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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

When Did You Last Take an Antibiotic?

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Approximately half of U.S. residents with health insurance filled an antibiotic prescription over a two-year period.

SOURCE: Olesen SW, MacFadden D, Grad YH. Cumulative probability of receiving an antibiotic prescription over time. *N Engl J Med* 2019;380:1872-1873.

Using the Truven Health MarketScan Research databases, researchers assessed the probability that enrollees comprising approximately one-fifth of the U.S. population received an antibiotic prescription filled at an outpatient pharmacy during 2011 through 2014. During those years, 100 million claims for outpatient antibiotic prescriptions were made for the 62 million enrollees in health insurance plans.

Consistent with their previous work, the researchers found that 33% of the cohort had an antibiotic prescription filled at an outpatient pharmacy during a single year. This increased to 47% over two years, 55% over three years, and 62% over four years. Females were more likely to fill an antibiotic prescription than males, as were residents of South Central region states compared to other regions (the North Central region was second, followed by the Northeast and the West.) The highest users were infants ages 0 to 2 years.

Not only was the probability of patients filling an antibiotic prescription remarkably high, reaching 47% at two years and 62% at four years, it was not homogenous throughout the enrollees. Thus, while approximately one-third filled prescriptions during any one year, another one-third never did so.

■ COMMENTARY

The number of prescriptions for antibiotics in the United States is remarkable, and this is

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[INSIDE]

Infectious Disease [ALERT]

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especially so in the southern region. This undoubted overuse, and especially the heterogeneity of use, reminds me of something mentioned in the 2005 report of a clonal outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) infections among players in the National Football League.[1] Examination of the 2002 pharmacy log for the team revealed that players received an average of 2.6 antibiotic prescriptions per year — a rate 10 times higher than age- and sex-matched individuals in the general population. At the same time, while approximately 60% of players reported receiving antibiotics during their 2003 season, 40% received no antibiotic at all.

Several groups have previously demonstrated the heterogeneity of antibiotic use in the United States based on, for example, geography.[2] They also found that extensive use, defined as many people receiving few prescriptions, and intense use, defined as a small number of individuals receiving many prescriptions, had different relationships to the prevalence of antibiotic resistance. Thus, they found that extensive use was associated more strongly with resistance than was intensive use, suggesting that the former could be a more effective focus of interventions. ■

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ABSTRACT & COMMENTARY

No Antibiotic Prescription Required

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Acquisition of antibiotics without a prescription can be easy in the United States.

SOURCE: Grigoryan L, Germanos G, Zoorob R, et al. Use of antibiotics without a prescription in the U.S. population: A scoping review. *Ann Intern Med* 2019 Jul 23. doi: 10.7326/M19-0505. [Epub ahead of print].

Grigoryan and colleagues performed a scoping review to assess the prevalence and factors influencing the use of antibiotics without a prescription in the United States. The purpose of a scoping review is to identify and map the available evidence at a time while the latter remains in flux.[1] As the evidence matures, a systematic review becomes more appropriate.

Only 31 of 17,422 screened articles met inclusion criteria for review. Venues where antibiotics were acquired included flea markets, pet stores, botanical stores, health food stores, and online sources. Additional sources were family and friends, markets or stores, leftover prescribed antibiotics, and other countries. Four populations were studied: patients or parents outside healthcare systems, those within healthcare systems, Hispanics/Latinos, and injection drug users. The prevalence of nonprescribed antibiotic use was highly heterogeneous, ranging from 1% to 68%, as was the intent to store an antibiotic for future use, which varied from 14% to 48%. Among patients in a primary care practice, 25% intended to use antibiotics without a prescription.

Factors that were reported to contribute to nonprescription antibiotic use were easy access to stores and markets that obtain antibiotics from outside the United States for under-the-counter sales, difficulties in accessing the healthcare system, costs and long waiting times associated with visits to clinicians, and transportation difficulties.

■ COMMENTARY

In 2002, a reporter for the *The New York Times* interviewed Marina Aguilera in her New York City West 135th Street apartment as she held a package of ampicillin tablets in her hand.[2] Ms. Aguilera, like many other Dominicans in her neighborhood, purchased them over-the-counter at her local bodega — no prescription needed. She said she took them for sore throats, earaches, chest pains, and bad colds, but she is doubtful that they are helpful in treating headaches.

The scoping review provides an estimate of the prevalence of the use of antibiotics absent a prescription and, more importantly, pointed to potential interventions to reduce nonprescription antibiotic use. Many of these undoubtedly apply in low- and middle-income countries in which evidence indicates that the high copays for drugs in the public sector actually may drive patients together with a requirement for prescriptions to settings where there is an incentive to provide such prescriptions.[3] The likelihood of antibiotic overuse in that circumstance is consistent with the investigators' finding that high drug copays are associated with a significantly increased prevalence of antibiotic resistance. ■

[The scoping review provides an estimate of the prevalence of the use of antibiotics absent a prescription and, more importantly, pointed to potential interventions to reduce nonprescription antibiotic use.]

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ABSTRACT & COMMENTARY

Prophylactic Antibiotics Significantly Reduce the Risk of Infection Following Operative Vaginal Delivery

By Richard R. Watkins, MD, MS, FACP, FIDSA

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

SYNOPSIS: In a multicenter, randomized clinical trial, researchers found that a single dose of intravenous amoxicillin/clavulanic acid significantly reduced the risk of infection following operative vaginal birth (forceps or vacuum extraction) compared to placebo (180 of 1,619 [11%] vs. 306 of 1,606 [19%], respectively; $P < 0.0001$).

SOURCE: Knight M, Chiocchia V, Partlett C, et al. Prophylactic antibiotics in the prevention of infection after operative vaginal delivery (ANODE): A multicentre randomised controlled trial. *Lancet* 2019;393:2395-2403.

Approximately one-third of births in the United States occur by cesarean delivery, a proportion that is widely criticized as too great. One potential way to reduce the number of cesarean deliveries is through the use of forceps or vacuum extraction, otherwise known as operative vaginal birth (OVB). However, it is estimated that 16% of women develop an infection following OVB. Despite this risk, routine antibiotic prophylaxis is not recommended by most experts, including the World Health Organization. Therefore, Knight et al investigated whether prophylactic antibiotics would lead to fewer infections up to six weeks following OVB.

The study was a randomized, placebo-controlled trial conducted at 27 centers in the United Kingdom. Women who had undergone OVB at 36 weeks or greater gestation were randomly assigned 1:1 to receive either a single dose of IV amoxicillin/clavulanic acid or placebo within six hours after delivery. The authors excluded patients who had a clinical indication for ongoing antibiotic administration postpartum or who had a history of penicillin allergy or anaphylaxis to another beta-lactam agent. The primary outcome was confirmed or suspected maternal infection within six weeks of the delivery. Infection was defined as a new prescription for antibiotics for perineal wound-related infection, endometriosis, urinary tract infection with systemic features (i.e., pyelonephritis or sepsis), or other systemic infection.

[At six weeks postpartum, the women who had received the antibiotic used fewer healthcare resources compared to those who had received placebo.]

There were 1,715 women randomized to the antibiotic group and 1,705 in the placebo group. Most of the births occurred using forceps (65%), while 35% were by vacuum extraction. The majority of the women (89%) underwent an episiotomy. The median time to receiving the antibiotic was 3.2 hours after delivery, and the median time to receiving the the placebo was 3.1 hours. Significantly fewer women randomized to the antibiotic group developed a confirmed or suspected infection (11%) compared to the placebo group (19%) (relative risk [RR], 0.58; 95% confidence interval (CI), 0.49-0.69; $P < 0.0001$). At six weeks after delivery, significantly more women in the antibiotic group reported less perineal pain, less use of pain medications, and less wound breakdown. There was no difference between the groups in the proportion of women who were breastfeeding, the reported dyspareunia, the length of hospital stay until discharge, the number of re-admissions, or the overall quality of life.

One woman in the placebo group reported a rash, and two women in the antibiotic group reported other allergic reactions, one of which was a serious adverse event. None of the women experienced anaphylaxis during the study. In a post-hoc analysis, the method of OVB did not have any impact on the primary outcome. Finally, at six weeks postpartum, the women who had received the antibiotic used fewer healthcare resources compared to those who had received placebo.

■ COMMENTARY

The study by Knight et al showed multiple benefits from a single dose of IV amoxicillin/clavulanic acid administered within six hours of OVB. Although there is never a convenient time for a patient to get an infection, certainly this is true for a mother dealing with a newborn. Indeed, a painful and infected perineum makes it very uncomfortable to sit and breastfeed. The decreased rate of infections in the antibiotic group, coupled with the low rate of adverse drug events, is compelling and may lead to changes in current guidelines and clinical practice.

OVB has been advocated by some experts as a way to decrease the number of cesarean deliveries. One drawback of OVB in the present study was that 89% of the women required an episiotomy. For many years, an episiotomy was believed to help prevent more extensive vaginal tearing during childbirth and to heal better than a natural tear. The procedure also was thought to help preserve the muscular and connective tissue support of the pelvic floor. However, research from the 1970s and 1980s disproved these assumptions, leading to a decline in the episiotomy rate from approximately 70% of all vaginal births to approximately 20% by 2000. Episiotomies carry an increased rate of infection, and the results from the study by Knight et al lend support to prescribing antibiotics in these cases.

The study had a few limitations. It was performed in a high-income setting, so the results might not be generalizable to low-income settings for which the rate of infection might be different. IV amoxicillin/clavulanic acid is not available in other countries, such as the United States, although IV ampicillin/sulbactam is similar and should cover the same spectrum of pathogens. Finally, patients with severe allergies were excluded and may have benefited from a different class of antibiotic.

Despite the strength of the findings, several unanswered questions remain. Does a single oral dose of amoxicillin/clavulanate work as well as IV amoxicillin/clavulanic acid? Is a single dose optimal or should multiple doses be prescribed? Would other antibiotics also be effective, such as for patients who are allergic to penicillin? Should an antibiotic be given prophylactically if OVB is anticipated? Should the antibiotic be given sooner than six hours after birth? Additional investigation is needed to clarify these and other issues. Until further investigation is done, no further evidence-based recommendations can be offered. ■

ABSTRACT & COMMENTARY

Mycobacterium chimaera Granulomatous Encephalitis

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Lau and colleagues describe a novel infectious problem — diffuse granulomatous encephalitis due to *Mycobacterium chimaera* infection occurring after cardiac surgery.

SOURCE: Lau D, Cooper R, Chen J, et al. *Mycobacterium chimaera* encephalitis post-cardiac surgery: A new syndrome. *Clin Infect Dis* 2019 Jun 18. doi: 10.1093/cid/ciz497. [Epub ahead of print].

Lau and colleagues at the University of Alberta described three patients who developed diffuse granulomatous encephalitis due to disseminated *Mycobacterium chimaera* infection that occurred after cardiac surgery, presumably as the result of contamination from a heater-cooler system used during cardiopulmonary bypass.

Two patients each presented 15 months after cardiac surgery with constitutional symptoms, pancytopenia, lymphadenopathy, hypercalcemia, and choroidal nodules. *M. chimaera* was recovered in blood cultures from each patient, and therapy was initiated with azithromycin, rifabutin, ethambutol, and amikacin. Clearance of mycobacteremia occurred after 18 days and 24 days, respectively. Nonetheless, each patient experienced progressive and profound neurocognitive decline. Brain imaging was limited because of the presence of acute kidney injury, precluding the use of contrast agents. PET-CT showed no brain abnormalities, while non-contrast MRI performed in one patient showed T2 white matter hyperintensities without restricted diffusion. Both patients died.

Although the third patient developed constitutional symptoms just four months after aortic valve and root replacement, the etiology was not determined until 12 months later with the recovery of *M. chimaera* in blood cultures. By the time of diagnosis, the patient was bed-bound. Choroidal nodules were detected on ophthalmological examination. Four-drug treatment was initiated with subsequent clearance of bacteremia, but with continued neurocognitive decline. Non-contrast MRI revealed multifocal T2 white matter hyperintensities, while gadolinium administration allowed detection of punctate lesions that enhanced and were thought to be consistent with granulomas. Despite the use of additional antimycobacterial agents, the patient experienced progressive neurological decline, leading to death.

Postmortem examination performed on all three patients revealed granulomatous inflammation in the brain as well as in multiple other organs and the cardiac bioprostheses. However, no brain specimens were submitted for culture. In the third patient, multiple acid fast bacilli were visualized in temporal lobe tissue.

■ COMMENTARY

The authors of a recently published review pointed out that two characteristics of *M. chimaera* infections after cardiopulmonary bypass are their prolonged latency and their high mortality, characteristics also found with other outbreaks of infection with nontuberculous mycobacteria.[1] Some delay in diagnosis is inevitable, even when the diagnosis is suspected, because the organism takes two to eight weeks before it becomes detectable in blood cultures. The investigators also pointed out that chorioretinal lesions are frequently observed, as they were in the three patients described by Lau and colleagues, and recommended that all patients with suspected post-bypass *M. chimaera* infection undergo a careful retinal examination.

Treatment of *M. chimaera* infections generally has been based on regimens that are used in patients with infection with the very closely related *Mycobacterium avium* or *Mycobacterium intracellulare*. A recent study performed in Ireland found that none of 88 clinical and environmental *M. chimaera* isolates tested were resistant to clarithromycin or amikacin, while resistance to moxifloxacin and linezolid was detected in 52% and 39%, respectively, tested using Clinical Laboratory Standards Institute (CLSI) breakpoints.[2] Using tentative epidemiological cutoffs,

[Clinicians must remain alert to the possibility of late-onset *M. chimaera* infections in patients who have previously undergone cardiopulmonary bypass.]

1% were resistant to streptomycin and 2% to rifabutin, while rifampicin and ethambutol resistance was detected in 18% and 11%, respectively, based on their pharmacokinetics and pharmacodynamics. Of note, the CDC recommends that only clarithromycin susceptibility testing be performed (many would also test amikacin) because of a lack of data demonstrating a correlation between presumed susceptibility or resistance and clinical therapeutic outcomes.

Meanwhile, clinicians must remain alert to the possibility of late-onset *M. chimaera* infections in patients who have previously undergone cardiopulmonary bypass. Among the syndromic presentations of which they must be aware that can be caused by this organism is a chronic progressive granulomatous encephalitis described by Lau et al. ■

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ABSTRACT & COMMENTARY

HIV Prevention Strategies in Africa

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Several strategies have proven effective in reducing transmission of HIV, including access to confidential testing and counseling, early introduction of HIV medications, and male circumcision. Three new studies show what actually affects the spread of HIV in populations, and results vary between different African settings.

SOURCES: Makhema J, Wirth KE, Pretorius Holme M, et al. Universal testing, expanded treatment, and incidence of HIV infection in Botswana. *N Engl J Med* 2019;381:230-242.

Havlir DV, Balzer LB, Charlebois ED, et al. HIV testing and treatment with the use of a community health approach in rural Africa. *N Engl J Med* 2019;381:219-229.

Hayes RJ, Donnell D, Floyd S, et al; HPTN 071 (PopART) Study Team. Effect of universal testing and treatment on HIV incidence – HPTN 071 (PopART). *N Engl J Med* 2019;381:207-218.

Last month, a single issue of the *New England Journal of Medicine* included three articles from different groups in Africa that dealt with population-level means of reducing the incidence and spread of HIV infection. Outcomes varied, presumably related to background situations in the different study settings.

Makhema and colleagues randomized villages in Botswana to receive either standard care or additional interventions, including HIV testing and counseling, ready access to care, antiretroviral treatment started earlier (higher CD4 counts) than is typical, and availability of male circumcision. The study ran from 2013 to 2018, and individual participants were followed for 29 months. In 2016, all HIV-positive patients in the country were offered antiretroviral treatment, whether the viral load was elevated or not and whether the CD4 count was low or not. Thirty villages were included, and approximately 20% of households were invited to participate; 12,600 individual participants were included.

At study entry, 29% of participants were HIV positive, and 83% of those knew they were HIV positive. Of those who knew they were positive, 87% were on antiretroviral treatment, and 96% of those had achieved viral suppression. A total of 4,487 HIV-negative individuals were enrolled and followed to

determine HIV incidence with and without the added testing and treatment interventions. The annualized incidence of contracting HIV infection was 0.59% in the intervention group and 0.92% in the standard care (control) group ($P = 0.05$). HIV viral suppression was greater in the intervention group, as was the use of circumcision (from 30% at baseline to 40% with the intervention). Declining incidence of HIV infection and increasing viral suppression in infected individuals suggest that the interventions were significantly beneficial. The authors suspected that recruiting infected individuals in communities in socially accepted manners that facilitated treatment initiation made the difference.

Havlir and colleagues studied 32 rural communities in Uganda and Kenya. They offered routine/standard care to the "control" villages. They provided annual HIV testing, access to antiretroviral therapy for all infected individuals, and patient-centered care to the intervention communities. Their study began in 2013 and went through 2017. Follow-up of patients continued for three years. After 2015, universal antiretroviral treatment became available in control communities as well. Baseline HIV positivity varied from 4% to 19% in the three geographic regions where the study took place. Circumcision rates in men varied from 14% to 46% in the various regions included. Approximately 150,000 individuals were included. With the intervention, HIV-positive individuals were more likely to begin antiretroviral treatment and were more likely to achieve viral suppression (79% in the treatment group vs. 68% in the control communities). The three-year cumulative incidence of new HIV infection in the intervention group was 0.77%, as compared to 0.81% in the control group (not statistically significantly different). However, death was less common among HIV-positive individuals in the intervention group than in the control group.

Hayes and colleagues randomized 21 urban and peri-urban communities in Zambia and South Africa to either standard treatment (control group) or to a bundle of interventions (home HIV testing, linkage to HIV care, and personalized treatment follow-up) with or without universal antiretroviral treatment for all HIV-positive individuals. The study was conducted from 2013 through 2018. In the intervention groups, uncircumcised males were encouraged to seek circumcision, and pregnant women were advised to seek prenatal care. Starting in 2016, universal antiretroviral treatment was provided for all HIV-positive individuals, regardless of initial treatment group. A total of 48,301 individuals were enrolled in the study. Baseline HIV positivity was 21-22% in the three groups. At baseline, a bit less than half of HIV-positive individuals had achieved viral suppression. The incidence of new HIV infections was 30% lower in the treatment groups than in the control group. Interestingly, universal antiretroviral treatment did not add benefit over standard treatment, perhaps because of limited rates of viral suppression.

■ COMMENTARY

Each of these three studies demonstrated favorable results with multifaceted HIV prevention interventions. Despite demographic differences (different countries and cultures, urban vs. rural settings, higher vs. lower baseline HIV incidence), the combination of personalized care (encouraging confidential testing and facilitating treatment adherence) and antiretroviral treatment reduced the spread of infection and/or reduced the death rate in the various intervention groups.

Single interventions are less likely than are multifaceted interventions to reduce the spread of HIV. It is likely that the personalized attention (and encouragement toward reducing risky behaviors and improving medication adherence) was a key part in the favorable outcomes of these studies. Simply making medication available in pharmacies likely is much less effective than connecting medication availability with trusted health workers who provide patient-centered care in the context of multidisciplinary teams. An editorial accompanying the three *New England Journal of Medicine* papers emphasized the challenge of overcoming denial of HIV risk and the stigma of seeking care.[1]

[Despite demographic differences ... the combination of personalized care and antiretroviral treatment reduced the spread of infection and/or reduced the death rate in the various intervention groups.]

The need for trusted multidisciplinary care was reiterated the following week in the *New England Journal of Medicine*'s report about the ongoing Ebola outbreak in the Democratic Republic of Congo. Despite great gains, the incidence of Ebola started rising in February 2019 related to militia attacks on medical workers and growing distrust of the Ebola response teams.[2] False beliefs and fear can compromise medical efforts — whether they are related to the stigma of seeking HIV care or anger at Ebola vaccination teams.

One of the three HIV studies included advice about condom use. Another group of authors speculated that their explanation about universal treatment might have prompted study participants to show less restraint with new sexual contacts. The urban study pointed out the risk of migration of sexual contacts into and out of the study population. Personal behaviors and population mixing still can affect the results of attempts at population-based interventions.

The three HIV studies remind us of the importance of ongoing attention to HIV infection, since prevalence rates were up to 29% in one study area. And they remind us of the value of multidisciplinary teams providing multifaceted interventions to combat complex problems on a population level. ■

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ABSTRACT & COMMENTARY

CRP and Reduction of Antibiotic Use in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Point-of-care C-reactive protein testing can safely and effectively reduce antibiotic use in patients with acute exacerbations of chronic obstructive lung disease.

SOURCE: Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med* 2019;381:111-120.

Butler and colleagues examined the value of point-of-care C-reactive protein (CRP) testing to guide the need for antibiotic therapy in patients > 40 years of age with exacerbations of chronic obstructive pulmonary disease (COPD). To this end, they performed a randomized, open-label, controlled trial at 86 general practices in the United Kingdom. An exacerbation was defined as the presence of at least one of the widely used Anthonisen criteria: increased breathlessness, increased sputum volume, or increased sputum purulence. Subjects were randomized to usual care alone or usual care guided by CRP testing.

Participating clinicians received guidance for the interpretation of CRP results, indicating that antibiotic therapy was unlikely to be beneficial and ordinarily should not be prescribed if the value was < 20 mg/L, that it was likely to be beneficial if CRP was > 40 mg/L, and that it may be beneficial for those with intermediate levels, particularly if purulent sputum is present. The clinicians also were told that general clinical factors should be taken into account in decisions about antibiotic use.

The median CRP in the 317 patients randomized to the usual care plus CRP group and in whom

the test was performed was 6 mg//L, with 241 (76.0%) < 20 mg/L, 38 (12.0%) were 20-40 mg/L, and 38 (12.0%) were > 40 mg/L. At the initial consultation, antibiotics were prescribed to 47.7% and 69.7% in the CRP-guided and usual care alone groups, respectively (adjusted odds ratio, 0.31; 95% confidence interval [CI], 0.21-0.45). Overall antibiotic use in the four weeks after randomization (a co-primary endpoint) was reported by 57.0% in the CRP group, while it was 77.4% in the usual care group (adjusted odds ratio, 0.31; 95% CI, 0.20-0.47). At two weeks, the adjusted mean difference in the Clinical COPD Questionnaire score was -0.19 points (two-sided 90% CI, -0.33 to -0.05) in favor of the group guided by CRP testing, demonstrating, at a minimum, a lack of harm from this strategy.

■ COMMENTARY

Given the frequency of COPD occurrence, it is somewhat disturbing that our knowledge of the role of antibiotics in the management of exacerbations seems so limited and confused. As stated in Murray and Nadel's *Textbook of Respiratory Medicine*, "The use of antibiotics for exacerbations of COPD is somewhat controversial."

A recent Cochrane review, while agreeing that antibiotics are beneficial in patients who require intensive care admission, concluded that the effects of antibiotic therapy on other inpatients and on outpatients are small and "inconsistent for some outcomes (treatment failure) and absent for other outcomes (mortality, length of hospital stay)."[1]

In previous studies, researchers have examined the use of procalcitonin measurements in these exacerbations. Thus, a meta-analysis concluded that although the quality of the available evidence was only low to moderate due to methodological limitations and small populations, the use of procalcitonin-based protocols was associated with reduced antibiotic use.[2] On the other hand, a retrospective study of 203,177 patients hospitalized for management of COPD exacerbations concluded that procalcitonin measurement had little effect on decisions to initiate antibiotic therapy.[3] Researchers also have studied the use of a comprehensive viral respiratory panel for which there is evidence of potential benefit.[4]

The study by Butler and colleagues is welcome in shedding a light on this subject. Their work demonstrates that point-of-care CRP testing can be used effectively and safely to reduce antibiotic use in patients with acute exacerbations of COPD. Further exploration of predictors of antibiotic benefit and work aimed at improving prescribers' behavior must follow. The issue of the importance of altering prescriber behavior is evident in the study by Butler et al since almost half of patients with low CRP levels nonetheless received prescriptions for antibiotic therapy. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Should We Be Looking for ESBL?

SOURCE: Zahar JR, Blot S, Nordmann P, et al. Screening for intestinal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in critically ill patients: Expected benefits and evidence-based controversies. *Clin Infect Dis* 2019;68:2125-2130.

Prevention strategies are necessary to limit transmission of multidrug-resistant organisms (MDRO) in the hospital, especially in high-risk settings. Identification of carriers of extended-spectrum beta-lactamase (ESBL)-producing organisms via active surveillance, and contact isolation of positives, has been recommended for certain high-risk groups (e.g., ICU).

To thwart transmission of MDRO/extensively drug-resistant organisms (XDRO), our facility implemented routine ESBL surveillance in high-risk individuals in 2015, using perirectal swab

specimens and chromogenic agar culture technique. High-risk groups were considered to be admissions from long-term care facilities or an outside facility and patients on hemodialysis. From 2015 to 2017, the prevalence of ESBL carriage steadily increased, up to 14% in patients admitted from skilled nursing facilities (SNF). This meant that many otherwise asymptomatic older SNF patients, who were simply ESBL carriers, now required contact isolation. However, in those who were critically ill or septic, identification of ESBL carriage provided the advantage of preemptively employing the use of a carbapenem as clinically appropriate. One other important advantage to the active surveillance program was that during the three years of surveillance, only one patient was found to have "hospital-onset" ESBL not previously identified on admission. Thus, the program successfully kept the "transmission rates" of MDRO remarkably low.

Ironically, as the prevalence of ESBL colonization in our screening population increased, so did the cost of the program. By 2017, the estimated the annual cost of ESBL surveillance was approximately $250,000 (based on laboratory costs and not the cost of isolation supplies). This was in addition to active surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA; required by California regulation), *Clostridioides difficile*, and carbapenem-resistant Enterobacteriaceae (CRE) (recommended by the CDC) in select patients and travelers. The burden to the micro lab was just too much. Thus, in 2017, the infection control team made the difficult decision to abandon ESBL screening. Our disappointment was mollified only by the knowledge that approximately half of such patients required isolation for other reasons (MRSA/*C. difficile*), since double and triple colonization was not uncommon.

The debate about active ESBL surveillance continues. These authors argued that enforcement of universal precautions and improved hand hygiene makes more sense and ultimately is likely to be a more effective strategy than "search-and isolate," for the following reasons:

- The cost of routine active surveillance is not insignificant (as above) and poses a considerable burden to the micro lab; such surveillance costs are not reimbursable by insurance or Medicare.
- The lag in retrieving results (which may be up to 48-72 hours) means that either individuals being screened must be isolated pending results — or those with ESBL colonization are not isolated initially.
- The frequency of false-negative surveillance samples may be as high as 25%, depending on technique and detectable levels of fecal colonization.
- Surveillance focused only on ESBL does not detect other MDRO, such as carbapenem-resistant pseudomonas or MDR-*Acinetobacter baumanii* — two important hospital pathogens.
- Defining high-risk groups for screening may overlook those without recognized risk factors (e.g., prior SNF stay or prior travel or residence in Asia or a developing country).
- Limited studies suggest negligible transmission from asymptomatic carriers of ESBL-containing organisms in the acute care setting.
- The "human" cost of isolation is not insignificant, from the donning and doffing of gowns and gloves, to the occasional distress of patients being screened with rectal swabs, and then the challenging explanation of why "Grannie is in isolation." We have had some families so totally overreact that they have prevented contact with the grandchildren.
- The authors argued that rather than being a useful clinical result, the detection of ESBL in perirectal swabs may contribute to the overuse of carbapenems. The authors argued that ESBL transmission in the critical care setting occurs "rarely" when hand hygiene compliance is maximized. With improved hand hygiene compliance, the authors of one study found little added value to the implementation of contact isolation on acquisition rates of Enterobacteriaceae in the ICU. Further, the use of single rooms and daily chlorhexidine body bathing also may reduce the risk of acquisition of potential pathogens.

[With improved hand hygiene compliance, the authors of one study found little added value to the implementation of contact isolation on acquisition rates of Enterobacteriaceae in the ICU.]

The balance in favor of active surveillance for MDRO could shift if more rapid and reliable (and cheaper, less labor-intensive) diagnostic tests were available. But, I wondered, if the risk of transmission of ESBL and other MDRO from asymptomatic individuals with stool carriage is ostensibly so low, as these authors argued, why is such a remarkable increase in ESBL colonization being observed in our local SNF population? ■

Close the Door to That OR!

SOURCE: Roth JA, Juchler F, Dangel M, et al. Frequent door openings during cardiac surgery are associated with increased risk for surgical site infection: A prospective observational study. *Clin Infect Dis* 2019;69:290-294.

As the battle for reduction in surgical site infection (SSI) wages (and everyone is pointing fingers at everything and each other), one glaring finding in recent audits of surgical orthopedic and spine cases was the number of times the doors to the OR were opened during the case. For one case alone, we counted 34 internal door openings by surgeons and staff, and that didn't count the three manufacturer representatives present. Occasionally the door was left open — a clear violation of OR policy.

> [In both univariate and multivariate analyses, an increased frequency of door openings was associated with an increased risk of SSI.]

Preliminary studies suggest that OR door openings during surgery may contribute to SSI. Door openings clearly increase the particulate matter in air, and are known to raise bacterial colony counts in the air. From 2016 to 2017, these Swiss authors performed a prospective evaluation of SSI in 688 consecutive cardiac surgery cases, counting the number of times the internal and external OR doors were opened. The doors to two designated ORs were equipped with automated door counters. SSI infection was defined as superficial or deep infection occurring within 30 days of the procedure. (For purposes of defining SSI in the United States, a window of 90 days is required for any procedure with a device, such as a valve.)

During the 17-month study, 688 cardiac surgeries were performed. Twenty-four (3.5%) SSIs occurred within 30 days of the procedure, including one case of mediastinitis, 12 cases of deep sternal infection, and 11 cases of superficial sternal infections. Patients in the non-SSI group were similar in age (approximately 70 years of age) to patients in the SSI group. However, compared with the non-SSI group, the SSI group included more women (24% vs. 41%), the OR times were slightly longer in the SSI group (226 minutes vs. 256 minutes), and procedures included fewer coronary artery bypass grafts (79% vs. 55%) and more valve surgeries (29% vs. 35%) performed in the SSI group. Compared with the non-SSI group, with 17.4 door openings per hour, the SSI group had 19.7 door openings per hour.

A total of 301,594 door openings were logged. Of these, 87,676 occurred between incision and skin closure (that is approximately 127 door openings per case). In both univariate and multivariate analyses, an increased frequency of door openings was associated with an increased risk of SSI (95% confidence interval [CI], 1.11-1.95; $P = 0.007$). When the analysis was limited to internal door openings only, the risk of SSI was greater (95% CI, 1.24-3.2; $P = 0.005$). No association with SSI was found with external door openings.

Studies in the United States have raised similar concerns, and there is simply no industry standard. In one study of orthopedic surgeries at Johns Hopkins, the OR door was opened on average every 2.5 minutes, for a total of 10 minutes of open door during an average 90-minute case. Another study of orthopedic surgery in Detroit measured 13.4 open doors per case. In one study, half of door openings were by nursing staff, 24% by anesthesia, and 13% by orthopedist staff. I am told the prime reason for nursing traffic in and out of the OR at our facility is the union requirement for breaks and shift change. We also have observed an increase in manufacturer representatives present, especially with cases requiring complex technical equipment or devices. The question remains, how can OR traffic be limited? ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding HIV infections in Africa?

a. HIV infection persists in both urban and rural areas.

b. HIV infection is nearly resolved.

c. HIV infection is easily treated with available medications.

d. HIV infection requires management in urban medical centers.

2. Which of the following is correct regarding point-of-care C-reactive protein (CRP) testing in patients with acute exacerbations of chronic obstructive pulmonary disease?

a. Withholding antibiotics based on a low CRP level (< 20 mg/L) is associated with an increased risk of subsequent hospitalization.

b. Its measurement is associated with an increased use of antibiotics.

c. Its measurement is associated with reduced antibiotic use.

d. Withholding antibiotics based on a low CRP level is associated with a subsequent worse Clinical COPD Questionnaire score.

3. Which of the following is correct regarding prophylaxis with amoxicillin/clavulanic acid in women undergoing vaginal delivery?

a. Its use has been demonstrated to reduce infections in women with both operative and nonoperative vaginal deliveries.

b. Its use has been demonstrated to reduce infections in women undergoing vacuum or forceps delivery.

c. To reduce infections, it must be administered within six hours prior to delivery.

d. To reduce infections, a total of at least six doses must be given.

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.