COMMENTS AND RESPONSES

bcl-2 Rearrangement in Mixed Cryoglobulinemia

TO THE EDITOR: In their interesting report, Zignego and colleagues (1) observed that the translocation t(14;18) involving the bcl-2 oncogene is much more common in patients with hepatitis C virus infection and mixed cryoglobulinemia, particularly those with type II disease. They measured Bcl-2 protein expression in the peripheral blood mononuclear cells (PBMCs) of two patients carrying the translocation and two controls and found overexpression of Bcl-2 protein in the former. In their Figure 3, they also showed that Bcl-2 expression in PBMCs is largely confined to B cells.

However, when Bcl-2 expression is compared in PBMCs, the number of B cells in the sample must be taken into account. My colleagues and I (2) examined Bcl-2 expression in patients with a disorder characterized by chronic B-cell proliferation, persistent polyclonal B-cell lymphocytosis (which is an expansion of memory B cells) (3). In persistent polyclonal B-cell lymphocytosis, a substantial number of peripheral blood B cells carry the t(14;18) translocation (1 to 3 in 1000, as measured by quantitative real-time polymerase chain reaction). When we compared unpurified PBMCs from patients with persistent polyclonal B-cell lymphocytosis and those from controls, we found that the patients had overexpression of Bcl-2 protein. However, when we compared purified B cells from patients and controls, this was no longer true, demonstrating that the apparent overexpression of Bcl-2 was due to the different number of B cells in the PBMCs of the two groups (50% to 80% vs. 5% to 15%, respectively) (2).

Since there can be also an expansion of peripheral blood B cells in type II cryoglobulinemia (4), Zignego and colleagues should have normalized the numbers of B cells in their samples when comparing Bcl-2 expression with that of normal controls. In addition, persistent polyclonal B-cell lymphocytosis reminds us to interpret the presence of the translocation t(14;18) with caution. In contrast to patients with hepatitis C virus infection and cryoglobulinemia, no clear case of transformation to frank lymphoma has been observed in patients with this obscure disorder.

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References

Health Care–Associated Bloodstream Infections

TO THE EDITOR: In a very ambitious study, Friedman and colleagues (1) suggested that empirical antibiotic therapy should be similar for patients with known or suspected health care–associated bloodstream infections and those with nosocomial bloodstream infections. Although the concept of “community” needs to be reformed, it is still too early to make such a categorical affirmation.

It is notable that around 50% of the health care–associated and nosocomial bloodstream infections in Friedman and colleagues’ study were associated with intravascular devices, producing a high rate of meticillin-resistant *Staphylococcus aureus* infection in both groups. According to previous studies, patients from the community using vascular devices could be infected by similar pathogens as patients in nosocomial settings, and that could guide empirical therapy (2). However, whether this is also the case for other types of infections remains unclear. Unfortunately, Friedman and colleagues did not discuss whether the causes of bloodstream infections secondary to urinary and gastrointestinal infections and pneumonia, as well as susceptibility of these infections to treatment, also differed among the studied groups.

Broadly speaking, the major risks for development of an infection caused by a resistant pathogen are host factors (underlying disease and severity), invasive medical procedures and devices, and previous antibiotic therapy (3). For their newly defined group, the authors “selected” from the community most of the patients who shared these risk factors. However, other groups also have some of these risk factors and could be included in this new group. On the other hand, subgroups of the group defined by the authors have not been shown to be associated with infections by some resistant bacteria, and persons in these subgroups could develop resistance if treated with unnecessary broad-spectrum antibiotics (4).

Friedman and colleagues’ major contribution is in pointing out the existence of a subgroup of the community that shares the mentioned risk factors for bloodstream infections. Future studies should examine whether this subgroup includes the persons suggested by the authors and whether this new group and patients with nosocomial infections should receive the same empirical therapy.

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References
IN RESPONSE: The primary objective of our study was to develop a new classification scheme for bloodstream infection that distinguishes among community-acquired and health care–associated bloodstream infections. Dr. Zetola states that subgroups within the health care–associated category we proposed have not been proven to be associated with infection caused by antimicrobial-resistant bacteria and that use of unnecessary broad-spectrum antibiotics might harm patients by leading to resistance. The most significant antimicrobial-resistant pathogen isolated in our study was methicillin-resistant Staphylococcus aureus (MRSA). This was the infecting pathogen in 19% of patients with health care–associated bacteremia and 20% of patients with nosocomial bacteremia but only 2% of patients with community-acquired bacteremia. Moreover, MRSA bacteremia occurred in all subgroups of the health care–associated category, including recently hospitalized patients; those receiving home intravenous therapy or nursing care, dialysis, or chemotherapy; and those in nursing homes. Enterobacteriaceae resistant to ampicillin–sulbactam or ciprofloxacin were infrequently cultured. However, they were recovered with similar frequency in nosocomial settings (18 of 40 patients [45%] and 2 of 40 patients [5%], respectively) and health care–associated settings (17 of 45 patients [38%] and 5 of 45 patients [11%], respectively) and less frequently in community settings (11 of 58 patients [19%] and 0 of 58 patients [0%], respectively).

Over the past decade, published studies have reported increasing rates of non-nosocomial MRSA bacteremia (1, 2), and we are currently studying the impact of health care–associated MRSA infections on university and community hospitals. In preliminary data from our university hospital, 405 of 1061 MRSA isolates taken from blood, sputum, and urine during 1994–2002 (38%) were acquired in non-nosocomial settings. During 1999–2002, 810 of 1119 MRSA infections (72%) occurring in patients from 10 community hospitals in the Duke Infection Control Outreach Network were acquired in non-nosocomial settings. These data suggest that there is a large burden of health care–associated MRSA in our health system. We encourage Dr. Zetola and others to study these subgroups in their hospitals.

At present, we believe it is wise to empirically treat all patients who have health care–associated infection with antimicrobial regimens similar to those used for patients with nosocomial infection. Although we agree that further validation of the concept of health care–associated bloodstream infections is appropriate, we disagree that giving vancomycin or broad-spectrum antibiotics (depending on the suspected pathogen) as empirical therapy for suspected health care–associated bacteremia and other serious infections would cause harm by promoting antimicrobial resistance. In fact, withholding such therapy pending culture results could result in an even more undesirable outcome: the death of patients.

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References
The Relative Safety of Ephedra Compared with Other Herbal Products

TO THE EDITOR: Bent and colleagues, in their report on adverse reactions to ephedra compared with other herbal products (1), stated, “Some industry experts claim that ephedra is safe and note that the number of adverse reactions reported among users of ephedra may not be greater than the background rate of events in the population,” and referenced a document I wrote about 3 years ago (2). First, I want to be clear that I have never claimed that ephedra is safe, nor do I believe that any informed scientist would do so. Second, I wrote the document in question precisely to demonstrate the need for a formal comparative study. The paper by Bent and colleagues is such a study, and I applaud the authors for their work. This type of study has been sorely needed and, along with a recent meta-analysis (3), provides critical data on the potential risks of ephedra.

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Disclosure: Dr. Kimmel has served as a consultant to the Ephedra Education Council and some companies that made ephedra-based products.

References

Clinical Observation

Anti–Cyclic Citrullinated Peptide Antibodies in Advanced Rheumatoid Arthritis

TO THE EDITOR: Background: Rheumatoid arthritis is a chronic systemic autoimmune disease of unknown cause. There is growing evidence that therapeutic intervention early in the disease course leads to better control and less joint damage. With more sophisticated types of therapy becoming available, it is now even more important to definitively diagnose rheumatoid arthritis at an early stage so that treatment can be administered sooner and major damage of joint tissue can be prevented (1). A disease-specific autoantibody that could be used as a serologic marker of the disease would be very useful.

Rheumatoid factor combined with clinical findings has been extensively used to support the diagnosis of rheumatoid arthritis. However, rheumatoid factor is also present in healthy persons as well as in persons with other autoimmune and infectious diseases. One promising new marker in this category is anti–cyclic citrullinated peptide (CCP) antibody. It binds to determinants rich in the unusual amino acid citrulline, which is generated by enzymatic digestion of arginine residues. Anti-CCP antibodies have been reported to be detected very early in rheumatoid arthritis, appear to be a good prognostic marker, and discriminate between erosive and nonerosive rheumatoid arthritis (2, 3).

Objective: To test for anti-CCP antibodies in patients with already established structural damage from rheumatoid arthritis, associated with high indexes of activity and long disease duration.

Methods and Findings: We tested for anti-CCP antibody in 150 patients with rheumatoid arthritis of long duration and attempted to correlate it with disease activity score (4). Presence of anti-CCP antibody was determined by enzyme-linked immunosorbent assay using a second-generation kit (Axis Shield Plc, Dundee, Scotland, United Kingdom). Details of the patient sample and drug treatment at the time of the study have been reported elsewhere (5). Of the 150 patients evaluated, 120 were found to have anti-CCP antibodies (sensitivity, 80%), and a strong correlation was found between the presence of anti-CCP antibodies and disease activity score ($r = 0.82$) (Table).

Conclusion: Our results in patients with rheumatoid arthritis of long duration confirm the observations made by others in patients with early rheumatoid arthritis. The presence of antibodies against CCPs is associated with disease severity and can be used in conjunction with rheumatoid factor to diagnose very early stages of rheumatoid arthritis. Although the role of CCPs in the pathogenesis of rheumatoid arthritis is yet to be elucidated, our data on advanced rheumatoid arthritis combined with reports on early rheumatoid arthritis suggest that anti-CCP antibodies may become a key serologic marker for rheumatoid arthritis.

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Table. Incidence of Anti–Cyclic Citrullinated Peptide Antibody in Patients with Advanced Rheumatoid Arthritis (Mean Disease Duration, 12 Years)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Rheumatoid Arthritis, %</th>
<th>Controls, %</th>
<th>Correlation with Disease Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for anti-CCP antibody</td>
<td>80</td>
<td>2</td>
<td>$r = 0.82$</td>
</tr>
<tr>
<td>Negative for anti-CCP antibody</td>
<td>20</td>
<td>98</td>
<td>$r = 0.12$</td>
</tr>
</tbody>
</table>

* CCP = cyclic citrullinated peptide.
Correction: Serum Ferritin Level Predicts Advanced Hepatic Fibrosis among U.S. Patients with Phenotypic Hemochromatosis

A recent article on serum ferritin level and cirrhosis in hemochromatosis (1) contained two errors. In Figure 2, point B was marked incorrectly on the receiver-operating characteristic curve. The corrected Figure has been reprinted here. Also, on page 630, in the first full paragraph in the right-hand column, the 95% CI for 65.0% specificity should be 58.1% to 71.9%, not 35.1% to 41.9%.

Reference

Correction: The Relative Safety of Ephedra Compared with Other Herbal Products

In its Discussion section, an article on the relative safety of ephedra (1) stated, “Some industry experts claim that ephedra is safe and note that the number of adverse reactions reported among users of ephedra may not be greater than the background rate of events in the population.” The reference provided for this sentence was a document presented in August 2000 at the U.S. Department of Health and Human Services Public Meeting on the Safety of Dietary Supplements and subsequently published by the Ephedra Education Council (2). This document, however, contained no explicit statement regarding the safety of ephedra.

References
COMMENTS AND RESPONSES

Airborne Dispersal of Staphylococcus aureus Associated with Symptomatic Rhinitis Allergica

TO THE EDITOR: Airborne transmission of Staphylococcus aureus is considered rare (1). However, previous studies showed that a viral infection can drastically increase the dispersion of S. aureus into the air by nasal S. aureus carriers (2–4). We investigated airborne S. aureus dispersal by a nasal S. aureus carrier with allergic rhinitis. The carrier was asymptomatic while receiving an antihistamine. Air cultures were performed in a chamber with high-efficiency particulate air (HEPA) filtration using four Andersen air samplers and settle plates (Thermo Andersen Corp., Franklin, Massachusetts) (4). During each study day, the cultures were done with the volunteer sitting in the chamber for three periods of 20 minutes, wearing, respectively, street clothes, sterile garb, and sterile garb with a surgical mask. The number of sneezing and coughing episodes was recorded. Allergic rhinitis symptoms were assessed by using a score (5), by counting the tissues used, and by determining the weight of the nasal mucus expelled. The volunteer was studied for 2 days while asymptomatic (baseline). He then interrupted his therapy. Seven days later, he was symptomatic and was studied for a further 10 days. The peak airborne S. aureus count increased significantly above the mean count at baseline while the volunteer was wearing clothes (from 0.5 colony-forming unit [CFU] to 19 CFUs; \(P = 0.006\)) and sterile garb (from 0 CFU to 20 CFUs; \(P = 0.032\)), but not while he was wearing sterile garb and mask (from 0 CFU to 2 CFUs; \(P = 0.164\) (Figure)). Ninety-five percent of the airborne S. aureus typed by pulsed-field gel electrophoresis was identical with the S. aureus in the volunteer’s nose. Independent predictors of increased airborne dispersal of S. aureus were sneezing (\(P < 0.001\)) and number of tissues used (\(P = 0.007\)). The quantity of mucus and coughing both correlated with decreased airborne dispersal of S. aureus. In this nasal carrier, symptomatic rhinitis allergica caused a significant increase in airborne dispersal of S. aureus.

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References

Osteoprotic Fractures of the Distal Humerus in Elderly Women

TO THE EDITOR: Epidemiologic information on the long-term trends of osteoporotic fractures is scarce, especially for fractures at the distal humerus. Although these fractures are not as common as those at the distal forearm, they are severe injuries that usually require surgical intervention, with accompanying long follow-up and rehabilitation, high costs, and increased risk for considerable morbidity. Previously, we reported that the number of Finnish women 60 years of age or older who were admitted to hospitals because of osteoporotic fractures of the distal humerus quadrupled from 1970 to 1995 (1). We followed fracture development for 5 more years (until the end of 2000) and completed the records for 1970 to 2000 by adding the previously missing years to the database.

We collected data on osteoporotic fractures of the distal humerus from the Finnish National Hospital Discharge Register. This statutory, computer-based register is the oldest nationwide discharge register in the world (in operation since 1967) and provides reliable data for severe injuries in the Finnish population of 5 million people (1–4). Throughout the study years, an osteoporotic fracture of the distal humerus was defined as a fracture occurring in persons 60 years of age or older as a consequence of moderate or minimal trauma only (for example, a fall from a standing height of \(\leq 1\) m). Fractures caused by traffic accidents and other types of high-energy trauma were excluded. In calculating the age-adjusted incidence of fracture (per 100 000 women \(\geq 60\) years of age), we adjusted for age by using direct standardization. The mean population between 1970 and 2000 was used as the standard population. The age-specific incidence
rates were calculated in 10-year age groups (60 to 69 years, 70 to 79 years, and ≥80 years).

The annual total number of osteoporotic fractures of the distal humerus among Finnish women 60 years of age or older increased considerably during the study, from 42 in 1970 to 208 in 2000 (Figure, top). The trend is most alarming in the oldest age group (women ≥80 years of age). The exact reasons for the dramatic increase in fracture incidence are unknown. An increase in the average individual risk for osteoporosis or falling (or both) may partly explain the phenomenon, or elderly people today may have more serious consequences from falls than their predecessors (4, 5). Our observations present great challenges for future fracture prevention. Cost-effective results could be achieved by concentrating on minimization of individual risk factors for bone loss, falls, and fractures in high-risk individuals (5).

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References

Angioedema as a Complication of Upper Endoscopy

TO THE EDITOR: Background: To our knowledge, angioedema has been reported as a complication of upper endoscopy only once in the English-language literature (1). We report what we believe to be the second case of angioedema occurring in the context of esophagogastroduodenoscopy. In the initial case report, Yakel and colleagues (1) attributed angioedema to midazolam. Here, we suggest that the cause was topical benzocaine spray (Hurricaine Spray, Beutlich Pharmaceuticals, Waukegan, Illinois). Benzocaine is routinely used for oropharyngeal anesthesia in many endoscopy centers, although not without some risk. The infrequent, sometimes fatal complication of methemoglobinemia has been reported, but benzocaine has not previously been associated with angioedema (2–4).
At presentation for upper endoscopy, the patient had no unusual symptoms to report. Findings on physical examination performed before the procedure were unremarkable. An experienced endoscopy nurse administered two brief sprays of 20% benzocaine to the oropharynx. Conscious sedation was then administered intravenously (midazolam, 5 mg, and fentanyl, 125 μg). The esophagus was intubated without difficulty. Erosive esophagitis was found at endoscopy, and no biopsies or other interventions were performed.

The initial recovery period was uneventful. However, approximately 1 hour after the procedure concluded, the patient, while in the recovery area, reported dysphagia and swelling of the tongue that rapidly spread to the neck and periorbital area. He did not report pruritus or respiratory symptoms. Physical examination now showed obvious macroglossia, periorbital and labial edema, and nonpitting edema of the neck. Nasopharyngoscopy showed mild pharyngeal edema. The patient rapidly improved after taking H1- and H2-blockers in combination with intravenous steroids. He recovered without incident and was doing well when seen in follow-up 1 week later.

Conclusion: This case of angioedema occurring in the context of upper endoscopy was probably due to administration of topical benzocaine spray. Although midazolam was thought to be the cause in the only other known reported case of angioedema during upper endoscopy, the authors did not report on the use of topical anesthetics (1). Our patient received both midazolam and fentanyl on several previous occasions without adverse sequelae.

This case report raises two important issues. First, clinicians and patients should be aware of this potential complication. Primary care physicians referring patients for upper endoscopy should inform the gastrointestinal consultant of this relevant medical history if it is present. Likewise, the endoscopist and patient should remain vigilant for symptoms suggestive of angioedema following the procedure. It is also important to note that the development of symptoms may be delayed, as suggested by their onset nearly 1 hour after endoscopy in our patient. Second, as was recently suggested by Gunaratnam and associates (5), endoscopists should reconsider the routine administration of benzocaine. Topical anesthesia could be provided with viscous lidocaine or possibly even abandoned altogether in patients receiving intravenous sedation.

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pharmaceutical companies and medical journals are hypersensitive reactions (3), development of antinuclear antibodies (3), possibly lymphoproliferative disorders (3), and reactivation of latent tuberculosis (4, 5). Serious hematologic reactions have been reported in patients treated with etanercept (7), a recombinant human TNF-α receptor that renders TNF biologically inactive. However, to our knowledge, no previous infliximab-related hematologic toxicity has been reported. In our patient, treatment with methotrexate could have played a role in the development of the cytopenias, but two facts argue against this. First, the patient had received methotrexate in the past, even at higher doses, with good hematologic tolerance, and second, the total dose that she received was too low to induce neutropenia.

The causal relation between TNF-α blockade and bone marrow hypoplasia is unclear. However, since TNF-α exerts its physiologic and immune functions through its ability to regulate some proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and granulocyte macrophage colony-stimulating factor, it is theoretically conceivable that its blockade could induce bone marrow failure by blocking stem-cell differentiation (8). In fact, early trials of infliximab documented a rapid decrease in levels of IL-1β, IL-6, and TNF-α R1 and R2, all of which are cytokines that play a role in stem-cell differentiation. Therefore, we think that neutropenia and thrombocytopenia in our patient were probably due to infliximab, or were at least related to the combination of infliximab and methotrexate, and should be added to the adverse effects of this drug. Although this is an anecdotal case report, clinicians and patients should be aware that new-onset fever in a patient beginning a treatment regimen containing infliximab requires a complete blood cell count to exclude neutropenia.

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References