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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Azithromycin Saves Lives 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: Approximately 200,000 preschool-aged children in communities in Malawi, Niger, and Tanzania were treated twice yearly with either azithromycin or placebo. Communities in which azithromycin was provided had 13.5% less all-cause mortality than did placebo-treated communities. In children 1 to 5 months of age, the mortality was 25% lower with azithromycin than with placebo.

SOURCE: Keenan JD, Bailey RL, West SK, et al. Azithromycin to reduce childhood mortality in sub-Saharan Africa. *N Engl J Med* 2018;378:1583-1592.

Azithromycin has been effective in reducing ocular morbidity due to trachoma, and large trachoma studies have suggested that widespread use of azithromycin also might be effective in preventing pneumonia, diarrhea, and malaria. Thus, the investigators sought to rigorously determine if preventive azithromycin might be effective in reducing mortality in African children.

Researchers undertook a prospective study in three countries of sub-Saharan Africa — Niger in West Africa, Tanzania in East Africa, and Malawi in South Africa. Realizing that reducing transmissible microbial colonization in one person might affect neighbors, the investigators randomized the study at a community level. Communities were assigned to either azithromycin (a single 20 mg/kg/dose every six months over three years) or placebo treatment of children 1 to 59 months of age. Overall, 1,533 communities were included, with 190,238 children involved at the beginning of the study (with others added or removed later as they grew in or out of the age range or moved in or out of the community).

Adverse effects of treatment were reported rarely and could not be tied causally to the use of azithromycin. Shifts in antibiotic resistance patterns were not evaluated.

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The rate of childhood death varied markedly by country at baseline (9.1 per 1,000 person-years in Malawi, 22.5 in Niger, and 5.4 in Tanzania) and after the study. Overall, mortality was 13.5% lower in communities that received azithromycin than in placebo-treated communities. In each of the three countries, mortality was lower with azithromycin treatment — 5.7% lower in Malawi, 18.2% lower in Niger, and 3.4% lower in Tanzania. Children 1 to 5 months of age were at the greatest risk of dying but also had the greatest reduction in mortality with azithromycin treatment (24.9%).

Verbal autopsies done after a randomized 250 of the deaths suggested that malaria accounted for 41% of deaths, diarrhea for 18%, and pneumonia for 12%. Malaria was a more common cause of death in Niger, and pneumonia was relatively more common in Tanzania.

The authors wisely pointed out the risk of hypertrophic pyloric stenosis when macrolides are used in young infants, and they reasonably cautioned about the development of antibiotic resistance when antibiotics are used widely in mass distribution campaigns. Nonetheless, they concluded that azithromycin was most effective in children who were 1 to 5 months of age and prevented one of four deaths that were expected among children of this age.

■ COMMENTARY

Millions of preschool-aged children die from infections in sub-Saharan Africa each year. Malaria caused by *Plasmodium falciparum*, pneumonia caused by *Streptococcus pneumoniae*, and diarrhea caused by enterotoxigenic *Escherichia coli* are common in Africa and potentially are preventable with the use of azithromycin.

Keenan and colleagues have performed a great service in showing that a community-wide treatment of 1- to 5-month-old children with a single dose of azithromycin every six months is associated with a significant reduction in childhood death.

The authors of this new paper carefully cautioned against generalizing these results to areas of varying mortality rates and varying causes of childhood mortality. They also noted that identifying and treating children in communities only once every six months means that some newborns would not be identified and could outgrow the window of greatest opportunity (1-5 months of age) before ever being identified and treated. However, individual treatment programs might miss some of the decreased contagiousness resulting from mass treatment programs.

It could be that we all will be advocating for prophylactic azithromycin for all infants in resource-limited areas of sub-Saharan Africa within a few years. However, there are lessons from recent history that remind us to be cautious about widespread implementation of new preventive techniques. We can learn from experience with a previous rotavirus vaccine, a new malaria vaccine, and deworming programs.

[There are lessons from recent history that remind us to be cautious about widespread implementation of new preventive techniques.]

Rotavirus is a common cause of childhood diarrhea around the world, and rotavirus vaccines can reduce the morbidity and mortality of rotavirus diarrhea. After licensure, a previous rotavirus vaccine was found to be associated with an increased risk of intussusception in the United States.[1] Use of that vaccine was halted, and new vaccines were developed. Fortunately, new rotavirus vaccines are not associated with an increased risk of intussusception in Africa.[1] Whenever a new product or treatment is used widely, ongoing surveillance for potential complications is warranted.

Early results with a malaria vaccine showed 36% protection during four years

of follow-up.[2] Although not protecting a majority of children, this vaccine still could have prevented thousands of childhood deaths in Africa. However, follow-up to seven years showed that there was a rebound with more malaria subsequently in vaccine recipients.[2] Even widespread interventions that start well might have longer term negative effects that unfavorably counter-balance the early positive effects.

Intestinal parasite infections are related to undernutrition and poor school performance in resource-limited areas. The World Health Organization has advocated mass deworming in areas endemic for soil-transmitted helminths, and this intervention has been considered a cost-effective approach to improve attendance at school in countries where helminths are endemic.[3] Even though it is inexpensive for individuals (less than 50 cents per child), the overall cost around the world to implement deworming is approximately $276 million per year.[3]

A recent systematic review of studies involving more than 1 million subjects now has shown that mass deworming is associated with no improvement in weight gain, no improvement in cognition, and no improvement in school attendance.[3] Nonetheless, it is possible that deworming still might be useful for certain individuals in some population subgroups.

Keenan and colleagues have taken global child health forward significantly with their data showing decreased mortality in communities where asymptomatic young children were treated with azithromycin. As further studies are conducted and as other potential side effects are evaluated, it could be that azithromycin will indeed prevent a significant number of deaths in sub-Saharan Africa without dangerous adverse effects. However, caution and subsequent surveillance are important when widespread interventions are considered and implemented. ■

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ABSTRACT & COMMENTARY

Antibiotic Cycling Is Not Useful for Reducing Antibiotic-resistant Gram-negative Pathogens in Patients Admitted to Intensive Care Units

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

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Dr. Watkins reports that he has received research support from Allergan.

SYNOPSIS: A randomized study that included eight intensive care units in Europe found no reduction in mortality or carriage of antibiotic-resistant gram-negative pathogens with antibiotic cycling compared to antibiotic mixing.

SOURCE: van Duijn PJ, Verbrugghe W, Jorens PG, et al. The effects of antibiotic cycling and mixing on antibiotic resistance in intensive care units: A cluster-randomised crossover trial. *Lancet Infect Dis* 2018;18:401-409.

Preserving the effectiveness of antibiotics is crucial for maintaining the tremendous advances in medicine that have occurred over the past century. Two strategies that aim to protect antibiotics include antibiotic cycling, defined as prescribing one drug during a set period followed by a rotation to another drug for another set period, and antibiotic mixing, in which a drug from an alternative class is chosen for each consecutive patient. van Duijn and colleagues sought to determine which of these strategies is better for reducing carriage of antibiotic-resistant gram-negative bacteria in patients in intensive care units (ICUs).

The study was multicenter with a cluster-randomized, crossover design including medical, surgical, or mixed ICUs from several European

countries. Following a four-month baseline period, ICUs were randomized to two nine-month periods of intervention (cycling or mixing) separated by a washout period of one month. The antibiotics used covered gram-negative pathogens and included cephalosporins, piperacillin-tazobactam, and carbapenems, but the selection of medication was left up to the treating physician. With mixing, the empiric treatment choice changed with each consecutive treatment course. With cycling, the preferred treatment was changed every six weeks. Investigators measured the unit-wide prevalence of antibiotic-resistant gram-negative bacteria by monthly screening cultures of the oropharynx and perineum of all patients in the ICU.

Antibiotic resistance was defined as carriage of *Enterobacteriaceae* harboring ESBL genes, phenotypical resistance to piperacillin-tazobactam, or carbapenemases for *Acinetobacter* spp. and *Pseudomonas aeruginosa*. The primary endpoint was the change in the prevalence unit wide of carriage, which could be from either culture site. Notably, it was possible for a single patient to be screened multiple times if they had a prolonged ICU stay. Secondary endpoints included mortality and length of ICU stay.

Three ICUs were assigned to the mixing approach followed by cycling and five were assigned to the cycling approach followed by mixing. Carbapenems were the most frequently used agents. During cycling, the prevalence of antibiotic-resistant gram-negative bacteria was 23%; during mixing, it was 22% (P = 0.64). There were no significant differences in the prevalence for specific bacterial species. The study antibiotics accounted for 42% of antibiotics used in the cycling group and 43% in the mixing group. In the ICU, mortality was 11% at baseline, 11% during cycling, and 12% during mixing (P = 0.38). Finally, there was no difference in the length of ICU stay between the mixing and cycling groups.

The researchers noted two major deviations from protocol. One involved an ICU in which the swabs were not collected during the final three months of the study, and the data from this period were excluded from the analysis. The other occurred when an outbreak of carbapenem-resistant *Klebsiella pneumoniae* made it impossible to adhere to the study protocol. Therefore, the investigators prolonged the washout period until the outbreak ended, which was five months, and antibiotic policy returned to what it had been before the outbreak.

■ COMMENTARY

The usefulness of antibiotic cycling and mixing has been debated for more than 20 years. The study by van Duijn and colleagues was well designed and strongly supports the idea that antibiotic cycling is not better than mixing for preventing the emergence and spread of antibiotic-resistant gram-negative bacteria. The investigators took care to limit confounding variables that could have influenced the results, such as the use of non-study antibiotics, infection control practices including hand hygiene, patient case mix, and changes to the proportion of patients who were colonized with antibiotic-resistant pathogens on admission to the ICU. Thus, since the study was high quality, it seems unlikely that another similarly designed trial would contradict these findings.

Given that the baseline mortality in the ICU did not change with cycling, it is reasonable to conclude that other antibiotic stewardship and infection control strategies should be given higher priority than either antibiotic cycling or mixing. For example, until an institution's hand hygiene compliance rate reaches 100% for all staff members, there is room for improvement. Perhaps just as important is the ongoing need to reduce the total volume of antibiotics prescribed in ICUs. This should lead to reduced selection pressure for the development of antibiotic-resistant bacteria.

The finding that carbapenems were the most frequently prescribed agents in the study is concerning given the ongoing spread of carbapenem-resistant pathogens, such as *Acinetobacter baumannii*. The study was conducted between June 2011 and February 2014 and it is unclear whether carbapenem use has changed in European ICUs since then.

One limitation of the study is that it was conducted in ICUs in five European countries, so the findings may not be applicable to other settings. Another is that it was underpowered to detect resistance at the species level. Finally, the sample size did not meet the initial value for calculating the main outcome, although the investigators attributed this to not taking into account the crossover design, which overestimated the sample size needed.

In summary, van Duijn and colleagues have demonstrated convincingly that antibiotic cycling does not reduce antibiotic-resistant gram-negative bacteria in the ICU setting. Therefore, antibiotic stewardship efforts should focus on different strategies to mitigate the spread of antibiotic-resistant pathogens and promote the judicious use of antibiotics. ■

ABSTRACT & COMMENTARY

PANDAS: Examining the Evidence for Treatment Options

By Jonathan P. Fischer, MPH, and Philip R. Fischer, MD, DTM&H

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Jonathan Fischer and Dr. Philip Fischer report no financial relationships relevant to this field of study.

SYNOPSIS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) is a proposed disorder first named in 1998 that has been the subject of controversy in the literature. Although the debate has waned somewhat in the United States, it remains a topic of discussion in many European medical journals. A recent systematic review found no evidence for antimicrobial or immunomodulatory treatment for this condition.

SOURCE: Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: A systematic review. *Neurosci Biobehav Rev* 2018;86: 51-65.

The diagnosis of PANDAS is based on a set of criteria first proposed in 1998.[1] These criteria include: obsessive compulsive disorder (OCD) and/or tic syndrome; prepubertal onset; abrupt onset with an episodic course; and association with group A streptococcus (GAS) infection (although this was not a uniformly required diagnostic criterion).

Discussion has been raised about these criteria, and other broader disease processes have been proposed that include non-OCD psychiatric symptoms, such as eating disorders, as well as other infectious etiologies beyond GAS. These alternative labels include Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders (PITAND), Childhood Acute Neuropsychiatric Symptoms (CANS), and Pediatric Acute Onset Neuropsychiatric Syndrome (PANS). Each term was proposed with its own set of diagnostic criteria, but they share common features, such as recurrent, episodic, and acute exacerbations of a psychiatric illness with a presumed autoimmune etiology. There is not yet consensus on these definitions, and the variety of terms and criteria perhaps have contributed to the complexity surrounding this disorder.

The proposed pathogenesis of PANDAS and its related disorders is similar to that of Sydenham's chorea. It is hypothesized that antibodies made in response to an infection cross-react in the basal ganglia and cortex to cause psychiatric disease. Because this proposed etiology differs significantly from typical psychiatric illnesses, a plethora of non-psychiatric treatments has been used to attempt to treat cases of suspected PANDAS. Last year, a consortium of clinicians and researchers released a series of practice guidelines, which recommend treating PANDAS and related disorders with standard psychiatric treatment, immunomodulatory therapy, and antibiotics.[2,3,4] The systematic review by Sigra and colleagues attempted to summarize the current data on treatment modalities, including those that are part of the new guidelines.

The review included studies that applied diagnostic criteria for any of the four proposed disorders (PANDAS, PITAND, PANS, and CANS). The authors found 12 papers that included diagnostic criteria and treatment or outcome data. There were four randomized controlled trials, one cross-over trial, two open trials, four observational studies, and one survey study. Sixty-five case series or case reports also were included.

Sigra et al summarized the findings of each of these studies. Three treatment studies that evaluated antibiotics were included. Data showed that antibiotics were not effective as prophylaxis against future symptom flares, but that they did reduce psychiatric symptoms during an acute flair using one measure (Clinical Global Impressions Scale-Severity of Illness), but not another (Children's Yale-Brown Obsessive Compulsive Scale). One treatment study evaluated plasma exchange therapy, which showed significant improvement over placebo at one year. Two treatment studies investigated intravenous immune globulin (IVIG) therapy. One study found that IVIG effectively reduced symptoms, while the other study found no effect over placebo.

There are ample studies about cognitive behavioral therapy (CBT) in typical OCD, but only two studies specifically about OCD in patients with a PANDAS,

PITAND, PANS, or CANS diagnosis. These two studies found that CBT effectively reduced symptoms. There also are observational studies, survey studies, case reports, and case series that described patients showing improved symptoms after receiving all of the above treatments as well as nonsteroidal anti-inflammatory drugs, corticosteroids, selective serotonin reuptake inhibitors (SSRIs), and no treatment.

It is interesting to note that the one case report that published the result of providing no treatment found that the patient experienced spontaneous remission. An observational study of tonsillectomy found no difference in symptom resolution compared to no treatment. Finally, there are a number of other treatments that have been described that were given in conjunction with the above treatments, and so were not studied individually. These included attention deficit hyperactivity disorder medication, antipsychotics, anxiolytics, mood stabilizers, probiotics, omega-3 fatty acid, vitamin D, homeopathy, gluten-free diet, sinus surgery, and rituximab.

However, it is important to note that 11 of the 12 papers included in the systematic review and all of the case reports were found to have a moderate or high risk for bias. Each paper was ranked on several criteria. All but one of the included papers had at least one major methodological issue, such as no control group, inadequate description of randomization, small sample size, reliance on self-reported data, administration of multiple treatments at once, or variable doses of medications given in a treatment arm. The only study that the review authors ranked as not having moderate or high risk for bias found that IVIG is not beneficial compared to placebo at reducing symptoms.[5]

The authors of this new systematic review concluded that, based on the poor quality of the available data, there is insufficient evidence favoring medication and immunomodulatory treatment of PANDAS. They highlighted the need for future studies on this topic. They also underscored the importance of reducing bias in future studies if reliable results are to be attained.

■ COMMENTARY

This systematic review highlights an interesting topic. Although PANDAS is rare (and its existence is not even fully established), this new systematic review provides interesting lessons that are broadly applicable. Two key questions are raised that provide insight to clinical practice more generally.

The first question that is sparked by this review is what should physicians do when there are insufficient data to guide decisions. Sometimes it is necessary to base treatment options on educated guesses using our understanding of pathophysiology, even when data are not available. On the other hand, it is important that clinicians "do no harm" and avoid exposing patients to unnecessary risks. This tension is especially salient in the case of PANDAS where, to date, there is no causal evidence that this disease exists.[6] As Sigra's review highlighted, there also are no high-quality data guiding what medications are most effective for patients with the symptoms attributed by some to PANDAS. Furthermore, many of the above treatments have known risks and side effects. Should clinicians treat aggressively when supportive data are lacking, or should they focus on doing no harm?

[Should clinicians treat aggressively when supportive data are lacking, or should they focus on doing no harm?]

Both possibilities have been argued in the literature. The fact that the review by Sigra et al included so many different experimental treatment methods is an indication that many clinicians have subscribed to the view of aggressive treatment. In fact, Sigra and colleagues ended their review by suggesting that in spite of the lack of available data, the guidelines to treat PANDAS with immunomodulatory therapy and antibiotics still should be followed.

Another commentary argued against this perspective.[6] Instead, treatments could include more holistic approaches to patient symptoms that, as one author stated, understand the child's symptoms from broader medical and psychosocial perspectives while considering tangible ways to overcome the problems.[7] Although patients may lose the theoretical benefit of the experimental therapies mentioned earlier, they also avoid the known harms associated with them. And, CBT, even without medication, does have proven effectiveness for children with OCD. For those with tic disorders, habit reversal therapy, with or without medication, also can be effective.

The second question arising from Sigra's review is how should studies with potential for bias be interpreted and applied. This review did an excellent job of scoring the included studies on the possible level of bias in their findings. Regarding PANDAS specifically, some have argued that the fact that it became a heated topic in the media and online forums perhaps has influenced researchers to conclude more readily that it is a distinct

illness from OCD.[8] (Even Swedo's original 1998 paper noted the limitation of using many patients from a patient support/advocacy group.[1]) Thus, it is even more important to maintain a critical eye when appraising medical literature on this topic to assess possible ways in which bias could have been introduced. The fact that the only study included in this review that was found

[In spite of these issues and the lack of consensus about the management of PANDAS, a full understanding of the current data can aid a clinician in providing relief to patients experiencing OCD and/or tics.]

to have a low level of bias also found no benefit over placebo for the studied treatment is telling. Could it be that methodologic issues influenced the other studies to find benefit in treatments that actually are not effective? Until more rigorous studies are conducted, this question may remain unanswered.

In spite of these issues and the lack of consensus about the management of PANDAS, a full understanding of the current data can aid a clinician in providing relief to patients experiencing OCD and/or tics. A recent editorial aptly indicated that the important point is not the physician's belief in the condition, but the physician's understanding that the patient experiences distress from the severe acute-onset neuropsychiatric symptoms.[7] Although some clinicians may disagree with the treatment recommendation of Sigra and colleagues, their systematic review provides a thorough understanding of the background of PANDAS and the current lack of evidence for medical treatment modalities. It also provides key lessons that can be applied to medical practice more broadly. ■

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ABSTRACT & COMMENTARY

Fosfomycin or Nitrofurantoin for Cystitis?

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: A single dose of fosfomycin was found to be less effective than five days of thrice-daily dosing of nitrofurantoin in the treatment of symptomatic lower urinary tract infection in women.

SOURCE: Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: A randomized clinical trial. *JAMA* 2018;319:1781-1789.

Huttner and colleagues performed an open-label, randomized clinical trial comparing single-dose (3,000 mg) fosfomycin (FOS) to thrice-daily dosing (100 mg per dose) of nitrofurantoin (NTF) for five days in the treatment of uncomplicated symptomatic lower urinary tract infection in women 18 years of

age and older. Patients had at least one symptom and positive leukocyte esterase or nitrite test on urinalysis.

Clinical response 28 days after completion of therapy (the primary outcome) was observed in 171 (70%) of the 244 NTF recipients and in only 139 (58%) of the patients assigned FOS; the 95% confidence interval (CI) for the difference was 4.1% to 21% with a *P* value of 0.004. A statistically significant difference also was observed at 14 days. The median duration of symptoms, however, was one day longer in NTF recipients (four days vs. three days), but this was not statistically significant.

A midstream urine specimen was obtained at study entry from 487 patients, and 377 (77%) were culture positive, defined as the presence of $\geq 10^3$ colony-forming units/mL of at least one organism. Of the positive cultures, 230 (61%) yielded *Escherichia coli*, while *Klebsiella* spp. and *Enterococcus* spp. each accounted for 7%, *Proteus* spp. for 5%, and *Enterobacter* spp. for 3%. The culture yielded mixed flora in 91 (18%).

The apparent superiority of NTF treatment at 28 days was even more pronounced among patients from whom *E. coli* was recovered, with 80 (78%) of 103 having a favorable clinical response compared to only 55 (50%) of 111 FOS recipients. The 95% CI for the 28% difference in response rates was 15% to 40% ($P < 0.001$). The overall microbiological response rate also favored NTF at both 14 days and 28 days, although the *P* value for the difference at each time point was only 0.04.

[The apparent superiority of NTF treatment at 28 days was even more pronounced among patients from whom *E. coli* was recovered.]

■ COMMENTARY

The results of this study appear to provide reasonable evidence that a single 3-gram dose of FOS is inferior to 100 mg thrice daily of NTF given for five days in uncomplicated cystitis in women. Consistent with this, as the authors noted, is recent evidence of significant inter-patient variability in achievable urine concentrations of FOS as well as evidence in an in vitro model of rapid regrowth of organisms after exposure to this antibiotic. However, several factors also must be considered, including at least two previous randomized trials that found no difference in outcome when comparing treatment with these two agents.

Furthermore, the open-label design used in this trial provides a potential for significant reporting bias in a study in which the primary outcome was subjective clinical response (although the seemingly paradoxically shorter duration of symptoms in FOS recipients, while not statistically significant, argues against this). Nonetheless, the microbiological response also favored the NTF regimen, particularly in the treatment of *E. coli* infections.

[The response rates in both treatment arms in this study were markedly lower than the 90% expected based on previous studies.]

As the authors also pointed out, the response rates in both treatment arms in this study were markedly lower than the 90% expected based on previous studies. One of the reasons for this could be that many of the patients included in the analysis did not, in fact, have bacterial urinary tract infections. Not all patients actually had a urine culture performed, and among those who did, approximately one in five yielded mixed flora and approximately two in five yielded an organism other than *E. coli* — both findings suggesting contamination of the specimen. Thus, a study comparing culture of midstream to catheterized urine specimens of premenopausal women with symptoms of cystitis found that the detection of *E. coli* in voided specimens was highly predictive of bladder bacteriuria, while detection of other organisms (enterococci and/or group B streptococci) was not.[1]

My conclusion is that a single dose of fosfomycin is, nonetheless, likely inferior to multiple daily doses of nitrofurantoin (and it should be noted that the Infectious Diseases Society of America recommendations for nitrofurantoin include only twice-daily dosing compared to the three times daily used in this study). It also is likely that FOS may be just as effective as NTF but that we have not yet determined the optimal way of dosing this drug, which is increasingly important as antibiotic resistance progresses. ■

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ABSTRACT & COMMENTARY

Another Reason to Get the Flu Shot Every Year

By Seema Gupta, MD, MSPH

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

SYNOPSIS: In a case-control study, among older adults, repeated vaccination for influenza was twice as effective in preventing severe influenza compared to non-severe influenza in patients who were admitted to the hospital.

SOURCE: Casado I, Dominguez A, Toledo D, et al. Repeated influenza vaccination for preventing severe and fatal influenza infection in older adults: A multicentre case-control study. *CMAJ* 2018;190:E3-E12.

Although seasonal influenza can cause mild to severe illness, serious illness, including hospitalization and death, occurs more frequently among older adults. In fact, it has been established that during most seasons, people ≥ 65 years of age bear the greatest burden of severe influenza. For instance, it has been estimated in recent years that 71-85% of seasonal influenza-related deaths have occurred in people ≥ 65 years of age and 54-70% of seasonal influenza-related hospitalizations have occurred among people in that age group.[1]

Based on data indicating that influenza vaccination programs produce a substantial health benefit in terms of averted cases, clinic visits, and hospitalizations, since 2010, the CDC and the CDC's Advisory Committee on Immunization Practices (ACIP) have recommended routine annual influenza vaccinations for all persons aged ≥ 6 months who do not have contraindications.[2] While vaccine effectiveness can vary each season, recent studies show that influenza vaccination reduces the risk of illness by 40-60% among the overall population during seasons when most circulating influenza viruses are well-matched to the vaccine. For persons ≥ 65 years of age, any age-appropriate inactivated influenza vaccine formulation (standard-dose or high-dose, trivalent or quadrivalent, unadjuvanted or adjuvanted) or recombinant influenza vaccines are acceptable options. ACIP makes no preferential recommendation for any specific vaccine product.[3]

With aging, several factors may interfere with a robust vaccine response in older adults, including the effects of immunosenescence and concomitant major chronic conditions. However, recent data demonstrate that vaccination might reduce the severity of illness among people who are vaccinated but still become ill, including reduced deaths, ICU admissions, ICU length of stay, and overall duration of hospitalization among hospitalized influenza patients, especially among patients ≥ 65 years of age.[4] But while influenza vaccination in previous seasons may retain some preventive effectiveness, there is a lack of data on the effectiveness of repeated influenza vaccination in averting severe influenza in the elderly.

Casado et al conducted a case-control study during the 2013-14 and 2014-15 influenza seasons to assess the effectiveness of vaccination in preventing influenza among community-dwelling adults (age ≥ 65 years) who were admitted to one of 20 hospitals in Spain for laboratory-confirmed influenza (130 inpatients with severe influenza and 598 inpatients with non-severe influenza). Cases were matched with inpatient controls by sex, age, hospital, and admission date. Researchers compared vaccinated patients with patients who were unvaccinated in the current and previous three seasons.

The adjusted effectiveness of vaccination in the current and any previous season was 31% (95% confidence interval [CI], 13-46%) in preventing admission to the hospital for nonsevere influenza, 74% (95% CI, 42-88%) in preventing admissions to the ICU, and 70% (95% CI, 34-87%) in preventing death. There was no significant effect on cases of severe influenza for vaccination in the current season only. Among inpatients with influenza, vaccination in the current and any previous season reduced the risk of severe outcomes (adjusted odds ratio, 0.45; 95% CI, 0.26-0.76).

■ COMMENTARY

The overall effect of seasonal influenza can vary from year to year and is based on several factors, including match of the vaccine strains to the circulating viruses. However, it is clear that influenza places a substantial burden on people's health and the U.S. economy each year. The CDC estimates that influenza has resulted in between 9.2 million and 35.6 million illnesses, between 140,000 and 710,000 hospitalizations, and between 12,000 and 56,000 deaths annually since 2010, with the elderly bearing the highest burden.[5]

Casado et al demonstrated that repeated vaccination for seasonal influenza in older adults may be highly effective in preventing severe and fatal infection caused by influenza. As this was observed mainly in patients who were vaccinated in both the current and previous seasons, the study clearly highlights another reason for annual influenza vaccination in older adults, thus reinforcing the existing ACIP recommendation. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

House Mice as Vectors?

SOURCE: Williams SH, Che X, Paulick A, et al. New York City house mice (*Mus musculus*) as potential reservoirs for pathogenic bacteria and antimicrobial resistance determinants. *MBio* 2018;9. doi: 10.1128/mBio.00624-18.

House mice may have become permanent houseguests, cohabiting your space and sharing your food. I remember as a kid at the cabin, they would run across our pillows at night while we were sleeping, getting caught in my hair. These researchers investigated whether these little pests may contribute to the spread of pathogenic bacteria and bacterial resistance in the home environment. They collected 416 house mice from the trash compactor area in the subbasement of several multifamily residential buildings in four different New York City boroughs, as well as from the kitchen and food storage area of a commercial building.

Researchers used a two-tiered approach, including bacterial 16S rRNA sequencing and commercial multiplexed anti-microbial resistance (AMR) gene marker PCR arrays of pooled fecal samples, followed by targeted PCR of anal swabs. In addition, they assessed the kidneys for *Leptospira* DNA, since the organism is concentrated more in the urinary tract than the gastrointestinal tract.

Bacterial 16S rRNA sequencing identified *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* as the dominant bacteria of the house mouse fecal biome. Multiple pathogens also were identified, including *Shigella*/EIEC (14%), *Clostridium perfringens* (12%), atypical enteropathogenic *Escherichia coli* (4%) and *Salmonella* spp. (3%). *Clostridium difficile* cytotoxin genes were found in 18 mice (4.3%). One of the ribotypes identified (RT106) was the most common cause of community-acquired *C. difficile* in a 2014 surveillance study.

Further, AMR genes encoding resistance to quinolones, macrolides, and beta lactams (*bla* and OXA-24) were common. Of the house mice sampled,

[These data suggest that house mice may serve not only as a marker of increasing bacterial resistance in the community, but may contribute directly to the circulation of potential pathogens and increasing bacterial resistance.]

153 (37%) harbored at least one potential pathogen and 96 (23%) harbored at least one AMR gene. One juvenile male mouse harbored five different potential pathogens, including *C. difficile*, *Shigella*/EIEC, atypical EPEC, *C. perfringens*, and *Klebsiella pneumoniae*.

Leptospirosis DNA was detected in 14/378 (4%) kidneys. Sequencing demonstrated two genotypes that most closely resembled *L. interrogans* and *L. kirschneri*, and the nearly complete 16S rRNA genes clustered within a larger complex of pathogenic *Leptospira* strains. House mice harboring *Leptospira* were found in Manhattan, Queens, and the Bronx. These data suggest that house mice may not only serve as a marker of increasing bacterial resistance in the community, but may contribute directly to the circulation of potential pathogens and increasing resistance in a large urban area.

Eat Your Fruits and Vegetables — or You Might Get TB!

SOURCE: Aibana O, Franke MF, Huang CC, et al. Impact of vitamin A and carotenoids on the risk of tuberculosis progression. *Clin Infect Dis* 2017;65: 900-909.

For years, nutritional status has been linked to the risk of developing tuberculosis (TB) disease. Two studies suggested that children and adult smokers with high intake of fruits and vegetables had a decreased risk of TB. Recently, vitamin A has been found to affect the immune system in myriad ways: retinoic acid helps to control transcriptional expression of important target genes, and retinol modulates the T-cell priming function of dendritic cells, as well as the function of T regulatory cells, including T-helper 1 cells, a critical part of the immune system response to TB.

These researchers followed a longitudinal cohort of household contacts of pulmonary TB cases in Lima, Peru. Case patients were defined as HIV-negative persons who developed active TB more than 15 days after identification of an index case. In all, 6,751 household contacts were followed for one year, and their vitamin A and carotenoid levels were determined. Two-hundred fifty-eight of these people were diagnosed with TB, although 66 cases were believed to be concurrent with an index case and not included in the analysis. Of the remaining 180 patients, 82% were microbiologically confirmed; 92% had pulmonary TB and 6% had extra-pulmonary TB. They were matched to 709 controls based on year of birth and gender.

Following adjustments for body mass index (BMI), alcohol intake, and socioeconomic status, logistic regression analysis demonstrated that diminished vitamin A levels were associated with a 10-fold increase in the risk for active TB ($P < 0.001$). This risk appeared to increase with diminishing vitamin A levels, such that the lowest quartile had six times the risk of those in the highest quartile.

[Low vitamin A levels were a strong predictor of developing TB in household contacts, especially in younger people.]

Young age also was a significant factor. In those with vitamin A deficiency, the risk of developing TB disease in 10- to 19-year-olds was nearly 20-fold higher (adjusted odds ratio [OR], 18.58, $P = 0.001$) and 10-fold higher for those older than 20 years of age. In addition, adolescents in the lowest quartile of carotenoid levels were at higher risk for TB disease. Lower levels of beta-cryptoxanthin also was associated with an increased risk of TB disease, as were combined vitamin A and vitamin D deficiencies.

Low vitamin A levels were a strong predictor of developing TB in household contacts, especially in younger people. Routine vitamin supplementation might be a simple, low-cost strategy for reducing the risk of developing TB. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

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

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5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME QUESTIONS

1. Which is a true association?

a. Azithromycin and intussusception

b. Rotavirus vaccine and pyloric stenosis

c. Deworming and school attendance

d. Malaria vaccine and increased long-term risk of malaria

2. Which one of the following is *not* among the criteria for diagnosis of PANDAS in 1998?

a. Post-pubertal onset

b. Abrupt onset with an episodic course

c. Obsessive compulsive disorder and/or tic syndrome

d. Association with *Streptococcus pyogenes* infection

3. Which of the following is correct regarding the comparison of single-dose fosfomycin to five days of multiple-dose nitrofurantoin treatment of uncomplicated lower urinary tract infection in women?

a. Nitrofurantoin was less effective than fosfomycin in patients with *E. coli* infections in terms of a microbiological response.

b. Overall, nitrofurantoin treatment was associated with a significantly greater incidence of clinical response.

c. The duration of symptoms was one day shorter in patients treated with nitrofurantoin.

d. *E. coli* was the cause of 95% of the infections.

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.