AHC Media
A RELIAS LEARNING COMPANY

Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

Vol. 39, Issue 22, November 30, 2017
AHCMedia.com

ABSTRACT & COMMENTARY

Antibiotics and Adverse Events: Doctors, Do No Harm

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

Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH

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

SYNOPSIS: A retrospective study found that among 1,488 hospitalized patients who received an antibiotic, 298 experienced at least one antibiotic-associated adverse drug event. Furthermore, 287 of the antibiotic regimens were not clinically indicated, and 56 of these were associated with an adverse drug event.

SOURCE: Tamma PD, Avdic E, Li DX, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med* 2017;177:1308-1315.

Antibiotics have saved countless lives and momentously improved human health since their use in clinical practice began more than 70 years ago. Yet, these miracle drugs have downsides, including adverse drug events (ADEs), organ toxicities, and promotion of antimicrobial-resistant pathogens. ADEs associated with antibiotics include allergic reactions, which can range from mild (e.g., rash or pruritus) to life-threatening (e.g., anaphylaxis), as well as the development of *Clostridium difficile* infection (CDI). Tamma et al sought to determine the incidence of antibiotic-associated ADEs in a cohort of adult inpatients at Johns Hopkins Hospital. The study was a retrospective analysis that included all patients ≥ 18 years of age admitted to the general medical service and who received antibiotics for at least 24 hours between September 2013 and June 2014. Patients were excluded if they received antibiotics for prophylaxis, inhaled or topical antibiotics, anti-tuberculosis antibiotics, and antibiotics for noninfectious indications. Both inpatient and outpatient medical records were reviewed to obtain follow-up data about ADEs. The investigators followed the patients' clinical course for ADEs up to 90 days after the first day of antibiotic administration for the development of CDI and multidrug-resistant organism (MDRO) infections and up to 30 days for other ADEs

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott Diabetes, Actavis, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Cempra, Janssen, Lilly, Merck, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Contributing Editor Louis Kuritzky, MD, is a retained consultant for and on the speakers bureau of Allergan, Daiichi Sankyo, Lilly, and Lundbeck. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Executive Editor Leslie Coplin; and AHC Media Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Internal Medicine
Evidence-based summaries of the latest research in internal medicine [ALERT]

Internal Medicine Alert,
ISSN 0195-315X, is published twice a month by AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to AHC Media, P.O. Box 74008694, Chicago, IL 60674-8694

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments
Please call Editor Jonathan Springston at (404) 262-5416 or email jspringston@reliaslearning.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.

Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

Back issues: $21. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION

Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Relias Learning designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins Jan. 1, 2017. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 1 AAFP Prescribed credit.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

(e.g., tendinitis, gastrointestinal, renal, hepatic, dermatologic, cardiac, neurologic, or hematologic toxicities). At least two infectious disease physicians or pharmacists decided on the association between the antibiotic received and the subsequent ADE.

Of 5,579 patients admitted to the medical service during the study interval, 1,488 received antibiotics for at least 24 hours and were included in the analysis. There were 324 unique ADEs, and 298 of the patients experienced at least one antibiotic-associated ADE. The most frequently prescribed antibiotics were third-generation cephalosporins (607), parenteral vancomycin (544), and cefepime (414) of regimens. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an ADE. There were 236 ADEs that occurred during the hospitalization, while 88 occurred after discharge, which included 11 cases of CDI and 44 MDRO infections.

The researchers determined that 287 of the prescribed antibiotic courses were not clinically indicated, such as treating asymptomatic bacteriuria or noninfectious respiratory conditions like exacerbations of congestive heart failure. Notably, of the nonindicated regimens, 20% were associated with an ADE. The most common ADEs were gastrointestinal, renal, and hematologic abnormalities. Aminoglycosides, trimethoprim-sulfamethoxazole, and parenteral vancomycin were the most frequent agents associated with renal injury. Two patients experienced QTc prolongation; one had received azithromycin and the other had received ciprofloxacin. Seven patients who received cefepime developed neurological side effects, including encephalopathy and seizures.

The rate of CDI was 3.9 (95% confidence interval [CI], 3.0-5.2) per 10,000 person-days for patients receiving antibiotics, which corresponded to 54 of the study patients. The antibiotics most commonly associated with CDI were third-generation cephalosporins (present in 52% of regimens preceding CDI), cefepime (present in 48% of regimens preceding CDI), and fluoroquinolones (present in 35% of regimens preceding CDI). Finally, 314 of the 324 ADEs were considered significant by the investigators, who defined this as resulting in a new hospitalization (n = 10), prolonged hospitalization (n = 77), additional office or ED visits (n = 29), and additional testing (n = 198). No deaths occurred as a result of an ADE.

■ COMMENTARY

The most important and alarming findings in the study by Tamma et al were that 27% of patients admitted to the medical service at Johns Hopkins Hospital received an antibiotic for at least 24 hours and 20% of them developed an antibiotic-associated ADE. While the specific ADEs were not novel and have been well described (e.g., nephrotoxicity from aminoglycosides and vancomycin), what is interesting is that the study provides quantitative data that can be used to estimate the risk of ADEs from antibiotics. That 19% of the prescribed antibiotic regimens were not necessary and were associated with a significant number of ADEs underscores the need for vigilant antibiotic stewardship. One of the key roles of antibiotic stewardship programs must be to educate all healthcare providers that antibiotics carry significant risk for ADEs. The same holds true when physicians discuss antibiotics with patients, especially when the decision has been made to stop or withhold antibiotics when they are not indicated.

There were a few limitations to the study. First, the patients had been referred to a large tertiary academic medical center and tended to be sicker and present with more underlying comorbidities than patients at other institutions. This likely made them more susceptible to antibiotic ADEs. Second, the hospital maintained an antibiotic stewardship program that was active during the study period, which probably caused a reduction in antibiotic-associated ADEs. Thus, the incidence of ADEs in institutions without an antibiotic stewardship program might be higher than the 20% rate reported by Tamma et al. Finally, accurate estimates of some infrequently prescribed antibiotics (e.g., tigecycline, ceftaroline, penicillin) could not be calculated.

Antibiotic-associated ADEs are common and produce significant consequences, including higher healthcare costs, longer length of stay, and harmful toxicities. Therefore, using antibiotics judiciously must be an essential goal for all conscientious physicians. The prophetic advice of Hippocrates to "do no harm" remains as relevant today as it was in 400 B.C. ■

ABSTRACT & COMMENTARY

Irritable Bowel Syndrome, Constipation, and Quality of Life in Women

By Chiara Ghetti, MD

Associate Professor, Obstetrics and Gynecology, Division of Female Pelvic Medicine and Reconstructive Surgery, Washington University School of Medicine, St. Louis

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

SYNOPSIS: Irritable bowel syndrome has a negative effect on women's quality of life and affects one-third of women who present for care with fecal incontinence.

SOURCE: Markland AD, et al; Pelvic Floor Disorders Network. Irritable bowel syndrome and quality of life in women with fecal incontinence. *Female Pelvic Med Reconstr Surg* 2017;23:179-183.

The objective of this study was to determine the prevalence of irritable bowel syndrome (IBS) in women presenting for treatment of fecal incontinence and to determine the effect of IBS on quality of life. This was an ancillary analysis of the Adaptive Behaviors among women with Bowel Incontinence (ABBI) study, a multicenter, prospective cohort study designed to evaluate adaptive behaviors among women with bowel incontinence. Eligible women experienced fecal incontinence of liquid stool, solid stool, or mucus occurring at least monthly for three consecutive months and planned to undergo treatment for fecal incontinence. Women reporting prior rectal or colon cancer, inflammatory bowel disease, pelvic irradiation, a current or prior rectal fistula(e), removal of any portion of the colon/rectum, rectal prolapse, or severe neurological conditions were excluded.

Subjects completed validated questionnaires in person or by telephone before treatment. Questionnaires included assessment of IBS symptoms using the Rome III symptom-based diagnostic criteria, and multiple validated general health-related and condition-specific quality-of-life scales, as well as validated assessments of other pelvic floor symptoms. In this study, IBS was categorized according to the Rome III clinical criteria. In addition, subjects could self-report whether they previously received a diagnosis of IBS.

The authors enrolled 133 women. Of these, 119 completed Rome III IBS questionnaires, and 111 reported whether they had received a previous diagnosis of IBS. According to the Rome III IBS criteria, 37 women had IBS. The most common subtypes were IBS-mixed (41%) and IBS-diarrhea (35%). Twenty-four of 111 patients had a previous IBS diagnosis. Of the subjects who met Rome III IBS criteria, 23 had never received a diagnosis of IBS. There were no significant differences in baseline sociodemographic characteristics, prior treatments, and stool consistency between subjects with fecal incontinence alone compared to subjects with IBS and fecal incontinence. Women with fecal incontinence and IBS reported significantly worse quality of life compared to women without IBS, despite similar fecal incontinence severity and stool consistency. More women with fecal incontinence and IBS reported premenopausal symptoms than women with fecal incontinence alone.

■ COMMENTARY

The findings reported in this study suggest that IBS affects one-third of women with fecal incontinence presenting for care in tertiary centers, and 76% of the women with IBS and fecal incontinence met clinical criteria for IBS-mixed and IBS-diarrhea subtypes. Two-thirds of the women who met criteria for IBS never had been told by a provider that they had IBS. Women with IBS and fecal incontinence experienced a significant negative effect on quality of life.

The strengths of this study include its prospective, multicenter cohort design and the use of validated questionnaires alongside IBS diagnostic criteria. The major limitation of this study is its small cohort size and small number of women with IBS. The authors were limited in the analyses performed and could not perform multivariable statistical modeling, thus limiting the strength of conclusions related to the differences found between women with fecal incontinence with and without IBS. Nonetheless, this study highlights the importance of assessing IBS symptoms in women presenting for fecal incontinence treatment. From my clinical experience, I would like to further emphasize the importance of assessing IBS symptoms and constipation in all women, and especially in women presenting with any pelvic floor symptom.

IBS has been estimated to affect 10-15% of the general adult population and is the most commonly diagnosed gastrointestinal condition. IBS symptoms are more prevalent in women than in men.[1] Jelovsek et al reported

19% prevalence of IBS or one of its subtypes in subjects with pelvic floor disorders presenting for care at a tertiary urogynecologic practice.[2] IBS is divided into four subtypes: IBS-C (constipation), IBS-D (diarrhea), IBS-M (mixed, equal diarrhea and constipation types), and IBS-U (unclassified). The Rome diagnostic criteria were developed as the diagnostic criteria for IBS. Now in their third iteration, the Rome III criteria state that a patient must have recurrent abdominal pain at least three days per month over the previous three months, and the discomfort must be associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in consistency of stool.[3,4] The American College of Gastroenterology Task Force has defined IBS as abdominal pain or discomfort that occurs in association with altered bowel habits over a three-month period. Studies have shown that patients with IBS have worse quality of life, higher economic burdens, and higher healthcare utilization compared to those without IBS. IBS is heterogenous in nature and is thought to be multifactorial. Patients who meet the clinical diagnostic criteria for IBS and do not have "alarm" features, including anemia, weight loss, and a family history of colorectal cancer, inflammatory bowel disease, or celiac sprue, require little formal testing to arrive at the diagnosis of IBS.[5,6]

Constipation also is also extremely common in the general population. It is thought to affect 16% of all adults and 33% of adults > 60 years of age. Heavy lifting and repetitive straining secondary to constipation long have been associated with pelvic organ prolapse and are considered risk factors.[7] Jelovsek et al reported a high prevalence of constipation in women with urinary incontinence and pelvic organ prolapse. Thirty-six percent of the 302 patients studied reported symptoms of constipation, with similar rates between women with either pelvic floor disorder.[2]

Constipation is defined as symptoms of unsatisfactory defecation characterized by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sensation of difficulty passing stool, incomplete evacuation, hard or lumpy stools, prolonged time to pass stool, or need to perform manual maneuvers to pass stool.[4,5] Chronic idiopathic constipation refers to the presence of such symptoms for at least three months.[4,5] The American Gastroenterological Association treatment algorithm for chronic constipation recommends a trial of fiber alone or alongside a laxative. In addition, biofeedback therapy has been reported to improve symptoms more than 70% in patients with defecatory disorders.[6]

IBS and constipation are very common in the general population. Markland et al focused on the presence and effect on women with fecal incontinence; however, functional bowel disorders are highly prevalent in women with all pelvic floor disorders. Not only is treatment of constipation considered a possible modifiable risk factor for pelvic floor disorders, but screening for and treatment of IBS and constipation may produce a significant effect on patients' quality of life and well-being. ■

REFERENCES

1. Chang L, et al. American Gastroenterological Association Institute Technical Review on the pharmacological management of irritable bowel syndrome. *Gastroenterology* 2014;147:1149-1172.e2.
2. Jelovsek JE, et al. Functional bowel and anorectal disorders in patients with pelvic organ prolapse and incontinence. *Am J Obstet Gynecol* 2005;193:2105-2111.
3. Occhipinti K, Smith JW. Irritable bowel syndrome: A review and update. *Clin Colon Rectal Surg* 2012;25:46-52.
4. Ford AC, et al; Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 2014;109(Suppl 1):S2-26; quiz S27.
5. American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;104(Suppl 1):S1-35.
6. Bharucha AE, et al. American Gastroenterological Association technical review on constipation. *Gastroenterology* 2013;144:218-238.
7. Jelovsek JE, et al. Pelvic organ prolapse. *Lancet* 2007;369:1027-1038.

ABSTRACT & COMMENTARY

Functional Outcomes After Receiving Life-sustaining Therapy in the ICU

By Betty Tran, MD, MSc

Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago

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

SYNOPSIS: Among patients who have spent at least three days in an ICU and required even brief mechanical ventilation and/or vasopressor support, almost half are dead and only one-third return to their baseline at six months. Several factors present on the first day of admission are associated with not returning to baseline status.

SOURCE: Detsky ME, Harhay MO, Bayard DF, et al. Six-month morbidity and mortality among ICU patients receiving life-sustaining therapy: A prospective cohort study. *Ann Am Thorac Soc* 2017 Jun 16. doi: 10.1513/AnnalsATS.201611-875OC. [Epub ahead of print].

Limited data are available concerning long-term outcomes of a general ICU population that could inform ICU discussions with patients and surrogates regarding expectations and prognosis. In this prospective cohort study of five ICUs (three medical, two surgical) within the University of Pennsylvania Health System, Detsky et al aimed to describe patients' survival and functional (physical and cognitive) outcomes at six months following an ICU admission of at least three days during which they received life-sustaining therapy in the form of mechanical ventilation for > 48 hours and/or vasopressors for > 24 hours within their first six days in the ICU.

Of 473 patients who met inclusion criteria, 303 ultimately consented to participate. Median age was 62 years (interquartile range, 53-71), 57.1% were male, and 37% were non-white. Prior to their ICU stay, 94.1% of patients resided at home, 28.4% were employed, and 68.0% demonstrated normal baseline function, defined as living at home with no self-reported deficits in cognition or abilities to ambulate up 10 stairs and toilet independently. ICU admission diagnoses were most common for respiratory failure (27.4%), sepsis (21.8%), and non-emergency surgery (17.8%).

Of the 303 enrolled patients, 72 (23.8%) died in the hospital, 21 (6.9%) were discharged to inpatient hospice, and 58 (17.5%) died between hospital discharge and the six-month follow-up. Of the surviving 173 patients at six months, 82.8% had returned to their original residence, 81.9% could toilet independently, 71.3% could ambulate 10 stairs independently, and 62.4% reportedly exhibited normal cognition. Surgical ICU patients experienced better survival and morbidity outcomes compared to medical ICU patients. Of the original 303 enrolled patients, 293 had complete data for six-month physical and cognitive outcomes and baseline characteristics, and were included in an analysis to identify predictors of return to baseline function. Of these, 91 (31.1%) returned to baseline at six months. Normal function prior to ICU admission was not associated significantly with increased likelihood to return to baseline. Independent predictors of not returning to baseline function included older age, being a medical (as opposed to a surgical) patient, non-white race, higher APACHE III score, hospitalization in the prior year, and a history of cancer, liver disease, neurologic condition, or any type of transplant.

■ COMMENTARY

This is a comprehensive cohort study that uncovered several important findings. First, six-month mortality among patients with ICU stays requiring life-sustaining therapy is quite high at 43%. Although hospitalization in the prior year was an independent predictor of poor return to baseline function in the multivariable model, it is notable that most patients (94.1%) resided at home, and 68% reported normal baseline function prior to their ICU hospitalization. Thus, an ICU hospitalization requiring life-sustaining therapy is a defining moment. A similar pattern has been observed in multiple studies focused on outcomes after hospitalization for severe sepsis.[1,2]

Second, the multivariable model presented is unique in its use of return to baseline status as an outcome that is important in ICU survivorship. Third, although six-month mortality is high, most patients who survive to six months are at home and functioning normally, albeit with cognitive impairments outnumbering physical ones. These findings are intriguing when viewed in the context of studies that have found that among patients on prolonged mechanical ventilation, only 9% are at home and independently functioning at the one-year mark.[3] To the extent that functional status is an important component of quality of life for patients, data from the Detsky et al study are informative, although the results do not mitigate the complexity of real-time decisions in the ICU, especially when the decision involves whether to continue aggressive care (and possibly tracheostomy and G-tube placement) vs. pursue comfort care/hospice. For patients requiring life-sustaining ICU support, even briefly as defined by this study, these data suggest that mortality is high, but if they survive, the majority can return home and achieve some degree of normal function by six months. However, based on data from other studies, if patients continue to remain dependent on mechanical ventilation for a longer period, at some point a threshold is crossed such that their chances of functional independence decline drastically. It is interesting to note that surrogate ratings overall were more pessimistic than reports from patients in the study. Although independent risk factors for return to baseline are presented, they have yet to be validated as part of an accurate scoring system for predicting the outcome of return to baseline. Currently, data from this study are probably most helpful as part of patient and/or surrogate discussions regarding what to expect in terms of recovery, even after brief, but intense, ICU stays. ■

REFERENCES

1. Prescott HC, Langa KM, Liu V, et al. Increased 1-year healthcare use in survivors of severe sepsis. *Am J Respir Crit Care Med* 2014;190:62-69.
2. Liu V, Lei X, Prescott HC, et al. Hospital readmission and healthcare utilization following sepsis in community settings. *J Hosp Med* 2014;9:502-507.
3. Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation. *Ann Intern Med* 2010;153:167-175.

Clinical Briefs

By Louis Kuritzky, MD

More Good News for GLP-1 RA in Type 2 Diabetes

SOURCE: Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:839-848.

Since 2008, the FDA has required all new diabetes medications to provide evidence of cardiovascular (CV) safety. The good news is that several classes of agents have demonstrated not only CV safety, but even efficacy in reducing CV events and (in some cases) all-cause mortality.

The glucagon-like peptide-1 receptor agonist (GLP-1 RA) liraglutide, the sodium-glucose co-transporter-2 inhibitors empagliflozin and canagliflozin, and the dopamine agonist bromocriptine have demonstrated beneficial effects on CV outcomes. Whether these results will be revealed as a class effect remains to be determined.

Alongside the favorable CV data, there is good news in relation to renal endpoints in some of these same trials, the most recent of which is reported from the liraglutide CV safety trial (LEADER). Renal outcomes showed favorable effects of liraglutide compared to placebo, primarily driven by a reduction in the number of patients who developed new macroalbuminuria (> 300 mg urinary albumin/24 hours). Similarly, the rate of decline in renal function, as measured by glomerular filtration rate, was statistically significantly less in patients treated with liraglutide than placebo.

Reductions in microvascular disease (early nephropathy, in the case of type 2 diabetes) has been a major justification for management of glucose for several decades. It is reassuring to confirm that the risk for more advanced nephropathy is ameliorated by use of liraglutide. ■

Menopausal Hormone Replacement

SOURCE: Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: The Women's Health Initiative randomized trials. *JAMA* 2017;318:927-938.

Hormone replacement therapy (HRT) reached its peak in the late 1990s based on observational data that suggested improvements in cardiovascular health, cognition, genitourinary health, and other factors. That changed drastically following the HERS trial and the Women's Health Initiative (WHI), both of which found not only no cardiovascular benefit associated with HRT but increased adversities such as breast cancer and venous thrombosis.

Women were enrolled in the WHI from 1993-1998, and have been followed through 2014, so clinicians can look at the long-term effects of their treatments for the six or seven years they participated in the trial through that date. There was no difference in all-cause mortality or cancer-related mortality between treated and untreated patients over 18 years of follow-up. It has been noted that younger women (age 50-59 years) in the WHI had a favorable outcome for all-cause mortality during the trial. This trend continued through the 18-year follow-up (hazard ratio for mortality, 0.87; confidence interval, 0.76-1.00).

For women who currently use or have used hormone replacement for menopausal symptoms, these data should be reassuring that their symptom relief does not come at a cost of increased total or cancer-related mortality. ■

A Link Between *Demodex* Mites and Rosacea

SOURCE: Chang YS, Huang YC. Role of *Demodex* mite infestation in rosacea: A systematic review and meta-analysis. *J Am Acad Dermatol* 2017;77:441-447.e6.

Rosacea is a common dermatologic disorder of uncertain etiology that often is refractory to therapy. Although numerous interventions have been tried, no cure for rosacea is at hand. Antibiotics (e.g., tetracyclines, metronidazole), beta-blockers (e.g., propranolol), alpha-beta-blockers (e.g., carvedilol), systemic steroids, and calcineurin inhibitors (e.g., tacrolimus) have demonstrated some degree of success, but many patients must rely on polypharmacy for adequate symptom control.

An association of the *Demodex* mite and rosacea has been recognized for more than 50 years. Indeed, antiparasitic medications (ivermectin, permethrin) recently have been shown to produce a favorable effect on rosacea. To better delineate the *Demodex*-rosacea relationship, Chang and Huang performed a meta-analysis of studies comparing the prevalence of *Demodex* and the *Demodex* density (intensity of mite colonization) in patients with rosacea vs. controls. Patients with rosacea were nine times more likely to be infested with *Demodex* than controls. Similarly, *Demodex* density was statistically significantly higher in rosacea patients.

The role of *Demodex* in rosacea appears to be well demonstrated. Since eradication of *Demodex* is insufficient to resolve rosacea, other pathophysiologic pathways also must be involved. ■

PHARMACOLOGY UPDATE

Fluticasone Furoate, Umeclidinium, and Vilanterol Inhalation Powder (Trelegy Ellipta)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

Fluticasone furoate, umeclidinium, and vilanterol oral inhalation powder (FF/UMEC/VI) is the first once-daily single inhaler triple therapy for patients with COPD. This fixed-combination includes an inhaled corticosteroid (fluticasone), a long-acting anticholinergic/antimuscarinic (umeclidinium), and a long-acting beta-2-adrenergic agonist (vilanterol). It is marketed as Trelegy Ellipta.

INDICATIONS

FF/UMEC/VI is indicated for the long-term maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema. It is targeted to patients who are taking fixed-dose combinations of fluticasone and vilanterol to reduce airflow obstruction and reduce exacerbations in those who need additional treatment of airflow obstruction or for patients who are already receiving umeclidinium and fixed-dose combination of fluticasone and vilanterol.[1]

DOSAGE

The recommended dose is one inhalation orally once daily.[1] The product is available as two foil blister strips of powder for oral inhalation. One strip contains 100 mcg of fluticasone furoate. The other contains 62.5 mcg of umeclidinium and 25 mcg of vilanterol.

POTENTIAL ADVANTAGES

FF/UMEC/VI offers the convenience of the first once-daily triple therapy for appropriate patients with COPD.

POTENTIAL DISADVANTAGES

FF/UMEC/VI is contraindicated in patients with severe hypersensitivity to milk proteins as the powder contains lactose, which contains milk protein.[1] FF and VI are substrates of CYP3A4; therefore, strong inhibitors of this isoenzyme increase systemic exposure to FF and VI.[1] Vilanterol shares the same box warning for asthma-related death as other long-acting beta-2-adrenergic agonists. The individual components also share the same class warnings and precautions.

COMMENTS

The efficacy of FF/UMEC/VI was based primarily on the coadministration of UMEC and FF/VI in two randomized, double-blind, parallel-group, 12-week studies.[1] At screening, subjects with COPD exhibited mean postbronchodilator percentage predicted forced expiratory volume (FEV_1) of 46% (range, 14-76%), FEV_1/ forced vital capacity (FVC) ratio of 0.48 (range, 0.21 to -0.70), and percentage reversibility of 13% (range, -24% to 86%). Each study contained 206 subjects. All subjects were randomized to UMEC or placebo plus FF/VI. The primary endpoint was mean change from baseline in trough (predose) FEV_1 at day 85. This was defined as the mean value obtained 23 and 24 hours after the previous dose on day 84. The mean change difference in FEV_1 from placebo for the two studies was 124 mL and 122 mL, respectively. Subjects on FF/UMEC/VI used less rescue medication and were more likely to show a decrease in score from baseline of 4 or more on the St. George's Respiratory Questionnaire.[2] This questionnaire is designed to assess health status (quality of life) based on three domains: symptoms, activity, and psychosocial impact.[2] A minimum change of four units is considered to be clinically relevant. Responses were 40% vs. 35% in study 1 and 35% vs. 21% for study 2. In a 24-week comparative trial, FF/UMEC/VI once daily (n = 911) was compared to budesonide/formoterol twice daily (n = 899).[3] Mean change in FEV_1 was 142 mL for FF/UMEC/VI vs. -29 mL for budesonide/formoterol. Additionally, there was a 35% reduction in the moderate/severe exacerbation rate. An economic analysis of the same study suggests that the additional cost of triple therapy is partly offset by lower non-drug costs.[4]

CLINICAL IMPLICATIONS

FF/UMEC/VI is the first once-daily, fixed-dose, triple regimen to be approved. When patients step up to three drugs, additional benefit may be achieved. This includes improved lung function, health status, and reduced exacerbations.[5] The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) recommends triple therapy (inhaled steroid, long-acting antimuscarinic agent, and long-acting beta-2-adrenergic agonist) in patients with persistent symptoms and further exacerbation (GOLD group D). A large (n = 10,359), 52-week, three-arm study was completed recently. Researchers compared efficacy and safety of FF/UMEC/VI vs. FF/VI or UMEC/VI in this population, with the primary outcome the rate of moderate and severe exacerbations.[6,7] The results have not been reported. The cost for FF/UMEC/VI is $247 for a 28-day supply. ■

REFERENCES

1. Trelegy Ellipta Prescribing Information. September 2017. GlaxoSmithKline.
2. St. George's University of London. St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C). Available at: http://bit.ly/2zp0OI3. Accessed Nov. 7, 2017.
3. Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: Once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196:438-446.
4. Ismaila AS, Birk R, Shah D, et al. Once-daily triple therapy in patients with advanced COPD: Healthcare resource utilization data and associated costs from the FULFIL trial. *Adv Ther* 2017 Sep 5. doi: 10.1007/s12325-017-0604-x. [Epub ahead of print].
5. Global Initiative for Chronic Obstructive Lung Disease. Pocket guide to COPD diagnosis, management, and prevention. Available at: http://bit.ly/2IWQd1F. Accessed Nov. 7, 2017.
6. Pascoe SJ, Lipson DA, Locantore N, et al. A phase III randomised controlled trial of single-dose triple therapy in COPD: The IMPACT protocol. *Eur Respir J* 2016;48:320-330.
7. ClinicalTrials.gov. A study comparing the efficacy, safety and tolerability of fixed dose combination (FDC) of FF/UMEC/VI with the FDC of FF/VI and UMEC/VI; administered once-daily via a dry powder inhaler (DPI) in subjects with chronic obstructive pulmonary disease (COPD). Available at: http://bit.ly/2zp9VZw. Accessed Nov. 7, 2017.

CME QUESTIONS

1. Which of the following is the best single answer regarding the findings of Tamma et al about adverse effects of antibiotic therapy at Johns Hopkins Hospital?
a. Of those who received an antibiotic, 20% experienced at least one adverse event.
b. There was no clinical indication for antibiotic therapy in 19% of those given an antibiotic.
c. Cephalosporins were the class of antibiotics most frequently associated with the development of *Clostridium difficile* infection.
d. All of the above

2. Irritable bowel syndrome and constipation:
a. are common only in women with fecal incontinence.
b. are very prevalent in women with pelvic floor disorders.
c. are not easily screened for.
d. have minimal effect on women's quality of life.

3. In the article by Detsky et al, approximately what percentage of patients died within six months of an ICU hospitalization requiring life-sustaining therapy?
a. 5%
b. 25%
c. 50%
d. 75%

4. Based on the study by Detsky et al, which of the following statements is true?
a. Most of the patients who survived to six months were at home.
b. Functional deficits at six months were mostly in the cognitive realm.
c. Non-white race was an independent predictor of not returning to baseline function.
d. Normal function at baseline was not associated significantly with an increased likelihood to return to baseline.
e. All of the above

CME OBJECTIVES

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Travelers Unaware of the Need for Pre-travel Vaccinations

Can Medical Therapy Improve Functional Mitral Regurgitation?