

Enterovirus D-68 presenting with acute pancreatitis

(JANUARY 2015)

TO THE EDITOR: We read the review on enterovirus D68¹ (EV-D68) with great interest, and we thought it merited comment.

During the current influenza season, we have had several adult cases of EV-D68 presenting as an influenza-like illness. EV-D68 was diagnosed by nasal swab viral film array polymerase chain reaction (PCR) testing. We agree with the authors that the clinical spectrum of enteroviral infection includes a variety of extraintestinal manifestations, eg, acute pancreatitis. As more cases of EV-D68 are described, the range of clinical manifestations will be increased.²⁻⁵

We recently saw a 27-year-old woman who presented with an influenza-like illness, but with a main complaint of right-upper-quadrant abdominal pain. She denied recent travel or contacts with sick children or adults. Her past medical history was unremarkable, and she was not taking any medications. The physical examination was unremarkable except for moderately severe tenderness in the right upper quadrant, with no rebound or guarding.

Results of laboratory testing at hospital admission included a white blood cell count of $7.3 \times 10^9/L$ (49% neutrophils, 41% lymphocytes, 7% monocytes, 3% eosinophils), a normal platelet count, serum lipase 73 U/L (reference range 5.6–51.3 U/L), and serum amylase 211 U/L (37–121 U/L). Serum aminotransferase and alkaline phosphatase levels were normal. Abdominal ultrasonography was unremarkable. Nasal swab for multiplex PCR testing for respiratory viruses was positive for human rhinovirus-enterovirus. Further PCR testing was positive for EV-D68 (New York State Department of Health, Wadsworth Laboratory). Her abdominal pain was treated symptomatically; she gradually improved and was discharged.

This instance of EV-D68 in a healthy 27-year-old woman presenting with influenza-

like illness and acute pain in the right upper quadrant is the first we have seen of EV-D68 presenting as acute pancreatitis. Clinicians should be aware that EV-D68, like influenza, may present with gastrointestinal manifestations.

BURKE A. CUNHA, MD
GINA WU, MD
MARIE DUMONT, CIC
EILEEN ABRUZZO, RN, CIC
MUHAMMAD RAZA, MBBS
Infectious Disease Division
Winthrop-University Hospital
Mineola, NY;
State University of New York
School Of Medicine, Stony Brook, NY

REFERENCES

1. Foster CB, Friedman N, Carl J, Piedimonte G. Enterovirus D68: a clinically important respiratory enterovirus. *Cleve Clin J Med* 2015; 82:26–31.
2. Tokarz R, Firth C, Madhi SA, et al. Worldwide emergence of multiple clades of enterovirus 68. *J Gen Virol* 2012; 93:1952–1958.
3. Oberste MS, Maher K, Schnurr D, et al. Enterovirus 68 is associated with respiratory illness and shares biological features with both the enteroviruses and the rhinoviruses. *J Gen Virol* 2004; 85:2577–2584.
4. Rahamat-Langendoen J, Riezebos-Brilman A, Borger R, et al. Upsurge of human enterovirus 68 infections in patients with severe respiratory tract infections. *J Clin Virol* 2011; 52:103–106.
5. Midgley CM, Jackson MA, Selvarangan R, et al. Severe respiratory illness associated with enterovirus D68 – Missouri and Illinois, 2014. *MMWR* 2014; 63:798–799.

doi:10.3949/ccjm.82c.06001

Eosinophilic esophagitis

(FEBRUARY 2015)

TO THE EDITOR: In the February 2015 issue of *Cleveland Clinic Journal of Medicine*, Dr. David A. Katzka reviewed the major clinical features of eosinophilic esophagitis and, having presented its allergic component, rightly assessed the inherent difficulties of detecting and eliminating food allergens involved in the development and course of this disease.¹ The inadequacies of serologic testing were mentioned, as well as the difficulties of endoscopy and biopsy “painstakingly performed with the removal and reintroduction of every suspected food allergen, requiring multiple biopsies weekly, which is impractical for safety and economic reasons.”¹

In a meta-analysis, Arias et al² showed that such an individualized approach for each food is not really necessary. Elemental diets with graded reintroduction of grouped foods were effective in detecting and treating the responsible food allergies in 90.8% of cases (95% confidence interval [CI] 84.7–95.5). In fact, the more pragmatic, simple, and inexpensive six-food-elimination diet was also reasonably effective (72.1% of cases, 95% CI 65.8–78.1). Both outcomes are far superior to elimination strategies directed at immunoglobulin E (IgE), which were effective in only 45.5% of cases (95% CI 35.4–55.7%).²

Franciosi and Liacouras³ described a practical and comprehensive elimination-reintroduction protocol consisting of four steps that, in combination with symptom diaries, can easily identify responsible foods.

In our practice, graded elimination-reintroduction diets—which, depending on history, may range from the basic six-food-elimination diet to the fully developed Franciosi-Liacouras protocol—along with food IgE testing and judicious use of IgG testing against selected foods, have yielded detection and successful treatment rates comparable to the 90.8% rate reported by Arias et al.² Upon identification of food allergens, a dual approach of diet restrictions and food immunotherapy is initiated. As a result of this approach, patients only need to undergo a single endoscopy and biopsy to demonstrate decreased eosinophil counts, usually 1 year after initiation of allergy treatment.

Of course, pharmacologic management is necessary in the treatment of eosinophilic esophagitis. However, the inclusion of montelukast in the standard first-line regimen for eosinophilic esophagitis is not yet a firmly established practice. Not all eosinophilia can be equated to allergy, and not all allergic inflammation is leukotriene-dependent. Furthermore, too little is known about the secondary effects of leukotrienes on immune regulation and whether their blockade is really desirable in eosinophilic esophagitis. But it is known that leukotriene receptor antagonists, especially montelukast, can trigger Churg-Strauss vasculitis, a syndrome whose eosinophil activation,

homing pattern, and subsequent proliferation—as well as its exclusive prevalence in allergic patients with asthma and chronic sinusitis—bear some similarity to those of eosinophilic esophagitis.

DEMETRIOS S. THEODOROPOULOS, MD
MARY S. MORRIS, MD
Allergy Associates of La Crosse
La Crosse, Wisconsin, USA

REFERENCES

1. **Katzka DA.** The 'skinny' on eosinophilic esophagitis. *Cleve Clin J Med* 2015; 82:83–88.
2. **Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ.** Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014; 146:1639–1648.
3. **Franciosi JP, Liacouras CA.** Eosinophilic esophagitis. *Immunol Allergy Clin North Am* 2009; 29(1):19–27.

doi:10.3949/ccjm.82c.06002

IN REPLY: I am most grateful to Drs. Theodoropoulos and Morris for their letter. I fully agree that we are getting smarter with diet elimination therapies by introducing more than one food at a time in the hope that we can lessen the number of endoscopies needed to isolate specific antigenic causes of eosinophilic esophagitis. This is not always successful, but in some of the more fortunate patients, we can get by with one or two endoscopies. It is my hope that with less-invasive tools such as the Cytosponge, the esophageal string test, and perhaps even serum evaluations, we can further embrace diet therapy as a standard treatment in more patients with eosinophilic esophagitis.

I think it is also important to note that although traditional radioallergosorbent and skin testing was only 45% accurate for eosinophilic esophagitis in the meta-analysis cited, this testing is still important, given the number of IgE-related allergies additionally uncovered in patients with eosinophilic esophagitis.

DAVID A. KATZKA, MD
Mayo Clinic
Rochester, MN

doi:10.3949/ccjm.82c.06003

The health care ‘iron triangle’

(FEBRUARY 2015)

TO THE EDITOR: In his article, Dr. Lehman¹ argued that because the Patient Protection and Affordable Care Act (PPACA) attempts to break the healthcare “iron triangle” by simultaneously improving access and quality while reducing costs, it may paradoxically make the situation worse on all three fronts. However, this line of argument fails to provide a comparison—that is, worse compared to what? While Dr. Lehman does not suggest a comparison, two come to mind that could be implied from his arguments: 1) doing nothing, or 2) targeting reform at only two sides of the triangle.

Prior to the PPACA, the US healthcare system had serious problems with access, quality, and cost.² While it is true that any reform could potentially be worse than doing nothing, none of the three seemed to be getting any better under the status quo. Both candidates for president in 2008 agreed that doing nothing was no longer an option.^{3,4} Alternatively, trying to improve two legs of the triangle (say, access and quality) while acknowledging that the third (cost) would suffer would have been just as politically untenable.

The true explanation for how the PPACA could expect to (and may still) improve access and quality while reducing healthcare costs (compared to no reform) is that the PPACA is not a single intervention, as is obvious from the 2,000-plus pages of the law. No single component of the law needs to do all three. For example, expanding Medicaid improves access and quality (especially for those without prior coverage) but undoubtedly raises costs. On the other hand, accountable care organizations should decrease costs by incentivizing providers to be more efficient and reduce waste (and ideally would also improve quality).⁵ Given the low bar set prior to implementation of the PPACA, it was not a stretch to have expected any major reform to improve (not fix) our problems with access, quality, and cost.

KEVIN R. RIGGS, MD
Johns Hopkins School of Medicine
Baltimore, MD

■ REFERENCES

1. **Lehman EP.** The health care ‘iron triangle’ and the Patient Protection and Affordable Care Act. *Cleve Clin J Med* 2015; 82:73–80.
2. **Berwick DM, Nolan TW, Whittington J.** The triple aim: care, health, and cost. *Health Aff (Millwood)* 2008; 27:759–769.
3. **McCain J.** Access to quality and affordable health care for every American. *N Engl J Med* 2008; 359:1537–1541.
4. **Obama B.** Modern health care for all Americans. *N Engl J Med* 2008; 359:1537–1541.
5. **Shortell SM, Casalino LP.** Health care reform requires accountable care systems. *JAMA* 2008; 300:95–97.

doi:10.3949/ccjm.82c.06004

IN REPLY: Many of the statements made by Dr. Riggs are indisputable. The conclusions drawn from these insights, however, are questionable.

The Patient Protection and Affordable Care Act (PPACA) was introduced under the premise that a patchwork of policies would improve access and quality of care while decreasing overall health expenditures. Dr. Riggs suggests that, since individual components are targeted toward some of these issues, the net effect of the PPACA is its breaking of the healthcare iron triangle.

Nothing could be further from the truth. This line of reasoning requires that the left hand knows not what the right hand is doing, and that each hand (ie, each component of the PPACA) can ignore the effects of the other, with each proclaiming success in its efforts. It is disingenuous to suggest that the PPACA, on the whole, improves upon the problems of access, quality, and cost if each of the program’s tenets addresses only one or two of the triangle’s vertices.

The PPACA suffers from its own lofty expectations. Rather than being a transformative law that shifts a paradigm, the PPACA is simply an evolution of an existing, broken system, cobbling together components everyone readily agrees are dysfunctional. It expands Medicaid, an insufficiently funded program for the most economically and medically disadvantaged Americans. It subsidizes private health insurance, which, for all its advantages, is likely responsible for the overconsumption of discounted healthcare. And it promotes the unproven concept of accountable care organizations, with no rational expectation that this approach would be

superior to preferred provider organizations or health maintenance organizations. It is illogical to expect the sum of many broken parts to yield a superior outcome.

Dr. Riggs notes that trying to improve two legs of the triangle (increased access and improved quality) while acknowledging rising costs is politically untenable. On this point, he is absolutely correct. Discussing the harsh reality that healthcare is a scarce commodity is a political nonstarter. Until Americans demand—and politicians provide—difficult answers to the question of how we will provide healthcare in the 21st century, simultaneously improving delivery of care on all three fronts remains a fantasy. Barring truly transformative change, the iron triangle continues to rule the economics of American healthcare.

ELMER PHILIP LEHMAN IV, MD, MPP
Division of Cardiology, Department of
Medicine
Duke University School of Medicine
Durham, NC

doi:10.3949/ccjm.82c.06005

Alcoholic hepatitis: An important consideration

(APRIL 2015)

TO THE EDITOR: I read with keen interest the high-quality review of the pathogenesis, diagnosis, and management of alcoholic hepatitis by Dugum et al.¹ They clearly emphasized the high morbidity and mortality rates associated with this condition.

An important consideration for healthcare practitioners is that the presentation of alcoholic hepatitis can mimic an infectious process, eg, presenting with fever and an elevated white blood cell count. Indeed, clinicians should be vigilant and should routinely evaluate for an underlying infection in patients with suspected alcoholic hepatitis, because patients with liver disease are immunocompromised and several problems can potentially coexist in any given patient.

Therefore, clinicians should focus on

the clinical history and examination (vital signs, mental status examination, presence of ascites) and should screen for common coinfections such as urinary tract infection and pneumonia with a white blood cell count with differential and other tests. Of particular importance, patients with ascites should undergo diagnostic abdominal paracentesis,² and empiric antimicrobial therapy for spontaneous bacterial peritonitis should be considered on a case-by-case basis.³

AIBEK E. MIRRAKHIMOV, MD
Department of Internal Medicine
Saint Joseph Hospital
Chicago, IL

REFERENCES

1. Dugum M, Zein N, McCullough A, Hanounieh I. Alcoholic hepatitis: challenges in diagnosis and management. *Cleve Clin J Med* 2015; 82:226–236.
2. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013; 57:1651–1653.
3. Lutz P, Nischalke HD, Strassburg CP, Spengler U. Spontaneous bacterial peritonitis: the clinical challenge of a leaky gut and a cirrhotic liver. *World J Hepatol* 2015; 7:304–314.

doi: 10.3949/ccjm.82c.06006

IN REPLY: We thank Dr. Mirrakhimov for his interest in our article¹ and for his comments on the importance of infection evaluation and treatment in patients with alcoholic hepatitis. We agree with the points he has raised and emphasized several of them in our article. We highlighted the need to evaluate for infections in these patients, as about a quarter of them are infected at the time of presentation.²

Importantly, patients with alcoholic hepatitis frequently have systemic inflammatory response syndrome criteria, which can be related to the overall inflammatory state of the disease itself or can reflect an active bacterial infection. Therefore, clinical monitoring for symptoms and signs of infection is crucial, and screening for infections is warranted on admission as well as repeatedly during the hospital stay for patients who experience clinical deterioration.³ Obtaining blood and urine cultures and performing paracentesis in patients with ascites to evaluate for bacterial

peritonitis are required. Indeed, infections are a leading cause of death in patients with severe alcoholic hepatitis, both directly and indirectly by predisposing to multiorgan failure.⁴

Another factor to consider is the increased susceptibility to infection in these patients treated with corticosteroids. A study by Louvet et al² showed that nonresponse to corticosteroids is the main factor contributing to the development of infection during treatment with corticosteroids, suggesting that infection is likely a consequence of the absence of improvement in liver function. More recently, results of the Steroids or Pentoxifylline for Alcoholic Hepatitis trial (which evaluated the treatment effect of prednisolone and pentoxifylline in the management of severe alcoholic hepatitis) showed that despite the higher rates of infections in patients treated with prednisolone, the mortality rates attributed to infections were similar across the treatment groups, regardless of whether prednisolone was administered.⁴

Finally, it is important to emphasize that criteria to initiate empiric antibiotics in

patients with alcoholic hepatitis are currently lacking, and the decision to start antibiotics empirically in patients without a clear infection is largely based on the clinician's assessment.

MOHANNAD DUGUM, MD
NIZAR ZEIN, MD
ARTHUR McCULLOUGH, MD
IBRAHIM HANOUNEH, MD
Department of Gastroenterology and Hepatology
Digestive Disease Institute
Cleveland Clinic

REFERENCES

1. Dugum M, Zein N, McCullough A, Hanouneh I. Alcoholic hepatitis: challenges in diagnosis and management. *Cleve Clin J Med* 2015; 82:226–236.
2. Louvet A, Wartel F, Castel H, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. *Gastroenterology* 2009; 137:541–548.
3. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012; 57:399–420.
4. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med* 2015; 372:1619–1628.

doi:10.3949/ccjm.82c.06007

CORRECTION

HPV DNA test

(APRIL 2015)

In the April 2015 issue, on page 214 in the article by Jin XW, McKenzie ML, Yen-Lieberman B, “Can the test for human papillomavirus DNA be used as a stand-alone, first-line screening test for cervical cancer?”, the source for the information on predictive values was not cited. The final bulleted item should have read as follows:

- HPV testing by itself performed better than Pap-HPV cotesting, with positive predictive values of 12.25% vs 11.04% and negative predictive values of 99.58% vs 99.52% (data presented to the FDA Medical Devices Advisory Committee, Microbiology Panel. March 12, 2014. FDA Executive Summary).

This oversight has been corrected in the online version of the article at www.ccjm.org.

doi:10.3949/ccjm.82c.06008