TO THE EDITOR: We read with interest the recent meta-analysis by Fuccio and colleagues (1). There is an ongoing Cochrane review on this subject; its protocol is published (2), and its results have been reported in abstract form (3). Fuccio and colleagues report that eradication therapy for Helicobacter pylori reduces the subsequent incidence of gastric cancer. However, we have serious doubts about the accuracy of their analysis. In the Methods section of their article, Fuccio and colleagues state that when they found multiple articles for a single study, they used the latest publication from each eligible study. However, the meta-analysis erroneously incorporated data from the same randomized, controlled trial (RCT) twice (4, 5). Tables 1 and 2 (1) showed “2” studies that were conducted in the Shandong province of China, commenced in 1996, had very similar numbers of participants, and used identical eradication regimens of the same duration. We contacted the original investigators of these studies (2, 3) directly when collecting data for our review. Those investigators confirmed that the 2 publications were in fact 5-year (4) and 10-year (5) follow-up studies from the same RCT.

The erroneous inclusion of repeated data led Fuccio and colleagues to report a statistically significant effect of H. pylori eradication therapy in reducing incidence of gastric cancer, when this is not the case. If only the 10-year follow-up data are included (5), the pooled relative risk for subsequent gastric cancer is 0.65 (95% CI, 0.42 to 1.01). Also, the pertinent trial publications reported fewer cases of gastric cancer after 10-year follow-up (5) than at 5-year follow-up (4), raising concerns about the accuracy of data collection or of reporting for the trial. Taken together, this information convinces us that the effect of eradication therapy on gastric cancer is not as clear-cut as Fuccio and colleagues suggest.

We delayed publishing our full Cochrane review because of these concerns about the duplicate Chinese studies. Our knowledge and experience regarding errors in meta-analyses and the fact that Annals published the meta-analysis with erroneous data highlight several important issues for authors of meta-analyses, for journal editors, and for peer reviewers. First, transparent reporting of follow-up studies conducted at various time points from the same RCT is needed to ensure correct identification of trials and to avoid miscounting of data by authors. Second, when studies are reported only in abstract form, or if the accuracy of the data is in doubt, authors should directly contact original investigators for clarifications. Finally, peer reviewers (and journal editors) may have difficulty confirming the results of systematic reviews and meta-analyses. In some cases, independent verification of the meta-analysis may be needed to ensure the results are truly accurate.

Alexander C. Ford, MBChB, MD
St. James’s University Hospital
Leeds LS9 7TF, United Kingdom

Paul Moayyedi, MBChB, PhD
McMaster University Health Sciences Centre
Hamilton, Ontario L8N 3Z5, Canada

Potential Conflicts of Interest: None disclosed.

References
1. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann Intern Med. 2009;151:121-8. [PMID: 19620164]
2. Moayyedi P, Hunt R, Forman D. Helicobacter pylori eradication for the prevention of gastric neoplasia. Cochrane Database Syst Rev. 2006;1:CD005583.
3. Moayyedi P, Hunt RH, Ford AC, Talley NJ, Forman D. Helicobacter pylori eradication reduces the incidence of gastric cancer: results of a systematic review of randomized controlled trials [Abstract]. Gastroenterology. 2008;134:A631-2.
4. Leung WK, Lin SR, Ching JY, To KF, Ng EK, Chan FK, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication. Gut. 2004;53:1244-9. [PMID: 15306578]
5. Zhou L. Ten-year follow-up study on the incidence of gastric cancer and the pathological changes of gastric mucosa after H. pylori eradication in China [Abstract]. Gastroenterology. 2008;134:A233.
Eradication treatment will probably give a huge advantage in terms of social health, especially in high-risk areas.

Lorenzo Faccio, MD
Leonardo Henry Eusebi, MD
Franco Bazzoli, MD
University of Bologna
40138 Bologna, Italy

Potential Conflicts of Interest: None disclosed.

Granulysin as a Marker for Early Diagnosis of the Stevens–Johnson Syndrome

Background: The Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening adverse drug reactions characterized by massive epidermal necrosis. In the early stage, clinical presentations of SJS/TEN are very similar to those of ordinary drug-induced skin reactions (ODSRs); therefore, SJS/TEN is difficult to diagnose and the start of treatment is often delayed, resulting in high mortality rates. Other investigators (1) reported that granulysin is the most highly expressed cytotoxic molecule in the blisters of patients with SJS/TEN and causes disseminated keratinocyte death. Because SJS/TEN progresses and spreads rapidly, the granulysin level should be increased in the serum of patients with active SJS/TEN if it is a key mediator of these diseases.

Objective: To determine whether serum granulysin levels are higher in patients with SJS/TEN than in healthy control participants or those with OSDRs.

Methods: We measured granulysin in the sera of 31 healthy control participants, 24 patients with OSDR, 13 patients with SJS, and 7 patients with TEN by using enzyme-linked immunosorbent assay (2). Disease onset in patients with SJS/TEN was defined as the day (day 1) on which the mucocutaneous or ocular lesion first eroded or ulcerated (3), and we collected sera from these patients from day 4 to day 10 days before to day 10 after ulceration. We used the Tukey–Kramer test to conduct multiple comparisons between groups.

Results: None of the 31 healthy control participants had a granulysin level greater than the upper limit of normal, which was 10 ng/mL (0% elevated; mean, 1.6 ng/mL [SD, 0.6]), and among 24 patients with OSDRs, only 1 patient had an elevated granulysin level (4.2% elevated; mean, 3.5 ng/mL [SD, 3.4]) (Figure). We obtained samples from 5 patients with SJS/TEN on day −4 to day −2, and we detected the highest granulysin concentrations (elevated in 80% of patients); mean, 24.8 ng/mL [SD, 21.2]). Granulysin levels were lower in the 14 samples collected on day −1 to day 2 (28.6% elevated; mean, 13.7 ng/mL [SD, 16.0]), and were even lower in the 10 samples collected from day 3 to day 5 (10.0% elevated; mean, 4.2 ng/mL [SD, 3.0]) and in the 13 samples collected from day 6 to day 10 (7.7% elevated; mean, 4.5 ng/mL [SD, 4.5]). When we compared granulysin levels from day −4 to day −2 among patients with SJS/TEN, patients with OSDRs, and healthy control participants, the differences were statistically significant (P < 0.010).

Discussion: Granulysin is cytotoxic for tumor cells, transplant cells, bacteria, fungi, and parasites, in which it damages negatively charged cell membranes because of its positive charge (4). It plays an important role in the host defense against pathogens, and it induces apoptosis of target cells by using a mechanism involving caspases and other pathways (4). Its potency makes it a credible mediator of skin damage in patients with SJS/TEN. Adding to this credibility is a report (1) that granulysin is the most highly expressed cytotoxic molecule in the blisters of patients with SJS/TEN. We show that serum granulysin levels in 4 of 5 patients with SJS/TEN were elevated before skin detachment or mucosal lesions develop. Soluble Fas ligand (sFasL) shares some properties with granulysin: It contributes to keratinocyte death in SJS/TEN (3, 5), and levels are elevated in the sera of patients with SJS/TEN (3). Serum granulysin levels, however, are approximately 100 times higher than those of sFasL on day...
Therefore, we believe it would be easier to develop bedside granulysin serum measurement, for example, by using immunochromatography, than it would be to develop a similar sFasL measurement. Monitoring serum granulysin might enable early diagnosis of SJS/TEN in patients with cutaneous adverse drug reactions that otherwise could not be distinguished from ODSRs.

Riichiro Abe, MD, PhD
Naoya Yoshioka, MS
Junko Murata, MD
Yasuyuki Fujita, MD
Hiroshi Shimizu, MD, PhD
Hokkaido University Graduate School of Medicine
Sapporo 060-8638, Japan

Potential Conflicts of Interest: None disclosed.

References
1. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med. 2008;14:1343-50. [PMID: 19029983]
2. Ogawa K, Takamori Y, Suzuki K, Nagasawa M, Takano S, Kasahara Y, et al. Granulysin in human serum as a marker of cell-mediated immunity. Eur J Immunol. 2003;33:1925-33. [PMID: 12884856]
3. Murata J, Abe R, Shimizu H. Increased soluble Fas ligand levels in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis preceding skin detachment. J Allergy Clin Immunol. 2008;122:992-1000. [PMID: 18692887]
4. Kaspar AA, Okada S, Kumar J, Poullain FR, Droouvalakis KA, Kelekar A, et al. A distinct pathway of cell-mediated apoptosis initiated by granulysin. J Immunol. 2001;167:350-6. [PMID: 11418670]
5. Abe R, Shimizu T, Shibaki A, Nakamura H, Watanabe H, Shimizu H. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble Fas ligand. Am J Pathol. 2003;162:1515-20. [PMID: 12707054]

Localized Amyloidosis at the Site of Enfuvirtide Injection

Background: Enfuvirtide is the first of a new class of antiretroviral agents that block fusion of the viral particle with the host target cell. Its safety and antiviral activity have been demonstrated (1, 2). In clinical trials, injection site reactions occurred in 80% to 100% of patients (3). The most common signs and symptoms reported were induration in 94%, erythema in 91%, and subcutaneous nodules and cysts in 70% (4).

Objective: To describe a case of amyloidosis at the injection site of enfuvirtide.

Case Report: The patient was a man aged 47 years who had a history of sexual intercourse with men and extensive treatment for HIV with a triple-class viral resistance profile. He also had longstanding leg pain thought to be secondary to HIV neuropathy and no history of intravenous drug use. There was no history of opportunistic or chronic infections.

Because of a persistently elevated viral load, enfuvirtide by subcutaneous injection was added to his highly active antiretroviral treatment regimen for 41 months; enfuvirtide therapy was then stopped in February 2007 because of intolerable injection site reactions. While he was receiving enfuvirtide, his viral loads were completely suppressed. Eighteen months after enfuvirtide therapy was stopped, large, tender, indurated reactions with fragile epithelial sur-
subcutaneous nodular amyloidosis is rare (7, 8). The lesions can present as waxy nodules with or without overlying atrophic epidermis, and they may ulcerate with minimal trauma, causing cutaneous hemorrhage (7–9). Some authors (7) have reported that nodular cutaneous amyloidosis may occur in relation to cutaneous plasmocytoma.

Amyloid formation at the site of drug injection has been described in 5 previous patients. Of these, 4 were receiving either porcine or human insulin for glucose control (10–13), and 1 was given injections of an unknown medication during the Korean War (14). To our knowledge, this is the first case of localized amyloidosis associated with the use of enfuvirtide. We believe that localized amyloidosis should be considered in patients with severe, persistent injection site reactions and suggest that subcutaneous hemorrhage may help make the diagnosis.

Miguel Emilio Morilla, MD
Mount Sinai School of Medicine, Englewood Hospital Program
Englewood, NJ 07631

Jeffrey Kocher, MD
Englewood Hospital
Englewood, NJ 07631

Marco Harmaty, MD
Mount Sinai School of Medicine
New York, NY 10029

Potential Conflicts of Interest: None disclosed.

References
1. Lalezari JP, Henry K, O’Hearn M, Montaner JS, Pilieno PJ, Trotter B, et al; TORO 1 Study Group. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med. 2003;348:2175-85. [PMID: 12637625]
2. Church JA, Hughes M, Chen J, Palumbo P, Mofenson LM, Delora P, et al; Pediatric AIDS Clinical Trials Group P1005 Study Team. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. Pediatr Infect Dis J. 2004;23:713-8. [PMID: 15295220]
3. Myers SA, Selim AA, McDaniel MA, Hall R, Zhang Y, Bartlett JA, et al. A prospective clinical and pathological examination of injection site reactions with the HIV-1 fusion inhibitor enfuvirtide. Antivir Ther. 2006;11:935-9. [PMID: 17302257]
4. Lazzarin A, Cloket B, Cooper D, Reynes J, Arastéh K, Nelson M, et al; TORO 2 Study Group. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med. 2003;348:2186-95. [PMID: 12773645]
5. Ball RA, Kinchelow T; ISR Substudy Group. Injection site reactions with the HIV-1 fusion inhibitor enfuvirtide. J Am Acad Dermatol. 2003;49:826-31. [PMID: 14576660]
6. Maggi P, Ladisa N, Cimori E, Attobella A, Pastore G, Filorico R. Cutaneous injection site reactions to long-term therapy with enfuvirtide. J Antimicrob Chemother. 2004;53:678-81. [PMID: 14985276]
7. Sterciuk A, Dompmartin A, Troussard X, Verneuil L, Macro M, Comoz F, et al. Cutaneous amyloidosis and possible association with systemic amyloidosis. Int J Dermatol. 2002;41:127-32; discussion 133-4. [PMID: 12010335]
8. Nguyen TU, Oghalai JS, McGregor DK, Jansen NM, Huston DP. Subcutaneous nodular amyloidosis: a case report and review of the literature. Hum Pathol. 2001;32:346-8. [PMID: 11274647]
9. Love WE, Miedler JD, Smith MK, Mostow EN, Cooper KD, Gilliam AC. The spectrum of primary cutaneous nodular amyloidosis: Two illustrative cases [Letter]. J Am Acad Dermatol. 2008;58:S33-5. [PMID: 18191697]
10. Stierkel S, Schneider HM, Müntener H, Kashiwagi S. Lateralgen, insulin-dependent, local amyloidosis. Lab Invest. 1983;48:108-11. [PMID: 6337294]
11. Swift B. Examination of insulin injection sites: an unexpected finding of localized amyloidosis [Letter]. Diabet Med. 2002;19:881-2. [PMID: 12358880]
12. Dische FE, Wermszt C, Westermann GT, Westermann P, Pepys MB, Rennie JA, et al. Insulin as an amyloid fibril protein at sites of repeated insulin injections in a diabetic patient. Diabetologia. 1988;31:158-61. [PMID: 3286343]
13. Cim CC, Barker D, Tysms DJ. Unexpected finding of amyloidosis at the site of insulin injection. Pract Diab Int. 2005;22:118.
14. Wei BP, Somers GR, Castles L. Dystrophic calcification and amyloidosis in old subcutaneous injection sites. ANZ J Surg. 2003;73:556-8. [PMID: 12864841]

CORRECTIONS

Correction: Can Helicobacter pylori Eradication Treatment Reduce the Risk for Gastric Cancer?

A recent article (1) that pooled data from 6 trials reported that, compared with no treatment, Helicobacter pylori eradication treatment reduced the relative risk (RR) for gastric cancer (0.65 [95% CI, 0.43 to 0.98]). The article described and counted data from “2” trials that the editors believe were actually 5- and 10-year follow-up data from the same trial (2, 3). Furthermore, the reported data for the eradication treatment group for the trial showed fewer cases of gastric cancer at 10-year follow-up (n = 2) than at 5-year follow-up (n = 4). Reported numbers for the 10-year follow-up were extracted from an abstract presentation (3). If the reported data from the 5- or 10-year follow-up are excluded, the pooled RR is 0.65 (CI, 0.42 to 1.01) or 0.70 (CI, 0.46 to 1.08), respectively. If reported data from both the 5-year and 10-year follow-up are excluded, the pooled RR is 0.71 (CI, 0.45 to 1.23).

References
1. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? Ann Intern Med. 2009;151:121-8. [PMID: 19620164]
2. Leung WK, Lin SR, Ching JY, To KF, Ng EK, Chan FK, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication. Gut. 2004;53:1244-9. [PMID: 15306578]
3. Zhou L. Ten-year follow-up study on the incidence of gastric cancer and the pathological changes of gastric mucosa after H. pylori eradication in China [Abstract]. Gastroenterology. 2008;134:A235.

Correction: Predicting Deep Venous Thrombosis in Pregnancy

There are 2 errors in a recent article on prediction of deep venous thrombosis in pregnancy (1). In Table 5, under “LEFT variables,” the second subheading should say “≤1 or >1,” and the first line under that should say “≤1.” The online version has been corrected.

Reference
1. Chan WS, Lee A, Spencer FA, Crowther M, Rodger M, Ramsay T, et al. Predicting deep venous thrombosis in pregnancy: out in “LEFT” field! Ann Intern Med. 2009;151:85-92.