patients who already have established bronchiolitis obliterans (with or without organizing pneumonia) since this particular manifestation is likely in part related to host response to the infection. ■

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Linezolid for Nosocomial MRSA Pneumonia: A Better Option?

By Brian Blackburn, MD

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Dr. Blackburn reports no financial relationships related to this field of study.

SYNOPSIS: Linezolid was non-inferior to vancomycin in patients with nosocomially-acquired MRSA pneumonia. Although mortality was similar among linezolid- and vancomycin-treated patients, several outcomes (such as clinical cure and microbiological cure) favored linezolid.

SOURCE: Wunderink RG, et. al. Linezolid in Methicillin-Resistant *Staphylococcus aureus* nosocomial pneumonia: A randomized, controlled study. *Clin Infect Dis* 2012;54:621-9.

The treatment of MRSA pneumonia is often regarded as problematic, with unacceptably high morbidity and mortality rates among affected patients. Two recent prospective, randomized, double-blind trials found that linezolid was non-inferior to vancomycin for the treatment of nosocomial pneumonia.1,2 In addition, post-hoc analysis of pooled data from these two trials found that survival (80% vs. 63%) and clinical cure (59% vs. 36%) significantly favored linezolid in the MRSA pneumonia subgroup.[3] However, the post-hoc nature of this subgroup analysis could have introduced bias, and vancomycin dosing was not optimized in these trials, leading to calls for a prospective, randomized, double-blind trial to verify these findings.

The authors thus undertook such a study comparing linezolid to vancomycin. Adult patients with radiographically documented nosocomial pneumonia (including those with both HAP [hospital acquired pneumonia; 84% of the cohort] and HCAP [health care associated pneumonia; 16% of the cohort]) and a respiratory culture positive for MRSA were randomized to receive either linezolid 600 mg every 12 hours or vancomycin 15 mg/kg every 12 hours. Dosing of the latter was subsequently adjusted based on serum vancomycin levels. Patients were treated for 7-14 days, although those with bacteremia were treated for 21 days. All patients received an antibiotic with Gram-negative (but without anti-MRSA) activity, which was discontinued if no Gram-negative pathogens were identified.

Although 1,225 patients were randomized to receive the study drug, only 448 (37%) were included in the modified intent-to-treat (mITT) analysis, with most patients excluded because MRSA was not identified in cultures. Only 348 patients were included in the per-protocol analysis. This population had a median age of 61 years, and 64% had ventilator-associated pneumonia. Median vancomycin serum troughs (μg/mL) were 12 at day 3, 15 at day 6, and 16 at day 9. Eleven percent of patients in the vancomycin arm had bacteremia, compared to 5% in the linezolid arm; slightly more patients in the vancomycin arm received mechanical ventilation than in the linezolid arm.

In the per-protocol population, clinical cure at the end-of-study assessment occurred in 95 (58%) of the 165 linezolid-treated patients, and in 81 (47%) of the 174 vancomycin-treated patients (P = .042). Microbiological cure occurred in nearly the same proportion of patients in both arms at the end-of-study analysis. All-cause mortality at the end-of-study analysis did not differ significantly - 28% in the linezolid arm and 26% in the vancomycin arm.

Renal failure occurred twice as frequently in the vancomycin arm (7.3%) as in the linezolid (3.7%) arm. The frequency of cytopenias did not differ between groups.

■ COMMENTARY

This prospective, randomized, double-blind trial seems to confirm the earlier post hoc subgroup analysis which suggested that linezolid may be superior to vancomycin for the treatment of nosocomial MRSA pneumonia. Although mortality did not differ between groups in this trial, linezolid was associated with higher clinical and microbiological cure rates than vancomycin. These results were consistent in most subgroups analyzed in the study, including among patients with mixed infections, among those who received mechanical ventilation, and among those who received systemic corticosteroids.

The apparent superiority of linezolid may have resulted from better intrinsic antimicrobial activity, better lung penetration, and more complete bacterial eradication. These findings are more robust than the previous post-hoc study, given the prospective, randomized, double-blind nature of this study, and that vancomycin dosing was optimized in this study based on serum levels. Linezolid also appeared safer than vancomycin, with less nephrotoxicity and no increase in hematologic toxicity, another compelling point in favor of linezolid (especially given that renal failure is a significant predictor of mortality in this setting).

Mortality was not lower among linezolid-treated patients, possibly in part because a lower-than-expected mortality was observed among vancomycin-treated patients. This might have been a result of the intensive dose optimization by serum drug level monitoring for vancomycin, but whether this is applicable to many real-world settings is unclear from this study.

Limitations of the study included the large number of patients excluded after randomization, which could have introduced bias. In addition, while the requirement of a positive culture for MRSA was a strength in terms of confirming the role of linezolid in patients with known MRSA pneumonia, it also introduces a limitation for real-world use, given that antibiotics are usually started empirically in patients with nosocomial pneumonia. It is common that no etiologic diagnosis is ever made in this setting, and this trial does not address the efficacy of linezolid in this situation. Another limitation was the slightly higher proportion of patients with bacteremia and mechanical ventilation in the vancomycin arm, which could have biased the results against vancomycin. Finally, even with linezolid, the clinical cure rates observed were relatively low, suggesting that we still do not have an optimal drug for this serious and difficult-to-treat condition.

Despite these limitations, this study provides compelling evidence to bolster the notion that linezolid may be superior to vancomycin for nosocomial MRSA pneumonia. If these findings result in enthusiastic demand for linezolid in this setting, careful stewardship is of paramount importance, given that widespread use of linezolid in this setting could prove very expensive, and might promote resistance to this drug. If linezolid does become the first-line anti-Gram positive agent for nosocomial pneumonia, perhaps limiting use to clinically and microbiologically well-documented cases of nosocomial MRSA pneumonia would be prudent, with empiric use limited to a short course if MRSA is not subsequently recovered from respiratory cultures. ■

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Should Cefazolin be Preferred Treatment for Methicillin-susceptible *S. aureus* Bacteremia Instead of Nafcillin?

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SYNOPSIS: In a retrospective, propensity-score-matched, case-control study, investigators compared clinical outcomes and drug tolerabilities between nafcillin and cefazolin in the treatment of MSSA bacteremia. The authors found that cefazolin was as efficacious as nafcillin in the treatment of MSSA bacteremia while causing fewer adverse drug events

SOURCE: Lee S, et al. Is cefazolin inferior to nafcillin for treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia? *Antimicrob Agents Chemother* 2011;55:5122-6.

Methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia is a commonly encountered infection in hospitalized patients that can have serious complications if not adequately treated. In a retrospective, propensity-score-matched,

case-control study, investigators compared clinical outcomes and drug tolerabilities between nafcillin and cefazolin in the treatment of MSSA bacteremia. The study was conducted between 2004 and 2009 at a tertiary care center in Seoul, South Korea. From August 2004 to August 2006 nafcillin was not available at the hospital because of supply issues. Patients with MSSA bacteremia were mainly treated with cefazolin during that period.

The authors examined the medical records of all patients with MSSA-positive blood cultures between January 2004 and June 2009 who received either nafcillin or cefazolin and placed them in two groups based on the antibiotic used. Logistic regression was used to create a propensity score based on risk factors for each patient. These risk factors included age, McCabe classification, high-burden disease, site of infection, and focus eradication. Patients in the cefazolin group were matched with patients in the nafcillin treatment group who had the closest propensity scores. The treatment failure rates were compared between the propensity-score-matched-groups 4 and 12 weeks after the start of nafcillin or cefazolin treatment.

Out of 174 patients during the study period with MSSA bacteremia, 84 were treated with nafcillin and 90 were treated with cefazolin. Forty-one patients in the cefazolin group were matched with the 41 patients in the nafcillin group with the highest propensity scores. Times to defervescence were 4.4 ± 4.9 days in the matched cefazolin group and 5.4 ± 9.3 days in the matched nafcillin group ($p=0.63$). The treatment failure rates at 12 weeks were 15% (6/41) in the cefazolin group and 15% (6/41) in the nafcillin group ($p > 0.99$). The rates of MSSA bacteremia-related mortality were 2% (1/41) in the cefazolin group and 12% (5/41) in the nafcillin group ($p = 0.22$). There was no significant difference between the two groups in 4 week mortality (4% vs. 4%). In four patients in the cefazolin group, the antibiotic was changed due to treatment failure (3 to vancomycin, 1 to nafcillin). Pneumonia and infective endocarditis have been previously shown to be predictors of treatment failure for MSSA bacteremia. After adjusting for these risk factors, cefazolin use was found to not be a risk factor for treatment failure for MSSA bacteremia.

None of the patients in the cefazolin group had their treatment interrupted due to adverse drug events. In contrast, 7 patients discontinued nafcillin because of adverse events including fever (n=4), cytopenia (n=2), and phlebitis (n=1). The median time to the discontinuation of nafcillin was 19 days (range, 7 to 24 days).

■ COMMENTARY

The authors of this study found that cefazolin was as efficacious as nafcillin in the treatment of MSSA bacteremia while causing fewer adverse drug events. One limitation is the retrospective design which could predispose to selection bias, although the authors attempted to compensate for this by using propensity scores and included patients in the cefazolin group when nafcillin was unavailable at the institution. Another limitation was that few endocarditis cases were treated with cefazolin (n =1). The number of patients in both treatment groups was small (n =41) which could limit the ability to detect differences in outcomes between nafcillin and cefazolin.

While a randomized, prospective clinical trial comparing nafcillin to cefazolin for treatment of MSSA bacteremia would be welcomed, it seems unlikely such a study will be conducted in the near future. Therefore clinicians must decide how to treat patients with MSSA bacteremia based on the best available evidence. Using cefazolin in this scenario seems to be a reasonable approach. In addition to fewer adverse drug events than nafcillin, cefazolin has a more convenient dosing schedule (every 8 hours compared to every 4 hours) and can be given at the end of a dialysis session in patients with renal failure. One caveat is that nafcillin should probably remain the first line therapy for MSSA endocarditis with brain emboli. Cefazolin poorly penetrates the blood-brain barrier, so metastatic infection of the brain from endocarditis might not be adequately treated with this drug. However, it is controversial and further studies on this are warranted. ■

ABSTRACT & COMMENTARY

The Most Common Cause of Encephalitis?

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Beginning in 2007 the California Encephalitis Project (CEP) found that many cases of encephalitis of unknown etiology were found to be associated with antibodies to N-methyl-D-aspartate receptor (anti-NMDAR). This was identified >4 times as frequently as HSV-1, WNV, or VZV and was the largest single cause of encephalitis in the cohort. 65% of cases of anti-NMDAR encephalitis occurred in patients < 18 years of age and 75% of patients were female.

SOURCE: Gable MS, et al. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis* 2012;54:899-904.

CEP first reported 10 cases of a newly recognized cause of encephalitis in 2009.[1] This updated report describes a total of 32 cases of anti-NMDAR encephalitis and compares the clinical characteristics of these cases vs. those caused by enterovirus (30), HSV-1 (7), VZV (5), and West Nile Virus (5). Age range of the anti-NMDAR cases was 2-28 years (median 12.5), 75% were female, 47% were Latino and 31% were Asian/Pacific Islander. Movement disorder, aphasia, ataxia, and autonomic instability, seizures, and hallucinations were commonly reported. MRI was abnormal in only 46% of anti-NMDAR cases whereas temporal lobe abnormalities were found in 100% of cases of HSV-1 encephalitis. CSF WBC ranged from 0 to 252 (median 23) and CSF protein and glucose were generally normal. 13% of patients with anti-NMDAR encephalitis were ill enough to require ICU admission and 1 patient (3%) died.

■ COMMENTARY

Anti-NMDAR encephalitis may be one of the more common causes of encephalitis, especially in children and women who present with characteristic signs and symptoms as noted above. Anti-NMDAR encephalitis is one of the immune-mediated encephalitides and is felt to be similar in etiology to the classic paraneoplastic syndromes associated with antibodies to intraneuronal targets with cytotoxic T-cell responses and to other autoimmune encephalitides in which the target epitopes are extracellular antigens. These latter entities include encephalitis associated with antibodies to other neuronal receptors such as 3-OH-5-methyl-4-isoxazolepropionic acid receptor (associated with lung, breast, and thymic tumors) and gamma-amino butyric acid B receptor (associated with small cell lung cancer) where a clinical picture of limbic encephalitis is seen.

Consideration of anti-NMDAR encephalitis and specific testing to confirm the diagnosis should be done early in the clinical evaluation of a patient with encephalitis presenting with a compatible clinical picture. While data from randomized controlled trials of various treatment modalities are not available, clinical experience suggests that the prognosis is better when immunosuppressive treatment is instituted earlier in the course of the illness. In addition, early diagnosis of anti-NMDAR encephalitis will reduce the inappropriate (and futile) empiric use of antibiotics and antiviral agents.

Interestingly, in this same issue of *CID*, investigators from Japan and Finland report on 4 cases of encephalitis in children (ranging in age from 8 to 60 months) where human bocavirus 1 or 2 was found in serum and CSF2, further expanding the differential diagnosis of the etiology of encephalitis. ■

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ABSTRACT & COMMENTARY

HPV-related Oral Cancers Increase by 225% in U.S. from 1988 to 2004

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SYNOPSIS: HPV infection is associated with 26,000 new cancers a year in the U.S.

SOURCE: Centers for Disease Control and Prevention. Human papillomavirus-associated cancers – United States, 2004-2008. *MMWR* 2012; 61:258-61.

Based on an analysis of data from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results programs, CDC determined that there was an average annual occurrence of 33,369 cancers at sites frequently associated with human papillomavirus (HPV) infection during 2004-2008. Using published data indicating the proportion at each of these sites associated with HPV, they were able to estimate that approximately 26,000 new cancers attributable to HPV infection, including 18,000 in females and 8000 in males, occurred annually. These included 11,500 cervical and 7400 oropharyngeal cancers; 5900 (79.7%) of the latter occurred in men and 1500 in women.

■ COMMENTARY

Cancers of the cervix, vulva, vagina, penis, anus, and oropharynx (especially at the tongue base and tonsils) are frequently associated with HPV infection. HPV 16 and 18 account for approximately 70% of cervical cancers and HPV 16 is responsible for the majority of noncervical cancers caused by HPV. The two commercially available HPV vaccines each protect against both HPV 16 and 18. Both vaccines protect against cervical precancers; the quadrivalent vaccine has also been demonstrated to prevent vaginal, vulvar, and anal precancers. Vaccination for prevention of HPV-associated genital warts and anogenital malignancies is recommended in the U.S. for females aged 9 – 26 years and males 9 -21 years of age.

Screening for cervical cancer continues to also be a critical element of prevention. The guidelines have recently been updated (*see box below*) and they now recommend screening intervals of 3 years for women aged ≥21 years if screening with a Papanicolaou (Pap) test alone, or, as an acceptable

U.S. Preventive Services Task Force Screening for Cervical Cancer Current Recommendation (*Release Date: March 2012)*

These recommendations apply to women who have a cervix, regardless of sexual history. These recommendations do not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).

- The USPSTF recommends screening for cervical cancer in women ages 21 to 65 years with cytology (Pap smear) every 3 years or, for women ages 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years. See the Clinical Considerations for discussion of cytology method, HPV testing, and screening interval. Grade: A Recommendation.
- The USPSTF recommends against screening for cervical cancer in women younger than age 21 years. Grade: D Recommendation.
- The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations for discussion of adequacy of prior screening and risk factors. Grade: D Recommendation.
- The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer. Grade: D Recommendation.
- The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years Grade: D Recommendation.

alternative for women >30 years of age, every 5 years if screening with both a Pap test and an HPV DNA test.[1]

The increased risk of anal cancer in HIV infected men has led some to recommend routine screening for this malignancy, but no consensus appears to have been reached. In additiion, the incidence of non-HPV associated oral malignancies, which are instead associated with tobacco and alcohol use, has decreased. In contrast, the incidence of HPV-related oral cancers increased by 225% in the U.S. between 1988 and 2004. Oral inspection remains the currently utilized means for detection of oropharyngeal malignancies.

The prevalence of oral infection with HPV 16 in individuals 14 to 69 years of age is 1%.[2] HPV infection is detected in 25% of head and neck squamous cell cancers and 90% of these are associated with HPV16. There is thus reason to believe that the available vaccines will protect against HPV related malignancies of the oropharynx. The cornerstones of prevention of HPV related malignancies are behavioral change, screening for premalignant lesions, and full utilization of the available vaccines. ■

References

1. Screening for Cervical Cancer, Topic Page. April 2012. U.S. Preventive Services Task Force: http://bit.ly/cyDcWj
2. Gillison ML, et al. Prevalence of oral HPV infection in the United States, 2009-2010. *JAMA* 2012; 307:693-703.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Half of U.S. TB cases in four States

Centers for Disease Control and Prevention. Trends in Tuberculosis – United States, 2012. *MMWR* 2012; 61: 181-185.

National data available for 2011 indicate that a total of 10,521 new TB cases were reported last year in the United States (incidence 3.4 cases/100,000 population), representing an overall decline of 3.8% from 2010. TB continues to disproportionately affect foreign born persons, and Asians became the single largest racial/ethnic group affected by TB, with a case rate 25 times higher than non-Hispanic whites. TB cases among Hispanics and non-Hispanic blacks fell slightly, but remained 7 and 8 times higher than non-Hispanic whites, respectively.

Remarkably, half (50.4%) of all TB cases in the United States occurred in 4 States in 2011 (California, Florida, New York, and Texas), although the case rate per population was the highest for Alaska (case rate 9.3 per 100,000 population).

Since 2000, a steady increase in TB has been observed in foreign born persons, with 62.5% of all TB cases in 2011 occurring in those who are foreign born. In contrast, cases in U.S.-born persons declined to a rate of 1.5 cases/100,000 population – an 80% decrease from 2003.

HIV test results were available for 81% of reported cases; among those with an available HIV test result, 7.9% were co-infected with TB and HIV.

Finally, drug resistance data (which was only available for 2010 and not yet available for 2011) indicates that 1.3% of all cases were multi-drug resistant. This figure is relatively stable compared with 2009. A total of 109 cases of MDR-TB and 4 cases of XDR-TB (all in foreign-born individuals) were reported in 2010. The risk for MDR-TB was four times greater in persons previously treated for TB compared with those receiving first time therapy. Programs targeting high risk ethnic groups have been associated with a lower risk of reactivation TB. For example, one program targeting predominantly black and Hispanic neighborhoods in Texas, emphasizing INH treatment for anyone with latent TB, resulted in a definite decrease in active TB cases. Perhaps larger clinics in certain high risk areas of the United States, like Sutter Health and the Kaiser Permanente systems could consider similar programs. ■

Probiotics a Plus

Hempel S, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea. A systematic review and meta-analysis. *JAMA* 2012; 307(18), p 1959-1968.

It seems that everyone receiving antibiotics nowadays requests probiotics, although they are not inexpensive and their use in the prevention of *Clostridium difficile* enterocolitis (CDI) has not been demonstrated. Antibiotic-

associated diarrhea (AAD) affects up to 30% of persons receiving antibiotics, and several studies have observed reductions in AAD in persons receiving various probiotic compounds. But how helpful are they, and are they worth the expense?

These investigators performed a meta-analysis of reported clinical trial data on the effectiveness of various probiotics in the prevention and treatment of AAD. An extensive query was conducted, without language restriction, specifically looking for randomized controlled trial data for the use of any of several probiotics (including Lactobacillus, Bifidobacterium, Saccharomyces Streptococcus, Enterococcus, and/or Bacillus), alone or in combination. Participants of any age group, any underlying disease, outpatient/inpatient, and any type of antibiotic use were included. Most trials indicated that probiotics were administered for the prevention and/or treatment of AAD, although most gave the probiotic substance simultaneously with the antibacterial, before the development of symptoms. The investigators noted that most of the studies provided limited follow-up, generally for the period of antibacterial treatment. The authors observed that the quality of the reporting for most of the studies was low, and only two of the studies met their criteria for high quality/low bias. Fifty-nine of the studies lack information by which to even gauge potential bias. Furthermore, most of the studies were not sufficiently powered to detect a statistically significant reduction in benefit.
A total of 82 randomized clinical trials met the study criteria for inclusion in the analysis. Most of the clinical trials were performed in the outpatient setting (24 included hospital patients); most included adults (n = 52). Twenty-four of the studies involved treatment for *H. pylori*. Sixteen studies evaluated the risk of AAD with the use of a single antibacterial agent (i.e., azithromycin, clarithromycin), although most did not restrict nor specify the type or duration of antibacterial therapy used. The products used were quite variable, and included lactobacillus alone/or in combination with other genera in 57 studies; yeast based products (e.g., S boulardii (cerevisiae)) were exclusively used in 16 studies.

Most of the clinical trials failed to demonstrate a statistically significant benefit for probiotic use. However, when probiotic use was examined across all 62 studies with sufficient participant data available (n = total 11, 811 participants), patients receiving probiotics were at significantly lower risk of developing diarrhea compared with those not receiving probiotics (pooled RR, 0.58, p <.001). To test the robustness of these results, each study was sequentially eliminated from the analyses, and all 63 results were similar. When the analysis was limited to those 44 studies that were specifically double-blinded, a significant reduction in AAD was observed in favor of probiotics (pooled RR, 0.61, p < .001). Further meta-analysis found the results for blinded and non-blinded trials were similar.

Results specific to different age groups were also examined where possible, including children (<18 years of age), adults, and older adults (>65 years of age), although most of the studies included 2 or more of these age groups. Sixteen clinical trials specifically enrolling children found a statistically significant reduction in the risk of AAD with probiotic use compared with controls (RR 0.55, p < .002). Similar results were observed for adults alone. Only 3 of the clinical trials examined the effectiveness of probiotic use specifically in the elderly. The pooled results from these studies failed to demonstrate a statistically significant benefit to probiotic use in the older age group.

In 20 studies enrolling hospitalized patients who received adjuvant probiotics in conjunction with antibacterial therapy, the risk of AAD was significantly lower (RR .55, p < .001) in the active treatment group compared with controls. The authors commented that in hospital patients especially, there was a wide range of antibacterial use and duration, not all of which was clearly specified, and the observed effectiveness of probiotic therapy was generally limited to the period of antibiotic use and not longer.
The effect on the risk of developing CDI in these studies was more difficult to gauge. Thirty-one of the clinical trials specified criteria for more severe diarrheal symptoms leading to a change in treatment or testing for *C. difficile*. CDI data was apparently available for only 14 of these studies. In pooled analysis of these 14 studies, it appears that the relative risk for developing CDI was statistically significantly lower in patients receiving probiotics compared with those who did not (RR 0.29, 95% CI, 0.17-0.48, p < .001).

Seventeen of the studies used products containing only lactobacillus; pooled data demonstrated a statistically significant reduction in risk for AAD, which was similar to those studies using exclusively

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yeast-based products. Those few studies that provided a head to head comparison between different products found no clear difference. Thus, the use of various probiotics, whether lactobacillus-based or yeast-based, in conjunction with differing antibacterial agents, appeared in this meta-analysis to have had a similarly beneficial effect and lowered the risk of AAD. The authors recommend that larger and better quality studies be performed, with clear symptom definition for diarrhea severity, and endpoints for C difficile testing. Complications of probiotic therapy, such as S. cerevisiae fungemia, albeit uncommon, were not reported or addressed by most of the clinical trials evaluated here. A larger trial could help to examine those types of adverse events, in addition to examining cost-benefit. ■

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.

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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. In light of a case series of fatal infections, which should be considered in the differential diagnosis of severe pneumonia complicated by respiratory failure?

A.Severe acute respiratory syndrome (SARS)
B.Pneumonic plague
C.*Mycoplasma pneumoniae*
D.Group A Streptococcus

2. Which of the following is correct with regard to the treatment of nosocomial pneumonia due to *Staphylococcus aureus* as found in the study by Wunderink and colleagues?

A. Linezolid treatment was associated with a significantly greater risk of renal toxicity than was vancomycin treatment.
B. Linezolid treatment was associated with a significantly lower mortality than was treatment with vancomycin.
C. Linezolid treatment was associated with a significantly lower rate of microbiological cure than was treatment with vancomycin.
D. Liniezolid treatment was associated with a significantly higher rate of clinical cure than was vancomycin treatment.

3. Which of the following is correct with regard to NMDAR-associated encephalitis?

A. It is associated with abnormal temporal lobe findings on magnetic resonance imaging.
B. Movement disorder, aphasia, and ataxia is commonly associated with it.
C. Cerebrospinal fluid pleocytosis is frequent and intense.
D. It is associated with high antibody levels directed at *Mycoplasma pneumoniae*

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

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

[IN FUTURE ISSUES]

Iron deficiency protects against severe malaria

Diagnosis and Treatment of Influenza Infection

Lessons learned from the H1N1 Pandemic

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Critical Drug Shortages Are on the Rise

In this issue: Drug shortages; metformin and cancer prevention; migraine prevention guidelines; and FDA actions.

What's causing the shortages?

Drug shortages are happening at an unprecedented rate. Just in the last 2 months, we have seen shortages of diazepam, methotrexate, leucovorin, naltrexone, oxymorphone, mitomycin, fentanyl, metoclopramide, pantoprazole, ondansetron, and dexamethasone among others. What is causing the shortages and is there any end in sight? Although it seems like a new problem, we have seen an increasing number of drug shortages going back to 2005. But while there were about 50 drug shortages in the mid 2000s, last year more than 260 drugs were in short supply, including many commonly used and clinically vital drugs. The cause of these shortages is multifactorial. Some sources in the industry blame price controls, especially for generic drugs. Medicare and Medicaid impose strict controls on most generics, squeezing pharmaceutical companies' ability to make a profit. Some companies have simply decided to drop out of the generic market altogether. Others blame fewer manufacturers. The *Wall Street Journal* reports that there were 26 vaccine makers in the United States in 1967, while currently there are only six. But even these issues do not explain the severe shortages we are seeing. Most experts agree the two major issues causing the current shortages are supply chain disruptions, especially disruptions in raw materials, and problems with manufacturing, especially safety issues, which force the FDA to shut down production of a product line or an entire factory. Safety shutdowns are the most common cause of shortages of sterile injectable drugs. But in other cases, companies limit production themselves when they either have an absolute shortage of raw materials or they decide to divert limited supplies of raw materials from less expensive generics to more expensive brand-name drugs. This is a current issue with some of the attention deficit hyperactivity disorder drugs that have been in short supply for several months. Last month, the FDA initiated a series of steps to increase the supply of critically needed cancer drugs, including allowing the importation of drugs in shortage from Europe and elsewhere. The agency is also fast tracking approval of new manufacturers for short-supply drugs like methotrexate. The FDA, as well as the Obama administration, is also requiring companies to give early warning of potential drug shortages. Finally, the Justice Department will aggressively pursue possible incidences of collusion or price gouging among drug distributors who may be taking advantage of shortages. Despite these steps, there will likely be no short-term easing in drug shortages. ■

Does metformin prevent cancer?

Last month, we reported that low-dose aspirin may be protective against some cancers. Now it looks like metformin may have similar properties. A new study from the American Association for Cancer Research suggests that the diabetes drug may improve the prognosis with pancreatic cancer. In a retrospective study, researchers at the University of Texas studied 302 patients with diabetes and

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

pancreatic cancer; 117 of these patients were taking metformin. The 2-year survival rate was 30.1% for the metformin group vs 15.4% for the non-metformin group ($P = 0.004$; x^2 test). The pancreatic cancer patients on metformin lived 4 months longer than non-metformin patients (15.2 months vs 11.1 months). The authors suggest that metformin should be evaluated as a supplemental therapy for patients with pancreatic cancer (*Clin Cancer Res* published online March 31, 2012; doi: 10.1158/1078-0432.CCR-11-2994). Data presented at the AACR meeting in Chicago earlier this year suggest that the drug may also be beneficial for men with prostate cancer, although further research is needed. ■

Migraine prevention in adults

The American Academy of Neurology and the American Headache Society have published their new guideline on pharmacologic treatment for episodic migraine prevention in adults. The highest level (Level A) recommendation for prevention was given to antiepileptic drugs, including divalproex sodium, sodium valproate, and topiramate. Other level A drugs included the beta-blockers metoprolol, propranolol, and timolol as well as the triptan frovatriptan, but this last agent is just for short-term use for menstrually associated migraine (MAM) prevention. Level B drugs included the antidepressants amitriptyline and venlafaxine, the beta-blockers atenolol and nadolol, and the triptans naratriptan and zolmitriptan (also only for short-term MAM prevention). Possibly effective medications included lisinopril, candesartan, some beta-blockers, and carbamazepine. There was little or no evidence to support any other drugs including selective serotonin reuptake inhibitors, calcium channel blockers, or acetazolamide. Drugs that should not be offered include lamotrigine and clomipramine. In a separate section on nonsteroidal anti-inflammatory drugs (NSAIDs) and complementary treatments, Petasites hybridus (butterbur) were given recommended status, while NSAIDs were listed as probably effective (*Neurology* published online April 24, 2012; doi: 10.1212/WNL.0b013e3182535d20, and doi: 10.1212/WNL.0b013e3182535d0). ■

Fibrate use in elderly patients

Fibrate use in elderly patients is associated with worsening renal function and increased risk of hospitalization, according to a new study. Researchers reviewed data from a large Canadian database of patients over the age of 65 who were started on a fibrate or ezetimibe (comparator). Many patients in both groups were also on statins. Fibrate users were more likely to be hospitalized for an increase in serum creatinine (odds ratio [OR] 2.4 [95% confidence interval (CI), 1.7 to 3.3]). Fibrate patients were also more likely to consult a nephrologist, but there was no difference in all-cause mortality or need for dialysis. In a subgroup of 1110 patients in which serum creatinines were available at baseline and within 90 days, 9.1% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine of 50% or more (OR 29.6 [CI, 8.7 to 100.5]). The risk was higher if patients had chronic kidney disease. The authors conclude that new fibrate use in the elderly is associated with an increase in serum creatinine and a small increase in hospitalization and nephrology consultation (*Ann Intern Med* 2012;156:560-569). ■

FDA actions

The FDA has approved the first PDE5 inhibitor in a decade for the treatment of erectile dysfunction (ED). Avanafil (Stendra) joins sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) as the fourth drug approved for this indication. Avanafil will be marketed as having a shorter onset and a shorter half-life than the other drugs in this class. Men should take avanafil as needed 30 minutes before sexual activity with onset of action as quickly as 15 minutes. The approval was based on three randomized, placebo-controlled clinical trials of 1267 patients with ED in which 57% of men achieved erections sufficient for intercourse, up from a baseline of 15% (compared to 27% with placebo). Like other PDE5 inhibitors, avanafil should not be taken with nitrates. Commonly reported side effects include headache, flushing, nasal congestion, nasopharyngitis, and back pain. Avanafil will be marketed by VIVUS of Mountain View, California, as Stendra.

The FDA is requiring new labeling on finasteride — Merck's testosterone blocker used for the treatment of benign prostatic hypertrophy (5 mg as Proscar) and male pattern baldness (1 mg as Propecia). The new labeling addresses sexual adverse events such as libido disorders, ejaculation disorders, orgasm disorders, and even male infertility and poor semen quality. Some of these issues, such as libido disorders and ejaculation disorders, may continue after stopping the drug, while infertility and poor semen quality improve or normalize after discontinuation. The labeling change is based on event reports filed with the FDA, although a clear causal relationship has not been made. Still, the agency is recommending that a discussion of the risks and benefits of finasteride include the possibility of sexual side effects. ■