

the Rheumatologist

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COMMON VARIABLE IMMUNODEFICIENCY

Genetic insights into a complex and baffling disease

>> By Daniel Myrtek, PhD, and Ulrich Salzer, MD

Common variable immunodeficiency (CVID) has been recognized as the most common symptomatic form of antibody deficiency diagnosed in adulthood since its first description by Janeway and colleagues.¹ The clinical spectrum of CVID is heterogeneous, but this condition is usually characterized by hypogammaglobulinemia and recurrent bacterial infections. However, the phenotypic and immunologic variability of this disease still marks the diagnosis “CVID” as a grab bag for multiple diseases. Thus, the etiology of CVID is believed to be multifactorial and still holds many unanswered questions. Recent discoveries in the molecular genetics and immunologic basis of this disease have shed important new light on its pathogenesis and raised prospects for earlier and better diagnosis and treatment.

CVID affects both genders equally, with an incidence estimated at 1 in 10,000 to 1 in 50,000.² In a small number of patients, the onset of disease may occur in childhood, but the mean age of onset for the majority of patients is about 23 for men and 28 for women. There is a significant delay—four to six years on average—between the median age of symptom onset and the age at diagnosis.³

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Early treatment lessens arthritis pain and disability, but challenges to early detection remain

>> By Sue Pondrom

This is Part Two of a two-part series on early arthritis clinics. (See Part 1 on page 1 of the May 2008 issue.)

Over the last 20 years, early, aggressive treatment has become the standard of care for patients with rheumatoid arthritis (RA). Yet, there are relatively few specialized early arthritis clinics (EACs) available to the 1.3 million RA patients in the United States, in spite of the tremendous success of

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WATCH the Walk

Gait analysis can improve the walk of patients with arthritis

>> By Greg Lavine

BOSTON—Most people give little thought to how they walk, but patients with arthritis who have joint problems may face significant challenges in maintaining proper walking techniques.

There are a number of both simple and old-fashioned as well as high-tech ways to analyze the gait of patients who have pain during walking, according to a pair of speakers at the ACR/ARHP Annual Scientific Meeting in Boston last November in a session called “Gait Analysis: Hip, Knee, and Foot Effects on Gait and How to Assess Them.”

“Gait involves everything from our heads to our toes,” says Carol Oatis, PT, PhD, professor of physical therapy at Arcadia University in Glenside, Pa. “Gait is purposeful.” Physicians can offer strategies that will not only help patients walk where they need to go, but will also leave them

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A Ghost Appears

We need to address the specter of ghostwriting in medical research >> By David A. Fox, MD

The opening scene of Shakespeare's great tragedy *Hamlet* takes place at night outside Elsinore Castle. Rumors of a ghost have the sentries, Bernardo and Francisco, on edge. Francisco, apparently mistaking Bernardo for an intruder, calls out, "Stand and unfold yourself," a phrase that could just as well be addressed to the ghost of Hamlet's father, who will shortly appear. Shakespeare may be implying that the person (or ghost) must have wrapped himself in layers of fabric in order to conceal something important, an identity or secret that will only be revealed when he obeys the command to "unfold yourself." Indeed, the shocking secrets that the ghost soon unfolds to Hamlet will drive the course of the play, and lead to the ruin or death of most of the protagonists. As Marcellus comments in Scene IV of Act I, "Something is rotten in the state of Denmark."

Haunted Research

Now fast-forward four centuries to the April 16, 2008, issue of the *Journal of the American Medical Association (JAMA)*. Four physicians—Joseph S. Ross, MD, MHS; Kevin P. Hill, MD, MHS; David S.

Egilman, MD, MPH; and Harlan M. Krumholz, MD, SM—publish an article entitled, "Guest authorship and ghostwriting in publications related to rofecoxib: A case study of industry documents from rofecoxib litigation." As paid consultants to the plaintiffs' attorneys, Dr. Ross and colleagues had access to a mass of internal Merck documents that were subpoenaed in connection with litigation concerning adverse effects of Vioxx. They found evidence that articles reporting clinical trials of Vioxx were often authored principally by individuals other than the ultimate first or second author of the published paper. Academics were recruited to be the lead authors as part of a planned strategy that involved ghostwriting by either Merck employees or contracted medical writers. In parallel, review articles were initiated by Merck, directly or through medical writing companies, and were ghostwritten. Recruited authors received honoraria, and such relationships were not fully disclosed. An online database of the documents that were analyzed was made available to allow independent validation of the authors' conclusions. Unfortunately, several members of the ACR are among the physicians implicated.

The editors of *JAMA* clearly view the paper of Ross et al. as highly important. In a lead editorial with the sweeping title, "Impugning the integrity of medical science: The adverse effects of industry influence," Catherine D. DeAngelis, MD, MPH, *JAMA* editor-in-chief, and Phil B. Fontanarosa, MD, MBA, executive deputy editor, pull no punches.

They call the behavior of at least some of the physicians identified by Ross et al. "unprofessional and demeaning to the medical profession and to scientific research." They then enunciate a series of proposals to rescue the integrity of clinical research and medical education, clarify the roles of medical writers, and penalize authors whose disclosures are incomplete. An especially interesting position of Drs. DeAngelis and Fontanarosa is that pharmaceutical companies should be prohibited from providing support for medical education, considering that the April 16th issue of *JAMA* contains several pages of drug ads, including the back cover of the journal. Notwithstanding this one paradox, their message is clear: Something is rotten in the state of medicine.

These publications in *JAMA* have attracted extensive media coverage. The *New York Times* headlined its article on this subject, "Merck wrote drug studies for doctors," and quoted Dr. Ross as saying that "it almost calls into question all legitimate research that's been conducted by the pharmaceutical industry with the academic physician." Another article published on ChicagoTribune.com was entitled,

"Drugs are hyped by ghostwriters, not sound science." And now Senator Chuck Grassley (R-Iowa) has launched an investigation.

When Is a Ghost Not Really a Ghost?

The article by Dr. Ross and colleagues deserves careful examination. It does clearly document examples of ghostwriting and inappropriate ordering of authorship, examples that I was able to confirm upon searching the public database of documents that Ross et al. analyzed. However, when I probed this database with the names of some of the ACR members whose articles were implicated, I found disturbing discrepancies between the available data and the conclusions of the *JAMA* article. For example, regarding a review article on COX-2 inhibitors authored by a single ACR member, the only document in the database that contains this author's name is a grant request (from someone unrelated) that cites an article by this author as a reference. And this grant request had been submitted to a different pharmaceutical company a decade ago, and had nothing to do with rofecoxib or any other anti-inflammatory drug. Why this document was even in the database is not at all obvious. And why this ACR member's review article was listed by Ross et al. in a table with the daunting title, "Published Financial Disclosures among Articles Describing Clinical Trial Results or Scientific Reviews (Including Journal Supplements) Discussed Internally within Merck Prior to Publication That Proposed an External, Academically Affiliated Investigator as an Author," is equally not apparent.

In another case, searching the database with the name of an ACR member who was the single author of a review article described as mentioned in documents "demonstrating that medical publishing companies played critical roles in overseeing the development, organization, and manuscript drafting of supplemental issues focused on rofecoxib" yielded no hits. Likewise, a search using the title of the article yielded no hits. While the supplement in which this article appeared may have had industry sponsorship, no evidence is available to suggest a role for Merck in this specific article.

These examples result from searching the database used by Ross et al. for only a small fraction of the authors and articles that they implicated in the *JAMA* article, which suggests to me that additional individuals may also have been incorrectly identified as being involved in ghostwriting and related practices. The *New York Times* quoted Steven Ferris, PhD, a New York University psychiatry professor as stating that the allegation that his work was ghostwritten was "simply false." Presumably, any errors in the study of Ross et al. were inadvertent, and due to a flawed strategy for analysis of the voluminous documentation that was collected for Vioxx litigation. But these examples beg the question: How many of the accusations are true and how many are not?

What Do We Do Now?

Let me be clear about my own views on ghostwriting: it's an unacceptable practice that has no place in the scientific and medical literature. The same goes for manipulation of data to falsely enhance perceptions of the efficacy and safety of pharmaceuticals. And there is, unfortunately, little doubt that these prac-

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Casting a broad net that traps the innocent with the guilty can reasonably be viewed an act of negligence, even recklessness that—just like ghostwriting—has no place in a medical journal.

tices are not unusual. The medical profession has become far too comfortable with “that affable familiar ghost which nightly gulls him with intelligence,” mentioned by Shakespeare in Sonnet 86.

So, given the importance of these issues, surely Ross et al., as well as the *JAMA* editors who highlighted their article and extended its conclusions, should have understood the necessity to ensure that their facts were entirely correct—100% correct. Their study, amplified by *JAMA*'s commentary, is not just a general discussion of the prevalence and undesirability of ghostwriting. It also has the effect of seriously compromising the integrity and professionalism of every single one of the authors who was cited, not to mention potentially making each of them the target of a Congressional investigation. Casting a broad net that traps the innocent with the guilty can reasonably be viewed an act of negligence, even recklessness that—just like ghostwriting—has no place in a medical journal. As in Shakespeare's plays, good intentions aren't good enough. After encounters with his father's ghost, Hamlet, in his zeal to achieve vengeance, accidentally murders the wrong person: the innocent, albeit bombastic, courtier Polonius. Hamlet's tragic error occurs because he fails to exercise enough care to ascertain the identity of his victim, and instead mistakes him for Hamlet's evil uncle, who had murdered Hamlet's father, usurped his throne, and married his widow.

Any damage that's been done in the pages of *JAMA* will need to be repaired. If an original article based on laboratory research was found to contain

two or three erroneous experiments due to a flawed data collection and analysis strategy, the likely outcome would be retraction of the whole article until the entire body of work could be repeated using a better protocol. It will be up to the editors of *JAMA* to decide whether that standard should also apply to the type of study done by Ross et al. At a minimum, sincere and prominent corrections and apologies will need to be extended to all those who have been inappropriately tainted.

Meanwhile, physicians, scientists, and their professional organizations should think seriously about the next steps we need to take. Why not upgrade authorship standards for clinical trials, review articles, and, indeed, all of the biomedical literature so that accusations of manipulation and ghostwriting would never be correct? If the ACR's code of conduct is not sufficiently explicit on these issues, shouldn't we revise it? In my view it would be a mistake to let any errors in the *JAMA* article deter us from a serious look in the mirror about these important issues.

Disclosure: My columns aren't ghostwritten, but I am grateful for review by and input from various ACR staff members and volunteers, most notably Tammy J. Tilley, ACR's senior director of communications, and Mark Andrejeski, ACR's executive vice president.

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Lessons from a Different Bench

What can college athletics show us about teaching medicine? >> By David S. Pisetsky, MD, PhD

Wasn't the NCAA final a great game? It was a titanic struggle, full of drama and excitement, as two top teams—the University of Kansas and the University of Memphis—battled for the championship. While I could say the game had ebbs and flows, when basketball is played at that level of intensity, tidal waves and rip tides would be more appropriate terminology.

When my Blue Devils exited in the second round, I switched my allegiance to the other North Carolina teams, first to upstart Davidson (Didn't you love watching Stephen Curry, a thin reed among the trees, blessed with a silky jump shot?) and then to the usually hated Carolina. When the finals came, I really didn't have a team to root for and I would have been equally happy whatever the outcome as long as the game was closely fought.

The match-up lived up to promise and the last two minutes of regulation time were thrilling. Whether the turn of events was a heroic comeback or a mortifying collapse is a matter of perspective. I had to stay up after my bedtime to watch the overtime period, but it was great TV and worth every minute, even if *American Idol* had a higher rating that week.

Medicine Through a Basketball Lens

At this point, I am sure, Dear Reader, you are asking what basketball has to do with the practice of medicine. This is *The Rheumatologist* after all, not *Sports Illustrated*, and I know that you want information about our profession, not the musings of a Frank DeFord wannabe. For those of you who read this column, you know that I like to write about sports because, in our society, sports are a metaphor for everything. Under the aegis of TV, sports has exploded in importance as the games of children have become a focus of billions of people who are told that these games have transcendent meaning.

Today, I heard a commentator on TV say that the Masters golf tournament “thrills the soul and replenishes the spirit.” Wow, I thought, that sounds very inspiring, but it is utter malarkey. Although sports have been touted far beyond what it is reasonable, they do provide a picture of human nature and, in sometimes bizarre ways, can illuminate other endeavors, such as medicine.

Patience, my friends, patience. Please wait and you will see where I am going.

Anyway, what intrigued me about the tournament was the attention accorded to the coaches. Just as pro basketball is a game of players, college basketball is a game of coaches. They are the stars and the marquee attractions, and often eclipse the players in fame. The players, alas, appear interested in being student-athletes until eligible for the pro draft. Despite their professed allegiance to their alma maters, however, college coaches are migratory birds, ready to take flight for a better offer. Coaches get big bucks, with University of Kansas coach Bill Self's victory in the NCAA final allegedly netting him a raise to over \$2 million a year.

Who are these coaches? They are larger-than-life figures. They are flamboyant, bombastic, and egotistical and they exude charm and charisma. They

overflow with emotion. They scream, they shout, they jump, they chew towels, they throw chairs, they excoriate the refs, and they rant at their players. They know how to win, however, and they get their players to buy into their creed, whether it is a match-up zone or a tough man-to-man defense.

Of the coaches in the finals, I liked John Calipari because of his behavior during the prelude to the final. Calipari is the coach of Memphis, a smooth

ly different undertaking. In house staff training, if an intern or resident does not perform well, there is no equivalent of benching or choice words fulminated at the sidelines. Can you imagine the following exchange between a chief resident and an intern?

“Pisetsky, you're stinking up the place tonight. You're dragging out there and your last differential didn't include vasculitis. You're through tonight! I'm not letting you take another admission until your

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Head coach John Calipari of the Memphis Tigers talks to his team during a break in the game.

talker who left frigid Massachusetts to go to the sunny South to assemble a champion team. Even though James Naismith, MD, invented basketball in the North, the South seems more suited to hardwood success.

One of the stars of Memphis was the center named Joey Dorsey. In some parlance, Dorsey would be called a strapping lad, but to the sportscasters he is a behemoth, a monster, a rock. At 6'9" and 265 pounds, he is all bulging and chiseled muscle. In the lingo of sports, his chest is big enough for a billboard. (My contribution to sports clichés: Dorsey is a mean mass of myoglobin.)

In the paint, Dorsey was a fearsome presence, a rebounding machine and ferocious shot blocker. When Dorsey swatted a shot, it rocketed into the upper deck like a cannon ball. Looking at Dorsey, I would have been afraid to drive against him even inside a Sherman tank. Nevertheless, during the UCLA game, Calipari pulled Dorsey to the sideline, got into his face, and fumed at him.

At a post-game interview, a reporter asked Calipari why he had berated Dorsey so mercilessly since Memphis was winning. Calipari replied, “I thought that he was a little bit timid. He's a beast and there were times today that he was not a beast.”

Certainly fooled me. If the Dorsey I watched was timid, I would hate to see him when he is angry.

Sideline Bench to Bedside

We are now getting to medicine, which is an entire-

write-ups show more detail.”

“Please, let me take another admission. I'll do better with the next case.”

“Forget it, Pisetsky. You've had your chance. Now, go home.”

I doubt such an exchange ever took place or ever will.

While the methods of sports coaches are sometimes primitive, manipulative, and even barbaric, they can be effective. In my next columns, I will discuss how we coach today's trainees in medicine and whether we are teaching them to play like winners and—may I dare say—to act like beasts.

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AMCs and Patient Safety

Quality adds new dimension to the three-part mission

>> By Joan M. Von Feldt MD, MS Ed, and Jennifer S. Myers, MD

In just one decade, the Institute of Medicine has changed the landscape of American healthcare with its consecutive reports *To Err is Human: Building a Safer Healthcare System* in 1999 and *Crossing the Quality Chasm: A New Health System for the 21st*

Century in 2001.^{1,2} These reports presented a vision and agenda for how healthcare needs to be radically transformed in order to meet the six attributes of ideal care: safe, effective, timely, efficient, equitable, and patient centered. This vision is easy to agree on

yet hard to implement, and hospitals across the nations continue to struggle to create an intelligently and effectively designed system in what was once a “systemless” array of professional autonomy, non-standardized practice, and free enterprise.

The leaders of academic medical centers (AMCs), with their competing missions of education and research, face additional challenges compared to their non-AMC colleagues, because such vast improvements in the safety and delivery of patient care cannot be achieved without prioritizing the safety and quality mission in parallel with the research and educational mission.

The Future of AMCs

Given the importance of these issues, a study published by Keroack and colleagues in *Academic Medicine* is notable for calling attention to the challenges AMCs face in the future.³ This study represents the first attempt to quantify, through a composite score of a wide variety of patient-level data, the quality and safety of care delivered in AMCs. In addition, the authors augmented their score by performing blinded site visits to validate their patient-level data with experiential observations and interviews. Such qualitative data allowed them to identify organizational themes that separate the high-per-

forming from the low-performing medical centers. These data can help leaders in average-performing AMCs answer the important questions: “What are we doing wrong?” and “How can we move the big dots in the right direction?”

Keroack and colleagues collected measurements on four of the six attributes of quality health care: patient safety, mortality, clinical effectiveness, and healthcare equity. Because consensus around measurements for patient centeredness and outpatient care were not available at the time of the study, the authors did not include these measures in their analysis. Seventy-nine AMCs in the University HealthSystem Consortium (UHC), an organization of 97 university teaching hospitals across the United States, were included in the study.

TABLE 1:

Characteristics of AMCs That Perform Highly in Quality and Safety

- > Leaders who are dissatisfied with the current state of quality and safety;
- > Chairs who accept responsibility for quality and safety within their departments;
- > Employees who value each other’s critical knowledge and whose relationships are characterized by collaboration;
- > Accountability, innovation, and redundancy at the unit level;
- > Focus on results, human behavior, and work redesign as the keys to improvement;
- > Service excellence added to the focus on quality and safety;
- > Shared sense of purpose among hospital leaders that patient care comes first; and
- > Strong alliance between the executive leadership and the clinical department chairs of the institution.

Safety measures were determined by evaluating preventable complications known as patient safety indicators (PSIs) as determined by the Agency for Healthcare Research and Quality (AHRQ). Such measures are abstracted from hospital discharge information and include conditions such as nosocomial infections, falls, and wrong-site surgery. Mortality measures were determined by evaluating risk-adjusted mortality rates for selected inpatient diagnoses. For the area of clinical effectiveness, the authors used compliance with the Joint Commission (JC) Core Measures and 14-day surgical readmission rates for the same condition or surgical complication as their measure of quality. Finally, equity of care was evaluated by analyzing JC Core Measure diagnoses looking for disparities of care across gender, race, and socioeconomic status.

The patient safety, mortality, and effectiveness domains were each weighted at 30% and equity was weighted at 10% in the creation of a composite score for each institution. The 79 AMCs were divided into five groups according to composite scores for quality and safety, with group one being the five highest-performing AMCs and group five being the 14 lowest-performing ones.

In phase two of the study, the authors selected three institutions from the top five-performing AMCs and three comparison institutions from the middle of the distribution for site visits by an expert team who were blinded to the performance scores of the institutions. The site visit was preceded by a review of documentation related to the quality program, leadership, goal setting activities, and board reports. During the site visit, the authors conducted formal interviews not only with key leaders, but also with front-line employees such as members of the residency programs and nursing staff.

During the interviews, multiple areas of leadership and organization were explored including leadership engagement, strategic planning and goal setting, accountability for quality and safety goals, interdisciplinary professionalism, the use of information technology, internal and external communication between the leadership and employees about quality and safety, and patient centeredness. Through inductive and iterative analysis of the interviews and documents, several themes were identified that distinguished the top performers from the average performers. Interestingly, although the site visit team was blinded, there was quick consensus about the status of the institutions as either top or average per-

formers in all six cases, indicating a level of clarity in distinguishing these two groups.

Characteristics of a Top-ranked AMC

The placement of patient care as first among the competing missions of patient care, research, and education in AMCs was clearly evident at the top performing institutions. These institutions were dissatisfied with the current state of quality, safety, and service and were focused on the journey between the current state and the future ideal state toward which they were striving. Leaders of the top institutions were engaged with and

organizational learning will take place through serendipity or as a byproduct of normal work. Instead, it actively promotes, facilitates, and rewards collective learning.⁸⁻¹² Successful companies have utilized techniques of organizational learning for years to maximize efficiency and productivity.

Recently, healthcare organizations have also identified organizational learning as a critical component of their success. This study begins to identify the characteristics that several top AMC performers have in the domains of quality and patient safety, and, as such, will be useful to academic medical centers as they continue in their quest for improvements in patient care.

All physicians need to increase their understanding of how system redesign and reducing waste and complexity can improve the care we deliver to our patients. Moving beyond simply understanding these changes, we need to be leaders in organizational change and exemplify the principles of accountability, transparency, and professionalism. For those of us in AMCs, we need to remind ourselves that the tripartite mission of research, education, and patient care has developed a fourth dimension—quality and safety—that we must not only practice, but teach. It's about time. | THE RHEUMATOLOGIST |

TABLE 2:

Strategies to Improve Patient Safety

- > Create a vision of patient centered care delivery;
- > Modify organizational culture through effective leadership;
- > Develop catalytic middle managers;
- > Create cultural rites that emphasize patient centeredness;
- > Promote accountability at every level of the organization; and
- > Provide a formal curriculum in patient safety for medical students and housestaff.

visible to the front-line staff. Senior leadership reinforced patient-centered care with a strong but subtle pressure to conform to the values of safety, quality, and service. Clinical chairs and service chiefs accepted accountability for quality, safety, and service on their units and were focused on results through the setting and dissemination of measurements at all levels of the institution. Innovation at the unit level was encouraged, celebrated, and often self-started and sustained. Finally, interdisciplinary collaboration and multidisciplinary teams were the rule rather than the exception.

In contrast to visits at top-performing institutions, the site visits at the average-performing institutions uncovered palpable conflict among the missions of patient care, education, and research. The clinical department chairs demonstrated inconsistency in their interest in the patient care missions, and the hospital leaders were either unable or unwilling to address this issue. Leaders were less engaged at the grass-roots level, and chairs often opted out of quality and safety initiatives, with leaders tending only to work with the more cooperative or engaged departments or chairs. Board members were much less engaged, and quality initiatives were not widespread. A sense of satisfaction with the current state of quality and safety was a prevailing theme.

Keys to Success

The authors suggest that their new composite scoring system represents an improvement over currently available institutional ratings on quality and safety, which include the well-known *US News and World Report* rankings, *Health Grades*, and *Hospital Compare*, citing the wide variety of patient-level measures used in their scoring system as its unique strength.^{4,6} The authors also acknowledge the weaknesses of their scoring system, including the absence of measurements for access to care and ambulatory care quality and coordination. Recently, a framework for healthcare organizations to develop and validate their own safety measurements has been described.⁷ It is important to note that this study did not address the educational activities of the AMCs. Because residents are frequently at the “sharp end” of healthcare delivery in AMCs, their attitudes and skills will affect patient safety and quality to a large degree. This relationship between resident education and involvement in patient safety activities and hospital outcomes should be studied further.

A learning organization is defined as one that actively creates, captures, transfers, and mobilizes knowledge to allow adaptation to a changing environment.^{8,9} Thus, the key aspect of organizational learning is the interaction that takes place among individuals.¹⁰ A learning organization does not rely on passive processes in the hope that orga-

Dr. Von Feldt is associate professor of medicine in the rheumatology division at the University of Pennsylvania School of Medicine in Philadelphia and a TR board member. Dr. Myers is assistant professor of clinical medicine in the division of general internal medicine and the patient safety officer at the Hospital of the University of Pennsylvania.

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2008 EDUCATION PROGRAMS

JUNE		
	11	Rheumatology Audioconference Series: The Impact of Public Health on Arthritis and other Rheumatic Diseases
	25	Practice Management Audioconference/Webcast: The Perils of E/M Coding & Reimbursement
JULY		
	30	Practice Management Audioconference/Webcast: Responding to an Audit Effectively
AUGUST		
	27	Practice Management Audioconference/Webcast: Improving Collections & Reducing Denials
SEPTEMBER		
	24	Practice Management Audioconference/Webcast: Power Up Your Chart Auditing Program or Get One
OCTOBER		
	24 - 29	ACR/ARHP Annual Scientific Meeting - San Francisco, CA

For more information, go to:
WWW.RHEUMATOLOGY.ORG

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From the COLLEGE

NEWS FROM THE ACR AND THE ARHP

PRACTICE UPDATES

Boost Revenue with Denials Management and Appeals

Denials management and appeals are the two most underestimated processes in rheumatology offices. Most practices lose thousands of dollars every year be-

cause they are not following up or writing off denied claims correctly.

To boost their revenue cycles, physicians and their staff must stay on top of denials. The following quick tips will help you prepare your practice for a revenue boost:

- > Make sure that the patient's identification num-

ber and name are correct, because this is the number-one denial for the Centers for Medicare & Medicaid Services (CMS). Neither insurance companies nor CMS will correct the number for you;

- > Make sure that your claims are re-filed in a timely manner;
 - > Make sure that all denial codes are resolved before resubmitting a claim; and
 - > Know your private carriers' contracts and your CMS carrier's local coverage determination (LCD).

To begin the process, a practice should review the insurance contract or CMS carrier's LCD and determine if the denial was appropriate. Occasionally, the denial does not provide enough information. At these times, a phone call to the carrier is the first step toward resolving the denial.

In some cases, there is only one way to handle a denial—appeal the decision. Each private carrier has its own rules and guidelines on how to appeal a claim. A practice should keep in mind that time is an important factor when trying to appeal a claim. Office staff should pay close attention to the time limit when appealing a claim with private payers; the deadline for filing an appeal could range from 30 days to one year.

CMS has explicit rules regarding appeals. The five levels in the CMS appeal process are:



- > **1. Redetermination by a Medicare carrier:** Practices have 120 days from receipt of the initial claim determination to file an appeal. There is no minimum dollar amount for this appeal level. CMS typically comes to a resolution within 60 days of receiving all supporting documentation for a request.
- > **2. Reconsideration:** Reconsideration is performed by a qualified independent contractor (QIC), which is made up of an independent panel of physicians and other healthcare professionals. A written reconsideration must be filed within 180 days of receiving the redetermination. A decision is typically made within 60 days. If the QIC cannot come to a decision within 60 days, the practice can then take the appeal process to the next level.

> **3. Hearing before an administrative law judge (ALJ):** The dispute must be over \$120. Most ALJ hearings are done by phone or by video-teleconference. If an in-person hearing is requested, the practice must show good cause for a hearing. The ALJ will typically issue a decision within 90 days of the hearing request. Practices may also ask the ALJ to make a decision without a hearing.

> **4. Request an appeals council review:** If the practice is not satisfied with the ALJ decision, it can request an appeals council review. There are no money prerequisites for this level, but the request must be submitted in writing within 60 days of receipt of the ALJ's decision. A decision will typically be made by the appeals council review within 90 days.

> **5. Judicial review in the U.S. District Court:** To file for a hearing in the U.S. District Court, the claim issue must be for at least \$1,180, and the request must be made within 60 days of the appeals council decision.

Not understanding the guidelines can cost a practice money. If practices successfully keep their denials and appeals under control, they can keep revenue where it belongs—in the office.

If you find that your denials management and appeals processes are not being handled correctly by the insurance companies or CMS, contact the ACR's Coding and Reimbursement Specialist, Melesia Tillman, CCP, CPC, at (404) 633-3777, ext. 820, or visit www.rheumatology.org.

Drug Safety Alerts: Moving Past the Pony Express to the 21st Century

Have you ever wondered why you are able to get up-to-the-minute sports scores, but it could take weeks to receive potentially lifesaving drug safety alerts? (And that is only if your front-office staff is able to separate the "Dear Doctor" letter from junk mail.)

With the Health Care Notification Network (HCNN), launched in late March, waiting for important drug alerts could be a thing of the past. With the new HCNN, practices are no longer at the mercy of various intermediaries and the U.S. Postal Service to receive critical patient safety information. The HCNN can rapidly deliver patient

CODING CORNER!

June's coding challenge:

An established 48-year-old female patient with fibromyalgia comes in for a scheduled follow-up visit for pain in her trapezius muscles and hips.

The patient is on amitriptyline, 25 mg, at bedtime and an aerobic exercise program three days per week. The physician performs three trigger point injections and renews the patient's prescription.

How would you code this? See page 19 for the answer.

safety, public health emergency, and bioterror information to U.S. physicians via e-mail. This service is free to all licensed U.S. physicians and ensures a more efficient and effective delivery of vital safety information by delivering the alerts directly to those who need them most—physicians, healthcare professionals, and their office staff.

The HCNN, operated by the iHealth Alliance, is the result of a three-year collaboration between U.S. medical society leaders, liability carriers, health plans, consumer advocacy groups, and government and industry leaders. The iHealth Alliance's mission is to protect

patients and providers as healthcare increasingly moves online.

Furthermore, the HCNN will be free of advertising and promotion, and will only be used to deliver patient safety alerts.

Why are so many health industry leaders joining in this effort when it will be free of promotional materials? The

answer is simple—increased system efficiency and patient safety leads to cost savings. Liability carriers predict that the delivery of product recalls and warnings immediately and directly to the those who prescribe medications—rather than through the traditional paper system that takes weeks and depends on those who sift through clinic mail to get the alerts—will improve patient safety and re-

duce malpractice claims. This could eventually result in the overall decrease of malpractice insurance premiums, according to an HCNN press release.

Pharmaceutical manufacturers—who currently pay for the U.S. mail-based system—and insurers are also backing the new e-mail-based alert system and encouraging providers to register with the HCNN, because they, too, will benefit from a reduction in adverse drug reactions caused by more timely notification.

For more information about the HCNN, or to sign up for alerts, visit www.hcnn.net or contact Itara Barnes in the ACR's practice advocacy department at (404) 633-3777, ext. 819, or ibarnes@rheumatology.org.

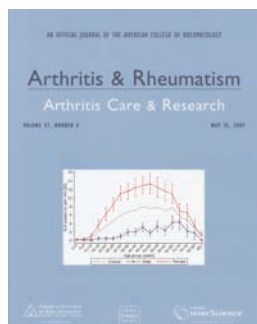
New Advance Beneficiary Notice

CMS has replaced the general and lab advanced beneficiary notice with the Advance Beneficiary Notice (ABN) of Non-coverage. The new titled notice requires physicians and other healthcare providers to use a new form when services are not expected to be covered by Medicare.

The revised ABN forms will replace the existing ABN-G (Form CMS-R-131G), ABN-L (Form CMS-R-131L), and NEMB (Form CMS-20007). For patients to be held responsible for noncovered Medicare expenses, rheumatology practices are required to have a signed ABN on file prior to performing services. In addition, the new ABN:

- > Replaces both the existing ABN-G and ABN-L;
- > Includes a mandatory field for cost estimates of the items and services at issue;
- > May also be used for voluntary notifications, in place of the Notice of Exclusion from Medicare Benefits; and
- > Offers a new beneficiary option under which

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Tips to Access Journals Online

Online access to *Arthritis & Rheumatism* and *Arthritis Care & Research* is a member benefit of the ACR and the ARHP. In order to use this benefit, you must activate your online access by creating a login specifically for the journals through a one-time registration process. Here is a Q&A to help you access journals online.

Q: I am a new member. How do I register to access the journals online?

A: Registration instructions are available on the members-only portion of the ACR Web site. Visit www.rheumatology.org and follow the Publications link from the left-side menu. Once you are on the Publications page, select either *Arthritis & Rheumatism* or *Arthritis Care & Research*. For registration instructions, follow the link for first-time users. The instructions will tell you how to set up your journal login and password, which will be different from your ACR membership number and password.

Q: I have been a member for some time, but I have never accessed the journals online. How do I do it?

A: Follow the new member instructions above.

Q: Can I use my ACR member number and password to access the journals?

A: No, your journal login and password are unique and used only for journal access. To create them, follow the new member instructions above. (Note: During this process, you do have the option to make your journal login and password the same as your membership login and password.)

Q: How will I be notified that a new issue is available?

A: Notification is sent via e-mail once a month. For each journal, you will receive a separate e-mail providing a quick view of the table of contents for the current issue of both *Arthritis & Rheumatism* and *Arthritis Care & Research*. This allows members to be the first to know what topics are being covered in the journals each month.

Q: When I click on the link in the e-mailed table of contents, what will I see?

A: You will be able to view any existing abstract, along with the full title and authors and their affiliations. If you want to view the full article, you will be prompted to enter the journal login information provided during the registration process. Your ACR membership number will not give you access.

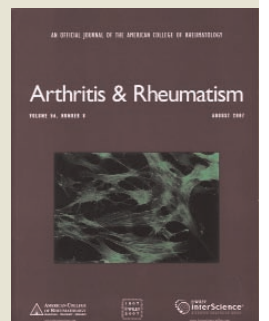
Q: Why do I sometimes only see the title of the article instead of seeing the abstract when I click on a link on the e-mailed table of contents?

A: The abstract will be displayed only if the article contains one. Some article types—such as editorials, letters, or clinical images—do not contain abstracts.

Q: I logged on previously from another location, so why am I asked to enter my password when I log in at home?

A: You only need to register once; however, if you save your password on one computer and then switch to a different computer (going from work to home, for example), you will need to use your password to log in on the new computer.

If you have additional questions about accessing journals online, e-mail membership@rheumatology.org.



an individual may choose to receive an item or service and pay for it out of pocket, rather than submit a claim to Medicare.

CMS is allowing a six-month transition period from when the new form was implemented on March 3, but providers and suppliers must begin using the revised ABN no later than September 1, 2008.

Visit the CMS Web site, www.cms.hhs.gov, for additional information or to download the revised ABN form. If you have any questions or concerns about these changes, contact Melesia Tillman, CCP, CPC, at (404) 633-3777, ext. 820, or mtillman@rheumatology.org.

PQRI Changes for 2008

CMS has announced alternative reporting periods and reporting criteria for the 2008 Physician Quality Reporting Initiative (PQRI).

PQRI provides bonus payments to practitioners who satisfactorily report on CMS-approved measures on a variety of topics, such as RA, osteoporosis, osteoarthritis, and pain management.

There are now nine possible reporting options—including claims- and registry-based reporting of individual measures and measure groups—for six- or 12-month reporting periods ending December 31, 2008. Three of the nine possible reporting options apply to rheumatology practitioners (the other six use measure groups that include non-rheumatology measures):

- > 1. Report through **claims** for **January 1–December 31, 2008**
- > 2. Report through **registry** for **January 1–December 31, 2008**
- > 3. Report through **registry** for **July 1–December 31, 2008**

The second and third options are contingent on the registry being on the CMS-approved registry list that will be posted on the CMS Web site by August 31, 2008.

There is no half-year claims-based individual measure reporting option. The half-year reporting possibility only applies if providers use a registry *or* if they report the largely non-rheumatology focused measure groups through claims. However, practitioners who did not begin claims-based reporting in early 2008 may still be able to successfully participate in full-year individual measure claims-based reporting by using measures that require reporting only once per year. Examples include measures #4 (screening for falls risk), #39 (osteoporosis screening), #41 (osteoporosis: pharmacologic therapy), and #108 (RA DMARD use).

Measures that must be reported after each visit should not be started mid-year because practitioners would likely not meet the minimum annual reporting requirements. Examples include measures #24 (osteoporosis: post fracture communication), #40 (osteoporosis: management following fracture), #109 (osteoarthritis functional assessment), #124 (electronic health records), and #125 (e-prescribing).

More information on PQRI and these recent changes is available at www.cms.gov/pqri.

meeting in San Francisco on October 24–29.

This year's attendees will experience a meeting like no other, with new offerings and the return of highly successful sessions and networking opportunities. The ACR's Committee on Education, Annual Meeting Program Planning Committee, ARHP Program Committee, and ARHP Clinical Focus Course Task Force used the 2007 attendees' survey results to identify areas of interest for this year's meeting. With these data, they developed scientific sessions to cover areas where gaps were identified and created concurrent sessions that will provide something for every interest.

Here's what you can expect at the 2008 ACR/ARHP Annual Scientific Meeting:

- > Pre-conference courses that appeal to attendees looking to catch up on cutting-edge medical studies and that are designed to offer unique learning opportunities to attendees with specific interests and

chances to interact with panel members at all levels;

- > A Clinical Research Conference that takes a close look at clinical trials and research methods, as well as observational studies of non-pharmacologic interventions;
- > An ACR/ABIM Maintenance of Certification course that offers 50 case-based questions from ABIM's 2007 and 2008 Update Modules and is designed to help rheumatologists navigate and excel at the recertification process;
- > A Basic Research Conference that provides an update of the most recent scientific developments in the field of rheumatology and offers something for all attendees, especially avid researchers; and
- > The 2008 ACR Review and 2008 ARHP Clinical Focus courses designed with clinicians in mind, offering breakout sessions that will allow one-on-one in-

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ANNUAL MEETING

Sneak Peak at the 2008 Annual Scientific Meeting

The 2007 ACR/ARHP Annual Scientific Meeting was well received by attendees, and the ACR and the ARHP are building on that foundation by offering a variety of in-depth sessions at the 2008

PATIENT FACT SHEET

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Osteoporosis is a condition of weak bone caused by a loss of bone mass and a change in bone structure. Glucocorticoid-induced osteoporosis is a form of osteoporosis caused by taking glucocorticoid medications, such as prednisone (Deltasone, Orasone, etc.), prednisolone (Prelone), dexamethasone (Decadron, Hexadrol), and cortisone (Cortone Acetate). These medications are used to help control many rheumatic diseases, including RA, systemic lupus erythematosus, and polymyalgia rheumatica.

Anyone who takes glucocorticoid medications for more than three months is at risk of developing osteoporosis and fractures. These medications have a direct negative effect on bone cells, resulting in a reduced rate of bone formation. They can also interfere with the body's handling of calcium and affect levels

of sex hormones, leading to increased bone loss. The most dangerous consequence of glucocorticoid-induced osteoporosis is fracture—including spine and hip fractures, which can lead to chronic pain, long-term disability, and death.

To determine if a patient has glucocorticoid-induced osteoporosis, you can measure the bone mineral density (BMD) at different parts of the patient's body, such as the spine and hip. Dual energy X-ray absorptiometry (DXA) is currently the best test to measure BMD. The test is quick and painless; it is similar to having an X-ray taken, but uses much less radiation. DXA results are scored in comparison to the BMD of young, healthy individuals, resulting in a measurement called a T-score. Patients with T-scores of -2.5 or lower are considered to have osteoporosis and are at a higher risk for a fracture.

According to patient fact-sheet writer Shreyasee Amin, MD, "the major goal in the management of glucocorticoid-induced osteoporosis is the prevention of fractures and to help decrease bone loss." At a

minimum, she suggests that "patients should take 1,000 to 1,500 milligrams of calcium and 400 to 800 IU of vitamin D supplements on a daily basis."

Of course, the first step in management of glucocorticoid-induced osteoporosis is for the patient to discuss it with his or her rheumatologist. To help prevent the possibility of a fracture, the dose and duration of glucocorticoid medication should be minimized, if it is possible for the rheumatologist to do so while keeping the underlying disease under control. Other modifiable risk factors for osteoporosis should be minimized, and weight-bearing physical activity should be encouraged. Finally, it is important to remind patients that the major goal in the management of their glucocorticoid-induced osteoporosis is the prevention of fractures, and it is important to help prevent trauma, which can increase the risk for fractures.

Download the complete glucocorticoid-induced osteoporosis fact sheet and other patient-education materials at www.rheumatology.org by following the links to patient education from the Practice Support Menu.

2008

CALENDAR

JUNE 1

> **Deadline:** Submission for Volunteer Applications for ACR Committees (2008-2009)

JUNE 9

> **Registration:** ACR/ARHP Annual Scientific Meeting Advance Housing and Registration Open to Non-Members

JUNE 11

> **Audiocast:** "The Impact of Public Health on Arthritis and Other Rheumatic Diseases"

JUNE 15

> **Reminder:** Last opportunity to qualify for the REF Circle of Leadership and exclusive donor benefits at the 2008 Annual Scientific Meeting

JUNE 25

> **Webcast/Audiocast:** "The Perils of E/M Coding and Reimbursement"

JULY 1

> **Grant Term:** REF grant funding term begins

JULY 15

> **Deadline:** Summer applications for ACR/ARHP Membership

JULY 30

> **Webcast/Audiocast:** "Responding to an Audit Effectively"

AUGUST 27

> **Deadline:** Application for REF awards and grants

> **Now Available:** *Within Our Reach* Grant request for proposals available online

SEPTEMBER 2

> **Deadline:** 2008 Annual Slide Competition entries due

SEPTEMBER 12

> **Deadline:** ACR/ARHP Annual Scientific Meeting advance housing and registration

SEPTEMBER 24

> **Webcast/Audiocast:** "Power Up Your Chart Audit Program or Get One"

OCTOBER 1

> **Deadline:** Fall applications for ACR/ARHP Membership

OCTOBER 23

> **Exam:** ABIM Rheumatology Board Certification
> **Exam:** ABIM Maintenance of Rheumatology Certification

OCTOBER 24-29

> **Meeting:** ACR Awards of Distinction and ACR Masters nominations

NOVEMBER 1

> **Now Available:** REF Preceptorship applications available online

NOVEMBER 14

> **Deadline:** ACR call for suggestions and ACR study group applications
> **Deadline:** ARHP call for proposals

For more information about these or any other ACR, ARHP, or REF activities, visit www.rheumatology.org.

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teractions geared towards clinicians' specialty areas.

As in previous years, attendees can expect to see the latest technologies and research data, making this a valuable educational experience.

The meeting's keynote speaker will be James Louie, MD, professor of medicine at the University of California, Los Angeles, who will offer unique insights on the creativity and determination of artists—both past and present—who lived with rheumatic diseases, including Pierre-Auguste Renoir, Raoul Duffy, and Paul Klee.

With the creation of new sessions and opportunities, the return of popular sessions and opportunities from past annual meetings, and an informational keynote address, the 2008 ACR/ARHP Annual Scientific Meeting offers something for everyone.

For more information about the meeting, visit www.rheumatology.org/annual—and look for highlights of new and returning sessions in future issues of *The Rheumatologist*.

REF NEWS

Rethink RA Research

Are there genetic indicators that can help rheumatologists identify the people who are at risk for developing the disease? Are there environmental factors that trigger rheumatoid arthritis (RA)? Simply put, what causes RA and how do we treat and cure it?

These are the questions the researchers funded by the *Within Our Reach: Finding a Cure for Rheumatoid Arthritis* campaign are trying to answer.

"We have moved well beyond symptom management and now have treatments capable of modifying disease progression in RA," says Leslie J. Crofford, MD, president of the ACR Research and Education Foundation (REF). "We remain, however, far from the elusive goals

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Apply for an REF Award

The REF offers an extensive awards program with research and education opportunities for clinicians, students, health professionals, researchers, and academic institutions. Apply online at www.rheumatology.org/REF.

of prevention and cure. *The Within Our Reach* grants capitalize on advances in basic, clinical, and translational research that will bring us closer to these goals. Our investment in the best science and scientists will help to create and sustain RA-focused research units across the country—with the expertise and resources to substantively move the field toward finding a cure.”

With that in mind, the REF has announced the second round of grant recipients of the *Within Our Reach* campaign. The following research grants were awarded to 16 researchers:

- > Innovative Basic Research Grants allow investigators to conduct exploratory research on new issues or approaches for which there is currently an insufficient theoretical or empirical basis for a competitive research project application;
- > Translational Research Grants support established independent physician-scientists who are dedicated to translational research, the two-way transfer between work at the laboratory bench and patient care; and
- > Clinical Practice Grants which focus on issues that directly affect the quality of care in clinical practice of rheumatology and patient access.

The REF will spend \$6.5 million in July to accelerate innovative research through the *Within Our Reach* campaign. View a complete list of first- and second-round grant recipients online at www.WithinOurReach.info.

ADVOCATING FOR YOU

Fredrica Smith, MD, Appointed to the PPAC

Fredrica Smith, MD, a rheumatologist in Los Alamos, N.M., was recently invited to become a part of the Practicing Physicians Advisory Council (PPAC), a congressionally mandated council that advises the secretary of the Department of Health and Human Services and the administrator of CMS on proposed changes in regulations.

The PPAC comprises 15 people, 11 of whom must be MDs or DOs. All must have submitted at least 250 claims for physician services in the previous year. The PPAC hears reports from various government agencies that have a role in creating regulations for physicians.

At the March 3 PPAC meeting, the council heard reports on several issues, including the Medicare fee-for-service National Provider Identifier implementation, the 2008 Physician Quality Reporting Initiative, and eHealth and Personal Health Records. These are the same issues that the ACR is monitoring and lobbying about.

Dr. Smith's appointment means that rheumatologists and rheumatology health professionals will have another avenue to shape regulations and voice their concerns on regulations that affect rheumatology.

Of her appointment, Dr. Smith says, “As a rheumatologist in a small town in the west, it is exciting to have been chosen to serve on PPAC. I am delighted to have an opportunity to work with other physicians as we meet directly with CMS to try to influence policy and bring issues facing patient care and medical practices to the attention of CMS.”

The PPAC holds quarterly meetings that are open to the public. Information discussed during these meetings is public record, and a transcript of each meeting



Do you have feedback on any of the articles you've read in *The Rheumatologist*? If so, send us a letter and share your thoughts. Please include your full name, credentials/title, a daytime phone number, and an e-mail address in case we need to contact you. We reserve the right to edit correspondence for space and clarity.

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Phone: (201) 748-7757

can be found at www.cms.hhs.gov.

For more information on PPAC or other regulation issues, contact Kristin Wormley, director of government affairs, at kwormley@rheumatology.org.

RheumPAC: One Year, One Contribution, One Opportunity

Responders to the recent ACR membership survey emphasized the importance of political advocacy for their practices and institutions. RheumPAC, the ACR's political action committee, was created in February 2007 to focus on the legislative issues affecting the rheumatology community.

RheumPAC offers a way for ACR and ARHP members to collectively raise money that will be used to contribute to campaigns of members of Congress—and will enhance rheumatology's political access to them as well. Since its inception, RheumPAC has raised over \$30,000, and recently made its first contribution. During the 2008

Advocates for Arthritis visit to Washington, D.C., the RheumPAC committee unanimously selected Representative Shelley Berkley (D-Nev.) to receive the PAC's first contribution.

Rep. Berkley is the lead sponsor of the "Medicare Fracture Prevention and Osteoporosis Testing Act" (H.R.4206) and she has shown incredible leadership regarding fair reimbursement for DXA.

Rep. Berkley was the keynote speaker at the "Advocates for Arthritis" welcome dinner held in Washington, D.C. in February. There, she received a standing ovation for her passionate—and humorous—speech about her first DXA scan. As the wife of a physician and a patient herself, Rep. Berkley understands the issues affecting physicians and has demonstrated great care for the rheumatology community and women's health issues.

As RheumPAC moves into its second year, the ACR

CODING CORNER!

Coding Corner answer (question on p. 13):

June's coding answer: 20553, single or multiple trigger point(s), three or more muscle(s). Diagnosis: 729.1, myalgia and myositis; fibromyositis NOS.

The CPT code 20553 is for the injection of three or more muscles. Trigger point injections are based on the number of muscles affected, not the number of injections performed. The code 20552 should be used for single or multiple trigger point injections involving one to two muscles.

This was a scheduled office visit for an injection, and the physician did not perform an examination. When a patient is scheduled for an office procedure, an E/M visit cannot be billed unless there is a significant, separately identifiable problem and the criteria are met for an E/M visit.

The CPT guidelines state that an office or other outpatient visit for the evaluation and management of an established patient requires two out of the three key components: history, examination, and medical decision making.

and ARHP encourage members to put their words into action by truly understanding the importance of political advocacy and the need for the entire membership to

get involved in grassroots movements.

Congress makes the laws. It has the authority to permanently fix the Sustainable Growth Rate, adequately reimburse physicians for DXA scans, pass the "Arthritis Prevention, Control, and Cure Act of 2007," and increase research funding to the National Institutes of Health. If each ACR and ARHP member commits to making one phone call, sending one e-mail, or joining one advocacy event, the impact on Capitol Hill will be great.

For more information on RheumPAC, or to learn more about advocacy, please contact Kristin Wormley or Aiken Hackett at (404) 633-3777 or kwormley@rheumatology.org or ahackett@rheumatology.org, respectively.

MEMBER NEWS

Coming Soon: Custom News Briefings for Members

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COMMON VARIABLE IMMUNODEFICIENCY

Genetic insights into a complex and baffling disease

>> By Daniel Myrtek, PhD, and Ulrich Salzer, MD

Clinical Features

Although the clinical phenotype of CVID may be heterogeneous, one key characteristic of this disease is an impaired ability to produce antibodies. This disturbance manifests in decreased levels of immunoglobulin (Ig) G, IgA, and, sometimes, IgM isotypes and in an impaired or even absent antibody response upon antigenic challenge. This results in a failure to respond to vaccinations and an increased susceptibility to infections. Infections are usually localized in the respiratory tract and a majority of patients have recurrent bronchitis, sinusitis, or otitis (which is more common in childhood-onset CVID), and have had one or more episodes of pneumonia.

Typical pathogens affecting patients with CVID are encapsulated bacteria like *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*. A significant number of CVID patients also suffer from gastrointestinal tract infections caused by

Giardia lamblia, *Campylobacter*, or *Salmonella* species. Pulmonary symptoms of CVID may be accompanied by an obstructive lung phenotype (e.g., chronic bronchitis) and asthma. The lung represents the Achilles' heel of the CVID patient and chronic lung damage (e.g., bronchiectasis, lung fibrosis, and emphysema) is one of the most common causes of morbidity and mortality in the CVID cohort.

The respiratory system of CVID patients may also be affected by granulomatous inflammation, characterized by sarcoid-like lesions in lymph nodes and other histology specimens. This accompanying disease is found in approximately 10% to 22% of CVID patients. In addition to the lung, virtually any other organ system can be affected, but the involvement of lung and liver in particular worsens the patient's prognosis and is often difficult to treat. High-resolution computer tomography is the method of choice to evaluate and monitor the status and progression of lung-related pathology in CVID patients.

Gastrointestinal diseases are frequent in CVID patients and manifest as chronic diarrhea, malabsorption, and weight loss. A significant number of patients suffer from inflammatory bowel disease.

The increased risk of developing autoimmune diseases underscores the sometimes paradoxical immune dysregulation observed in CVID patients. The most common autoimmune manifestations in CVID

are idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA). ITP or AIHA may occur years before a patient presents with an immunodeficiency.⁴ A subgroup of CVID patients clinically presents with a combination of ITP/AIHA, splenomegaly, and granuloma formation.⁵ Other observed autoimmune diseases include pernicious anemia, autoimmune thyroiditis, rheumatoid arthritis, and vitiligo.

CVID patients have an increased risk of developing malignancies, especially lymphoma and gastric cancer, and patients should be screened regularly for these potential complications.³

Immunological Features

During the past five decades, numerous studies have identified a plethora of immunological abnormalities in patients with CVID. CVID pathogenesis has been attributed to defects in T cells and their subsets, antigen presenting cells, and B cells. Despite convincing evidence that alterations of T cell function and subset distribution are associated with the CVID phenotype, recent research points to the impaired terminal differentiation of B lymphocytes as the hallmark of the disease.⁵⁻⁷

Several groups have now demonstrated that the formation of memory B cells is severely impaired in the majority of CVID patients and leads to a con-

comitant depletion of long-lived plasma cells and a drop of serum Ig levels. The altered distribution of B cell subsets observed in CVID patients is now applied in disease classification.⁵⁻⁷

Diagnosis

The rare incidence and high clinical variability of CVID can present a diagnostic challenge. Because there is no specific test for diagnosing CVID, diagnosis is made by excluding similar conditions. First, the clinically more frequent secondary causes for hypogammaglobulinemia must be ruled out (See Table 1, below). Then other primary immunodeficiency disorders have to be excluded, and suspected CVID should be validated, as outlined in Table 2 (p. 22).

The first step is the assessment of the clinical and family history, including a detailed description of the type, duration, and frequency of infections. In addition to recurrence of infections, unusual severity and development of complications (e.g., empyema, bronchiectasis) can indicate an underlying immune defect. Identifying underlying pathogens is very helpful in evaluating any immunodeficient patient, with infections by encapsulated bacteria being the most common type in CVID. Whenever possible, use direct detection methods for pathogens (e.g., microbial culture, antigen-ELISA, PCR) to evaluate the cause of infection, because serology is futile in patients with an antibody deficiency.

A systematic assessment of the patient's immunological status is the next step. This includes basic laboratory analyses such as a complete blood count, serum immunoglobulin levels (IgG, IgA, and IgM), and total complement levels (CH50). The determination of IgG subclasses (IgG₁ to IgG₄) is especially useful in patients who have only slightly de-

creased or low-normal IgG serum levels but suffer from recurrent infections.

Next, perform a quantitative flow cytometric analysis of lymphocyte phenotypes. This analysis should include T cell subsets (CD4⁺, CD8⁺, and memory) as well as total (CD19⁺) B cell numbers and B cell subsets. The numbers of class-switched memory B cells (CD27⁺/IgD⁻), non-switched memory B cells (CD27⁺/IgD⁺), and other peripheral B cell subsets provide useful information. While total numbers of B cells in CVID are usually normal or only slightly reduced in about 90% of patients, class-switched memory B cells are reduced in up to 75% of CVID patients.^{6,7}

Of particular importance is the assessment of specific antibody responses to different antigens (protein and polysaccharide antigens) upon vaccination.⁸ The results of these tests are helpful in determining whether a patient requires immunoglobulin replacement therapy, especially when a patient is hypogammaglobulinemic but has not yet had recurrent infections.

Genetic testing and specific in vitro tests (e.g., flow cytometry studies of surface markers and specialized functional testing) are available in immunodeficiency centers and specialized laboratories. Although genetic tests for CVID are only accessible to a small subgroup of patients so far, the recent discovery of the first single gene defects permits a definite diagnosis of CVID for the first time.

New Genetic Insights in the Pathogenesis of CVID

It has long been known that CVID also has a genetic component. While most cases of this disease occur sporadically, in 10% to 20% of CVID cases, at least one additional family member either suffers from

CVID or selective IgA deficiency.⁹ With a ratio of about 4 to 1, autosomal dominant inheritance is more common than recessive inheritance in CVID families. Genetic linkage studies have revealed that the genetic defect involved in this disease cannot be reduced to a single gene locus.

Candidate loci for CVID have now been demonstrated at the HLA region on chromosome 6, chromosome 4q, and chromosome 16q. This genetic heterogeneity—which probably mirrors the variable clinical presentation of this disease—is further increased by the recent discovery of four candidate genes which were found to be mutated in CVID independently of the results of previous linkage and association studies. These genes—*ICOS*, *TACI*, *CD19*, and *BAFFR*—encode for cell surface receptors on lymphocytes that play crucial roles either in peripheral B cell development or in B cell function.⁹

ICOS (inducible costimulator on activated T cells) was the first gene defect described in patients with CVID and has so far been described in nine individuals from four families, all of whom inherited the same mutation from a common founder.¹⁰ *ICOS* is expressed on activated T cells and is of critical importance for correct T cell–B cell cooperation during the adaptive immune response. It belongs to the family of T cell co-stimulatory molecules and interacts with *ICOS-L* on B cells, leading to the release of IL10, IL-17, and several other cytokines from T lymphocytes (See Figure 1A, p. 22). These cellular signals enable B cells to undergo class switch recombination.

In addition to the effects on class switch recombination, *ICOS-L/ICOS* interactions seem to be crucial for the development of a highly specialized CD4⁺ T cell subpopulation called follicular T helper cells, which direct the formation of germinal centers in peripheral lymphoid organs.¹¹ *ICOS* expression loss causes functional germinal center development to fail and therefore leads to impaired terminal B cell differentiation and hypogammaglobulinemia. Childhood onset of the disease was observed in one *ICOS*-deficient family. All but one adult *ICOS*-deficient patient had severe peripheral B cell lymphopenia and almost no memory B cells.¹²

Transmembrane activator and calcium-modulating cyclophilin ligand interactor (*TACI*) deficiency was the second molecular genetic defect found in patients with CVID.^{13,14} *TACI*, which is encoded by the gene *TNFRSF13b*, is a member of the tumor necrosis factor (TNF) receptor superfamily. *TACI* interacts with the ligands *BAFF/Blys* (B cell activating factor, B lymphocyte stimulator) and/or *APRIL* (A proliferation inducing ligand)—both members of the TNF ligand superfamily. Together with its closest relatives—*BAFF-R* and *BCMA* (B cell maturation antigen)—*TACI* forms a complex signaling network. *TACI* directs immunoglobulin class switch recombination and negatively regulates B cell homeostasis (See Figure 1B, p. 22). It has been shown that *TACI*-deficient mouse models develop lymphoproliferation, autoimmunity, and immunodeficiency, a triad reminiscent of the clinical phenotype observed in some CVID patients.

In about 2% to 3% of CVID patients, both *TACI* alleles are mutated, causing receptor function loss and ultimately resulting in an antibody deficiency. Simple heterozygous *TACI* mutations are found in up to 8% of CVID patients. These heterozygous changes are believed to act as disease modifiers rather than causing the disease because they are also observed in the normal population, albeit at lower frequencies.¹⁵ The clinical spectrum in *TACI* deficiency is diverse and there is no specific B cell or immunological phenotype. *TACI*-deficient individuals may be prone to develop lymphoproliferative and autoimmune complications.¹⁶ To unravel the genetic complexity and mechanism of particular *TACI* mutations and to correlate this to the clinical and im-

TABLE 1:

Differential Diagnosis of Hypogammaglobulinemia

CVID can only be diagnosed by excluding primary or secondary causes for the clinical picture of hypogammaglobulinemia.

Differential diagnosis	Examples	Suggested procedures and tests	
Secondary antibody deficiency	Systemic disorders:	<ul style="list-style-type: none"> > Excessive loss of immunoglobulins (e.g., nephrosis, protein losing enteropathy, severe burns) > Hypercatabolism of immunoglobulin (e.g. proximal myotonic myopathy) 	<ul style="list-style-type: none"> > Clinical history and presentation > Urine analysis for protein > Clinical history and presentation > Genetic testing (ZNF9)
	Malignancy:	<ul style="list-style-type: none"> > Chronic lymphocytic leukemia > Immunodeficiency with thymoma (Good's syndrome) > Non-Hodgkin's B cell lymphoma > Myeloma 	<ul style="list-style-type: none"> > Clinical history and presentation > Bone marrow biopsy > Immunofixation electrophoresis > Diagnostic imaging
	Drug induced:	<ul style="list-style-type: none"> > Anticonvulsants (e.g., carbamazepine, phenytoin) > Gold salts > Glucocorticoids > D-penicillamine > Antimalarial agents > Methotrexate 	<ul style="list-style-type: none"> > Clinical and medication history
	Infectious diseases:	<ul style="list-style-type: none"> > Epstein-Barr Virus (EBV) > congenital infections with rubella, cytomegalovirus, or toxoplasma gondii 	<ul style="list-style-type: none"> > Direct testing for antigen (ELISA and PCR)*
Other primary immunodeficiencies:	<ul style="list-style-type: none"> > X-linked agammaglobulinemia > Hyper IgM syndromes > Ataxia telangiectasia > Late onset adenosine deaminase deficiency > Atypical forms of Severe Combined Immunodeficiency Disease > X-linked lymphoproliferative disorder (EBV associated) > Chromosomal anomalies (e.g., chromosome 18q-syndrome, monosomy 22) 	<ul style="list-style-type: none"> > Clinical and family history > Mode of inheritance > Ig levels in serum > Lymphocyte phenotype and function in vitro > Genetic testing > Karyotyping 	

*Serology of any kind is of limited or no value in patients with antibody deficiency.

continued on page 22

TABLE 2:

A Stepwise Approach to Diagnosing CVID

STEP 1	STEP 2	STEP 3	STEP 4
History: <ul style="list-style-type: none"> > Clinical history > Type and frequency of infection > Family history Exclude: <ul style="list-style-type: none"> > Secondary causes of antibody deficiency > Other primary immunodeficiencies (See Table 1, p. 21) 	Basic laboratory tests: <ul style="list-style-type: none"> > Complete blood count > Serum immunoglobulin levels (IgG, IgA, and IgM) > Total complement levels (CH50) > IgG subclasses* (IgG₁ IgG₄) 	Advanced laboratory tests: <ul style="list-style-type: none"> > Lymphocyte phenotypes > B cell subset analysis > Response to mitogens and antigens in vitro > Response to vaccination in vivo 	Genetics: <ul style="list-style-type: none"> > Mutation analysis (ICOS, TACI, CD19, BAFF-R) Special laboratory test: <ul style="list-style-type: none"> > E.g., flow cytometry staining for ICOS, TACI, BAFF-R > Functional testing

*Determination of IgG subclasses should be considered in patients with recurrent infections but normal or only slightly reduced total IgG and in patients with symptomatic selective IgA deficiency.

munological presentation of TACI-deficient CVID patients is a main research focus for my colleagues and I.

CD19 deficiency is a very rare cause of CVID and, up to now, has only been described in four patients worldwide.^{17,18} The CD19 molecule is expressed solely on B cells and is therefore one of the most widely used surface markers to identify the B cell lineage in flow cytometry. CD19 forms a receptor complex with CD21 (CR2), CD81, and CD225 (Leu13), which is referred to as the CD19-complex. This signaling complex fine-tunes and amplifies B cell receptor (BCR) signals after antigen binding (See Figure 1C, below). CD19-deficient patients have decreased or even no expression of CD19 on the surface of their B cells and an impaired antigen-dependent Ca²⁺ signaling, resulting in diminished B cell responses upon BCR triggering. In these patients, the formation of memory B cells and CD5⁺ B cells is also reduced, consequently leading to hypogammaglobulinemia and absent vaccine responses in vivo.

My colleagues and I were able to identify two cases of homozygous BAFFR deficiency in one single kindred.¹⁹ BAFF-R is closely related to TACI and BCMA and interacts exclusively with BAFF. The BAFF-BAFFR interaction mediates signals important for B cell survival and regulates peripheral B cell homeostasis (See Figure 1D, below). BAFF-R deficiency presents with a distinct immunological phenotype which had been inferred by BAFF-R-deficient mouse models: peripheral B cell numbers are low, transitional B cell numbers are proportionally increased, and IgA production is intact.

Therapeutic Management of CVID

The primary objective of CVID therapy is reducing the frequency and duration of recurrent and chronic infections, especially sinusitis, bronchitis, otitis, pneumonia, and gastrointestinal infections and their sequelae. Immunoglobulin replacement therapy is the treatment of choice and forms the foundation of therapy.

The standard dosing recommendation for intravenous immunoglobulin (IVIG) is 400 mg per kilogram body weight every three to four weeks. Immunoglobulins may also be administered subcutaneously in weekly intervals. An IgG trough level (the IgG level before the next infusion) of at least 5 g/L should be attained. The individual patient's clinical history and

outcome will determine the amount of IVIG required; some patients (e.g., those with bronchiectasis, diarrhea, or IgG hypercatabolism) may require higher IVIG doses to reach the mandatory trough level. To maximize treatment success, the dose, frequency, way of administration, and product type should be adapted to each individual needs.

Antimicrobial therapy is the other main component of CVID therapy, because immunoglobulin replacement alone may not adequately prevent or treat local and/or persistent infections. Consider prolonged and intensified therapeutic regimens (e.g., intravenous antibiotics for patients with known bronchiectasis).

In addition, the accompanying diseases and sequelae of CVID require adequate treatment. Corticosteroids and cyclosporine A are effective for granulomatous manifestations and autoimmune diseases, although long-term treatment efficacy may be limited due to side effects.

From recent case reports, novel monoclonal anti-B-cell antibodies are promising new agents to combat autoimmune and granulomatous complications in CVID. However their effectiveness needs to be assessed in systematic double-blind, randomized clinical trials.

Conclusion

CVID comprises a genetically and clinically heterogeneous group of diseases in which diagnosis is often delayed or even missed. In the majority of cases, CVID remains a clinical diagnosis of exclusion. However, the identification of the first genetic defects associated with a CVID phenotype mark substantial progress for clinical immunology. These findings not only allow a definite diagnosis in a

small subgroup of patients, but also serve as models for understanding the pathogenesis of CVID as well as the function of the normal immune system. The discovery of additional genes associated with CVID and the mechanisms by which the mutation promotes CVID will be essential for the future diagnosis and treatment of this disease. Genetic testing may also reduce the time delay between onset of initial symptoms and diagnosis, improving patient outcomes.

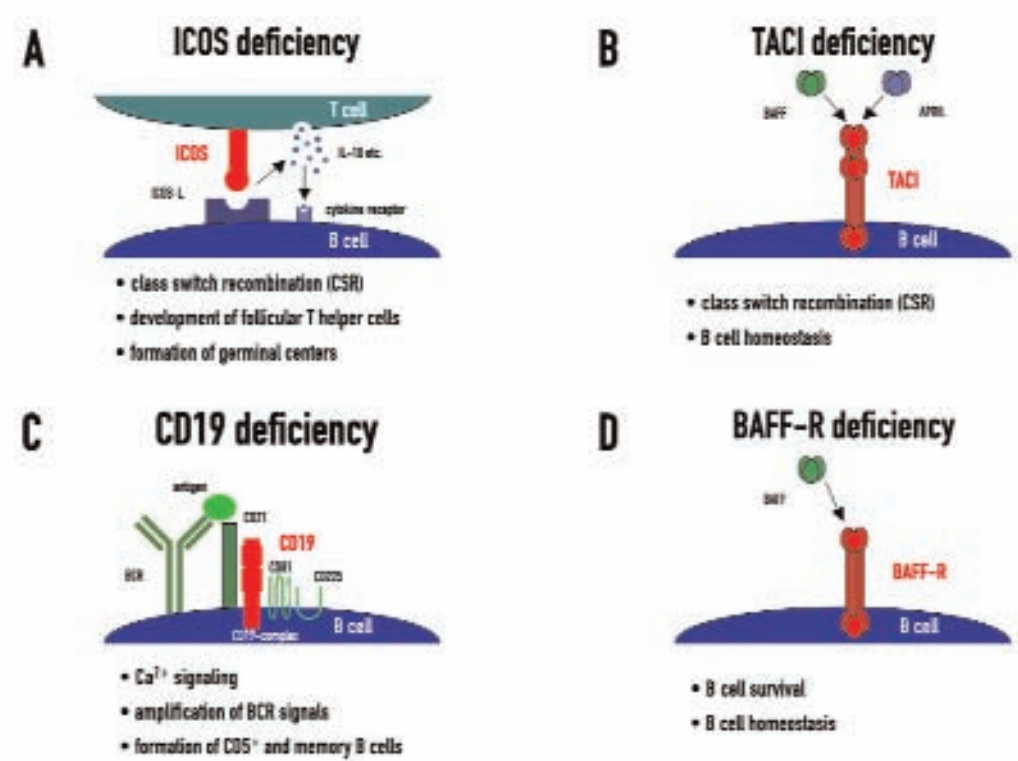
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FIGURE 1: Four genetic defects in cell surface receptors on lymphocytes in CVID patients. The figure highlights their cellular expression pattern, interacting molecules, and major biological functions.



watch the Walk

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Gait analysis can improve the walk of patients with arthritis >> By Greg Lavine

with enough energy to complete their tasks and make the return trip.

Gait, Piece by Piece

Gait is split into two main phases: swing and stance. During the swing phase, the body moves a leg forward in anticipation of planting that leg to support the other leg's upcoming swing phase. In the stance phase, one or both legs must support the entire weight of the body. There is a brief period of double support—where both legs share support of the body—at two points during each gait cycle.

The stance phase absorbs the impact shock from the body's weight hitting the ground. It is not enough to merely keep the body upright in this phase, because the legs must also be positioning themselves to move forward in the next cycle of gait, says K. Douglas Gross, ScD, MPT, a research technologist in the clinical epidemiology research and training unit at Boston University. During stance, the heel is the first part of the leg to make contact with the ground, followed by the rest of the foot. As the body propels itself for-

ward, the heel pushes off before the toe leaves the ground in anticipation of the next step.

Challenges that can impair the stance phase include problems in lower extremity strength, coordination, motor control, balance, and joint mobility and alignment. When a patient complains of pain when walking, it is important to determine at what phase of gait the problem arises, says Dr. Oatis. The problem could occur when the foot is hitting the ground and absorbing shock, or when the foot is pushing off the ground as momentum is transferred.

During the swing phase, the swing foot must clear the ground and land in a position where it will not trip the next swing foot. If the swing foot moves too far forward, creating a wide stance, it can hinder the proper transfer of momentum, says Dr. Oatis. Challenges faced during the swing phase include strength problems, coordination issues, trouble placing the foot in good position, and joint mobility issues.

The Pain Factor

When pain comes into play, it can affect walking speed, which in turn forces people to expend more energy. "The caloric cost of gait is minimized when we walk at our free speed," says Dr. Oatis. "If we walk faster or slower, then we expend more energy."

During the swing phase, there is little activity in any of the leg muscles. Most of the movement relies on energy transfer from the muscles in the hip to the knee and from the ankle muscles to the knee. Muscle movements in the hip and ankle are responsible for propelling the knee, which is slightly flexed, through the swing phase of each step. As a result, even patients with healthy knees may experience walking problems if they have hip or ankle problems. In walking, the knee is relatively passive.

Despite the knee's relatively passive role in gait, stiffness in this joint can still impair walking speed during the swing phase. "Even if all the muscles are working," says Dr. Oatis, "if the knee joint is stiff, this energy transfer becomes compromised because the knee isn't freely [moving]."

When physicians or other health professionals examine a patient's gait, they should not simply focus on the problem joint. Hip and ankle problems also play a prominent role in gait disturbance. When watching a patient walk, the health professional may notice too little or too much pronation of the foot, which normally turns inward during gait. For patients with too much pronation, there are orthopedic shoes that can control excessive motion. Underpronation, which is also known as supination, can be helped with special shoes or by adding extra cushioning to existing shoes.

Patients in pain tend to alter their gait in the stance phase to lessen the load on weight-bearing joints. In some cases, patients may change their line of gravity by leaning to one side during their stride. In other circumstances, they may adjust the timing of their gait or walk more slowly to lessen the burden on a painful joint. While slow walking speed and exaggerated leans may be easy to spot, it can be difficult to spot more subtle problems that can hinder a patient's walking ability, says Gross.

Tools for Gait Analysis

One high-tech solution for gait analysis is an instrumented walkway. The patient is asked to walk across a special mat that is equipped with sensors to detect the length and timing of steps, toe and heel position at various points of gait, and time spent in single or double support. Analyzing these data can be easier than trying to watch for all the various factors that come into play for gait, says Gross.

Another technological trick is to provide patients with smart activity monitors, which are microprocessor devices worn on the waist. The devices are able to record information similar to that given by the instrumented walkway, but can also show how much time patients spend walking, running, or climbing stairs.

For health professionals who may not have access to such devices, there are more traditional ways to analyze gait. Physicians can ask patients to try walking in different positions—such as leaning a certain way or changing the position of their foot—to see how gait alters. Other ways to change gait include changing footwear, wearing braces, placing tape around the ankle, and using assistive devices, such as canes or walkers.

Physical therapists can help teach patients how to alter their gait by changing the timing of their steps, the size of each step, or the position of a foot when pushing off the toes, among other things, says Gross. In some cases, correcting a patient's gait problems and pain can be as simple as changing footwear—for example, not wearing high heels as frequently. ■ THE RHEUMATOLOGIST ■

Greg Lavine is a freelance journalist based in Maryland.

RA

TIME IS OF THE ESSENCE

Early treatment lessens arthritis pain and disability, but challenges to early detection remain

>> By Sue Pondrom

EACs in Europe. Why is this?

According to physicians interviewed by *The Rheumatologist*, there are many reasons for the paucity of this type of clinic:

- > America's healthcare system differs from that of Europe—it's not designed for early, easy patient access;
- > The referral base is not adequately educated about the nature of early inflammatory synovitis and the importance of early diagnosis and treatment;
- > Medical schools aren't teaching new doctors enough about RA;
- > The effort needed to start an EAC does not appear to justify the time and expense; and
- > Many rheumatologists believe they can handle early RA patients within their existing schedules.

However, in spite of good intentions, most RA during the early stages of disease isn't being seen in a timely manner.

Challenges for EACs in the U.S.

Ninety percent of patients with musculoskeletal and autoimmune disorders are receiving rheumatology care from their primary care physician (PCP), ac-

ording to data gathered by Stephen A. Paget, MD, chair of the division of rheumatology at the Hospital for Special Surgery in New York City. In fact, less than 50% of RA patients are referred to specialists within the first six months of symptom onset.¹ The actual percentage may be considerably lower, according to research by rheumatologist John J. Cush, MD, chief of rheumatology and clinical immunology at Presbyterian Hospital of Dallas. He says fewer than 5% of RA patients are seen by rheumatologists in the first six months, and the average new RA patient comes in with disease duration of two to three years.

Is the solution to increasing access to establish an EAC? Not necessarily. It takes money to establish infrastructure, hire and train staff, and advertise to physicians and the public. Just because the EAC concept worked in Europe doesn't mean it will in the U.S. For example, while Europe has an easier-to-negotiate single-payer insurance system, the U.S. has hundreds of payers, complicating the financial aspects. Also, European medical communities are relatively small, making it easier to educate and get referrals from local physicians. If an EAC is established in an American community, will the medical office get appropriate referrals?

"My calculation is that there are probably 75,000 new cases of RA every year in the U.S.," Dr. Cush says. "If every rheumatologist made an exceptional effort to get those patients, it would mean an extra 20 to 30 patients a year, and they could absorb that with no problem. However, to capture these patients, the rheumatologist will have to see many more patients, as the yield for early inflammatory arthritis is usually less than 10%, even when promoting referral rules to primary-care physicians. You might have to see hundreds of patients with fibromyalgia to get one with early RA. So, why should somebody in practice revamp for what seems to be very little gain?"

Another challenge for rheumatologists is being referred a patient with symptom duration of one to two years. "In the last several years, I don't remember seeing a patient with true early synovitis," says Gary Firestein, MD, chief of rheumatology and immunol-

ogy at the University of California, San Diego School of Medicine.

In the typical RA case, he says, a patient will stay at home and self-medicate for a few months. When there's finally a doctor visit, the signs and symptoms of inflammatory synovitis may not be recognized; treatment will usually be conservative, perhaps with a non-steroidal anti-inflammatory drug. Another month or so may pass. When the patient returns to the doctor with continuing pain, tests are run and another couple of weeks go by before there's a referral to the rheumatologist—who may have a wait of two or three months for an appointment.

How Early Is Early?

Although today's ideal is early treatment, the actual definition of "early" varies. While some advocate treatment as early as three months, others prefer to wait.

"I think we need to be careful and not overtreat a patient with symptoms of joint pain," says Larry Moreland, MD, professor of medicine at the University of Pittsburgh and formerly at the University of Alabama, Birmingham, who has participated in an EAC. "Often times patients have self-limiting problems and do not require treatment in the first few weeks," he says, "and in about a third of the cases, the symptoms will resolve without therapy." He adds that, "what we don't want is to have a patient with RA go untreated for six to 12 months."

However, "most PCPs have a hard time making the diagnosis of RA, even if it's clear RA," notes Dr. Moreland. "That's because it often isn't clear. Patients have vague symptoms. Making an RA diagnosis for me as a rheumatologist is pretty easy. But if you're out there on the front line where you're seeing all kinds of problems, it's not easy."

Dr. Firestein agrees. "The primary care doctors have to be trained to know exactly what to look for," he says. According to Dr. Paget, "because medical school and house staff training in the recognition, diagnosis, and treatment of such disorders is so poor, it is a surprise that well-intentioned physicians on the front line either miss or mistreat these diagnoses or patients altogether because they don't even know what they don't know?"

"It's, in many ways, a grassroots effort with medical schools," Dr. Paget says, urging rheumatologists to get involved. "The schools have 'x' amount of time and

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resources to do a huge amount of education. They basically cram it in. As a result, a specialty like rheumatology suffers.”

Dr. Cush, who runs an EAC and frequently lectures, says that, while education is certainly needed, most PCPs want to know who and when to refer. Therefore, with his PCPs, he promotes the “Referral Rules” advocated by Paul Emery, MD, professor of rheumatology at the University of Leeds, U.K., that require six weeks of joint symptoms and one of the following symptoms: three or more swollen joints a positive metacarpophalangeal (MCP) or metatarsophalangeal (MTP) squeeze test, morning stiffness for more than 45 minutes, or abnormal labs (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], rheumatoid factor [RF], or classical complement pathway [CCP]).

Dr. Cush believes that “the guy in the trenches, the primary care internist or physician, has no intention of

going to a lecture designed to educate them on early RA. They’ve got too many things to deal with already. Thus, we have to create rules that can facilitate patient referral.” To get the word out about the rules, Dr. Cush suggests a \$5–10-million national advertising campaign aimed at both PCPs and the general public. He suggests it might be funded by stakeholders (e.g., pharmaceutical companies, foundations, societies, etc.).

“My idea is to make Tuesday ‘Early Arthritis Day,’ ” he says. “Your rheumatologist will see patients every Tuesday and all the PCP needs to do is fill out a prescription pad for the walk-in visit.”

A new initiative is starting at Dr. Cush’s EAC. He is working with the hospital’s public relations department to reach all local primary care doctors in the community, providing referral rules and indicating that nine

doctors in the EAC will see patients within two weeks of referral. In Birmingham, Dr. Moreland’s EAC was established by sending out letters to all PCPs in Alabama, saying that his group will try to see all patients in a timely manner. In smaller communities, such as Santa Barbara, Calif., it’s easier for a dedicated rheumatologist to spread the message to area primary care physicians. Timothy Spiegel, MD, MPH, a rheumatologist in Santa Barbara, Calif., who has been in private practice for the past 20 years, knows all the local PCPs and says he has trained many of them to recognize early RA. He makes sure to see referred patients within a week.

Dr. Paget’s EAC at the Hospital for Special Surgery is considered by many to be a model EAC. He says he got referrals with the help of a \$1-million private donation. “Each medical group or center will have its own way to set

up an EAC,” he says. “What we focused on was clinical and basic research, and on getting the word out.” His team developed a Web site, designed programs for patients, met with managed care and third-party payers to develop practice algorithms, and met with community organizations to recruit and educate patients. The hospital public relations staff arranged local news stories, and an advertising agency was hired to prepare educational ads for the public.

However, Dr. Paget says physicians don’t need a large financial windfall to start an EAC. “It’s very simple to do some of the things I’ve mentioned. My personal feeling is that what’s necessary is a partnership with pharmaceutical companies (particularly ones making drugs for arthritis), with academic medical centers, the American College of Rheumatology, and the Arthritis Foundation. They are already getting the word out, but more needs to be done.”

EAC with a U.S. Twist

Noting that a European-style EAC is not ideal in the U.S., Dr. Cush says “the vast majority of rheumatologists need alternative ways to take early RA patients in their practices.” He suggests using one or more of the following models:

- > A once-a-week clinic;
- > A physician extender (nurse practitioner, physician assistant) for intake/screening;
- > Chart reviews to prescreen and avoid wasted time;
- > Physician-to-physician phone calls for consultation;
- > Flexible scheduling (hold spots, then fill with regular patients if early RA patients don’t come); and
- > “Meet and Greet Rapid Slots” scheduled on top of regular office visits, where a patient fills out a questionnaire, the rheumatologist does a joint exam and makes a spot decision, then asks the patient to come back for tests and/or an appointment.

“The reason to have an EAC,” says Dr. Moreland, “is for a system in place for academic centers to do research and develop databases. In private practice, an EAC may help rheumatologists see patients sooner, rather than later.” THE RHEUMATOLOGIST

Sue Pondrom is a medical journalist based in San Diego.

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Reading RHEUM

HANDPICKED REVIEWS OF CONTEMPORARY LITERATURE

SPINAL STENOSIS

Is Surgical Decompression the Best Treatment for Lumbar Spinal Stenosis?

>> By David G. Borenstein, MD

Weinstein JN, Tosteson TD, Lurie JD, et al. *Surgical versus nonsurgical therapy for lumbar spinal stenosis*. N Engl J Med. 2008;358:794-810.

Abstract

Background: Surgery for spinal stenosis is widely performed, but its effectiveness as compared with nonsurgical treatment has not been shown in controlled trials.

Methods: Surgical candidates with a history of at least 12 weeks of symptoms and spinal stenosis without spondylolisthesis (as confirmed on imaging) were enrolled in either a randomized cohort or an observational cohort at 13 U.S. spine clinics. Treatment was decompressive surgery or usual nonsurgical care. The primary outcomes were measures of bodily pain and physical function on the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) and the modified Oswestry Disability Index at six weeks, three months, six months, and one and two years.

Results: A total of 289 patients were enrolled in the randomized cohort, and 365 patients were enrolled in the observational cohort. At two years, 67% of patients who were randomly assigned to surgery had undergone surgery, whereas 43% of those who were randomly assigned to receive nonsurgical care had also undergone surgery. Despite the high level of nonadherence, the intention-to-treat analysis of the randomized cohort showed a significant treatment effect favoring surgery on the SF-36 scale for bodily pain, with a mean difference in change from baseline of 7.8 (95% confidence interval, 1.5 to 14.1); however, there was no significant difference in scores of physical function or on the Oswestry Disability Index. The as-treated analysis, which combined both cohorts and was adjusted for potential confounders, showed a significant advantage for surgery by three months for all primary outcomes; these changes remained significant at two years.

Conclusions: In the combined as-treated analysis, patients who underwent surgery showed significantly more improvement in all primary outcomes than did patients who were treated nonsurgically.

Commentary

In 2005, the Cochrane Review group reported the lack of clear or decisive data concerning the efficacy of surgical decompression for treating spinal stenosis. Although clinical studies on surgical therapy have been published, they have been limited by, among other things, the inclusion of patients with spinal instability (spondylolisthesis) who required fusion as a component of surgical therapy. The studies included small groups of patients without significant improvement from surgical intervention. In response to paucity of clinical trials studying an adequate number of similar stenosis subjects, the Spine Patient Outcomes Research Trial (SPORT) group completed a clinical trial investigating the relative benefit of surgical versus nonsurgical therapy for patients with spinal steno-

sis without spondylolisthesis.

The conclusion of the Weinstein et al. article is that surgical decompression offers greater improvement in pain and physical function than nonsurgical therapy. Have the authors, however, identified those individuals who are good surgical candidates and have they demonstrated a “good” outcome for these spinal stenosis sufferers? The study had 654 individuals: 400 surgical and 254 nonsurgical participants. The individuals eligible to participate in this trial had neurogenic claudication for a minimum of three months and radiographic evidence of spinal stenosis at one or more levels without instability; they were also judged to be surgical candidates although this criterion was never fully defined.

The authors describe the group who underwent surgery as younger, working, with more pain,

2) an observational cohort who self-selected therapy (n=365). A major complicating factor of this study was that 33% of surgical patients who chose medical therapy, and 43% of nonsurgical patients who underwent laminectomy. The authors completed both an intention-to-treat and as-treated analysis because of the frequent crossovers. A partial summary is included in Table 1 (below).

At two years, in the intention-to-treat analysis, surgical patients had a significant improvement in pain but not in physical function or disability. In the as-treated analysis, however, the superiority of surgical decompression over nonsurgical therapy was shown in pain and physical improvement. The as-treated group included individuals who chose the therapy that they thought would help them the most in the setting of their pain severity and physical dys-

TABLE 1:

Outcome Results for Intention-to-treat and As-treated Cohorts

Intention-to-treat cohort	Baseline	3 Months		6 Months		2 Years	
		S	NS	S	NS	S	NS
Number of patients	278	116	135	120	135	108	113
	M	MC		MC		MC	
SF-36							
Bodily pain	31.9±1.1	11.2±2.4	7.9±2.2	21.0±2.2	16.1±2.1	23.4±2.3	15.6±2.2
Physical function	35.4±1.4	7.4±2.5	11.6±2.3	17.6±2.3	15.1±2.2	17.1±2.4	17.1±2.3
Oswestry Disability Index**	42.7±1.1	-7.6±2.1	-8.1±1.9	-14.6±1.9	-13.7±1.7	-16.4±1.9	-12.9±1.8
As-treated cohort	Baseline	3 Months		6 Months		2 Years	
		S	NS	S	NS	S	NS
Number of patients	803	378	313	256	271	335	198
	M	MC		MC		MC	
SF-36							
Bodily pain	31.4±0.6	27.9±1.1	11.8±1.2	29.5±1.3	12.9±1.2	26.9±1.2	13.3±1.4
Physical function	34.9±0.8	24.8±1.2	10.0±1.2	26.9±1.3	10.6±1.3	23.0±1.3	11.8±1.4
Oswestry Disability Index**	43.2±0.6	-21.4±0.9	-7.6±1.0	-22.9±1.0	-8.8±1.0	-20.5±1.0	-9.3±1.2

*The SF-36 scores range from 0 to 100, with higher scores indicating less severe symptoms.

**The Oswestry Disability Index ranges from 0 to 100, with lower scores indicating less severe symptoms.

M=mean; MC=mean change; S=Surgery; NS=no surgery.

lower level of function, psychological distress, more severe stenosis, and with worsening symptoms. A slim majority of participants had symptom duration of more than six months, but the scope of the persistence of radicular pain was not mentioned. An incongruity arises when matching duration of symptoms with the radiographic grading of stenotic severity. A majority of individuals are described with evidence of severe stenosis at one or more levels. I would have expected these individuals to have been symptomatic for a longer period of time than six months.

The most frequent comorbidity in these individuals with an average age of 65 was the presence of other joint disease. The impact of this finding on physical function is not mentioned. Nonsurgical therapy was left to the discretion of the practitioner who was most likely an orthopedic surgeon. The nonsurgical candidates may not have been individuals who failed medical therapy, but those who never received a full complement of educational, pharmaceutical, physical, and injection interventions.

The study design included two groups: 1) a randomized cohort assigned to one therapy (n=289) or

function. I believe that the general applicability of the conclusions of the study is diluted both by the very specific clinical characteristics of the study subjects and the absence of randomization for a significant proportion of patients. The Cochrane Review group will probably say that more randomized studies are needed, despite the addition of this clinical trial to the medical literature.

So what are busy clinicians going to recommend to their spinal stenosis patients? I think clinicians need to explain the nonsurgical and surgical options to patients. Patients who are younger, with no associated joint disease, with single-level stenosis, and without spondylolisthesis who want surgery have a good opportunity to improve with surgical intervention. Patients who chose medical therapy may be more symptomatic for a period of time, but will become better over the subsequent two years.

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IMMUNOLOGY

Potential New Model to study immunological disturbances

>> By Maripat Corr, MD

Yang YG, Lindahl T, Barnes DE. *Trex1* exonuclease degrades ssDNA to prevent chronic checkpoint activation and autoimmune disease. *Cell*. 2007;131:873-886.

Abstract

Trex1 is the major 3' DNA exonuclease in mammalian cells, and mutations in the human *TREX1* gene can cause Aicardi-Goutières syndrome, characterized by perturbed immunity. Similarly, *Trex1* (-/-) mice have an autoinflammatory phenotype; however, the mechanism of Trex1-deficient disease is unknown. We report that Trex1, ordinarily associated with the endoplasmic reticulum (ER), relocates to the S phase nucleus after gamma irradiation or hydroxyurea treatment. Notably, Trex1-deficient cells show defective G1/S transition and chronic ATM-dependent checkpoint activation, even in the absence of exogenous stress, correlating with persistent single-stranded DNA molecules produced in S phase, which accumulate in the ER. Our data indicate that Trex1 acts on a single-stranded DNA polynucleotide species generated from processing of aberrant replication intermediates to attenuate DNA damage checkpoint signaling and prevent pathological immune activation.

Commentary

In 1984, two French pediatric neurologists—Jean Aicardi and Françoise Goutières—described, in a Portuguese family, a rare neurological condition that is attracting attention as a model to study immunological disturbances in autoimmunity. This condition, Aicardi-Goutières syndrome (AGS), shows autosomal recessive inheritance and is characterized by encephalopathy with elevated lymphocytes in the cerebrospinal fluid, calcification of the basal ganglia, and white matter demyelination.¹ In infancy, AGS typically manifests as progressive microcephaly, spasticity, dystonia, and psychomotor retardation. However, AGS is a heterogeneous disorder and phenotypic variability includes patients with apparently static or slowly progressive disease, sometimes presenting after several months of normal development.

Recently, mutations in *TREX1* and in the genes encoding the three nonallelic components of the RNASEH2 protein complex have been identified in AGS.²⁻⁴ *TREX1* encodes the major 3'→5' DNA repair exonuclease in mammalian cells, DNase III/*TREX1*. Several monoallelic mutations in *TREX1* have recently been described in individuals with systemic lupus erythematosus and familial chilblain lupus.⁵ Despite these known clinical associations, the mechanisms by which *TREX1*-deficiency promotes disease have remained obscure. In an important new study, Yang et al. describe the accumulation of cytoplasmic single stranded (ss) DNA that is associated with this defect in cell cycle modulation, which could provide a link between this deficiency and chronic inflammation.

The investigative group observed that the protein *TREX1* can translocate from the ER in the cytoplasm to the nucleus at the time of DNA synthesis for replication. Fibroblasts from *TREX1*-null mice did not progress normally through the cell cycle, however, and proliferated slowly. Furthermore, *TREX1* deficient cells failed to arrest properly in S and G2/M-phases of the cell cycle following DNA damage with irradiation. Molecular dissection of the checkpoints in the cell cycle associated with DNA damage repair indicated that the *TREX1*-deficient cells exhibited chronic activity of the ataxia-telangiectasia mutated (ATM) kinase, resulting in lower CHK2 levels and increased levels of active p53 and p21.

As *TREX1* was previously described to use ssDNA as a substrate, the researchers hypothesized that loss of *TREX1* activity could result in ssDNA accumulation. Indeed, *TREX1*-null fibroblasts exhibited a marked in-

crease in the amount of ssDNA polynucleotides between 60 and 65 bases. Surprisingly, the accumulation was not in the nucleus, but in the cytoplasm. Using fluorescent microscopy they demonstrated—by co-localization with an ER-specific marker, calreticulin—that the ssDNA is associated with the ER. Experiments with primary fibroblasts from AGS patients with homozygous mutations in *Trex1* demonstrated a similar cell cycle profile as the murine cells and an increase in ER-associated ssDNA.

From these studies, it appears that *TREX1*-deficiency results in chronic activation of the ATM kinase-dependent checkpoint and the accumulation of ssDNA oligonucleotides within the cytoplasm of replicating cells. Despite the aberrant cell cycle and checkpoint activity, mice that lack *TREX1* and AGS-affected individuals do not have an increased tumor incidence. Rather, the hallmark of AGS is the presence of elevated levels of interferon- α in the CSF, mimicking congenital infections (pseudo-TORCH syndrome). Aberrant immune activation is also indicated by the chilblain lesions and the small number of AGS-affected children who develop antinuclear antibodies, hypothyroidism, and type I diabetes.³ Innate immune receptors, including the Toll-like receptors, recognize strands of nucleic acids as ligands, but have not been identified as a specific pathway for the interferon- α production in the pathogenesis of AGS.⁶

An alternative mechanism for the effects of *TREX1* deficiency on autoimmunity concerns its role in cell death. *TREX1* activity has been implicated in a specific caspase-independent cell-death pathway utilized by cytotoxic T lymphocytes (CTL) and natural killer (NK) cells during antiviral responses.⁷ Type I interferons stimulate the activity of these cells. In turn they release granzymes and perforin to induce death in target cells. Defective granzyme A activity as a result of *Trex1* defi-

ciency could result in the inability to eliminate autoreactive lymphocytes. Alternatively, genetic defects in perforin have resulted in sustained cytokine production by NK cells and CTLs, which may occur in AGS.⁸ The identification of the malfunctioning proteins in AGS provides evidence that a defect in DNA processing can lead to chronic expression of inflammatory cytokines, including interferon- α and autoimmunity. As often occurs in science, insights into disease can come from unexpected places and it is intriguing that a study of a relatively rare neurological disease may enhance our understanding of more global mechanisms underlying autoimmunity.

THE RHEUMATOLOGIST

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