biosupplytrends
QUARTERLY
WINTER 2022 CRITICAL CARE

COVID-19

How the Pandemic Has Affected Medical Resources

Gene Therapy:
A CURE FOR HEMOGLOBINOPATHIES?

Debunking IG Therapy Myths
TO IMPROVE PATIENT OUTCOMES

THE INCREASING PREVALENCE OF Metabolic Syndrome

TRANSITIONING HEALTHCARE TO THE Retail Sector

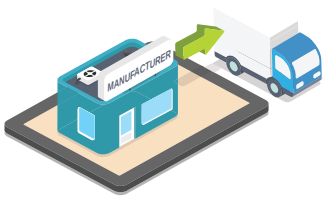
NEW DEVELOPMENTS IN UNIVERSAL FLU VACCINES | PAGE 46

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

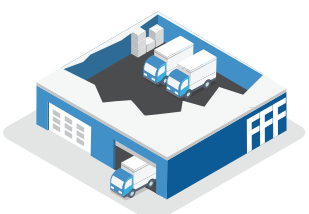
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

Storage

The healthcare products we store and transport are sensitive to temperature variations. Our state-of-the-art warehouse is temperature-controlled, monitored 24/7, and supported with backup generators in the event of power loss. In addition, we only stack products double-high to minimize pressure on fragile bottles and containers.



STEP 3

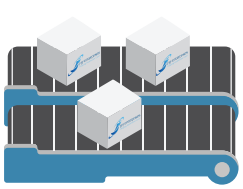
Specialty Packaging

At FFF, we use only certified, qualified, environmentally-friendly packaging, taking extra precautions for frozen and refrigerated products.

STEP 4

Interactive Allocation

FFF's unique capability of interactive allocation allows us to do that through our field sales team's close relationship with our customers. Our team understands customers' ongoing requirements, responds to their immediate crises, and allocates product in real-time to meet patients' needs.



Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

800.843.7477 | Emergency Ordering 24/7

STEP 5

Delivery

Our delivery guidelines are in compliance with the State Board of Pharmacy requirements. Products we deliver must only be transported to facilities with a state-issued license, and only to the address on the license. We make no exceptions. And we will not ship to customers known to have a distributor's license.

STEP 6

Methods of Delivery

We monitor for extreme weather conditions, and when the need arises, we ship overnight to maintain product efficacy. We also track patient need during life-threatening storms to make sure products are delivered when and where patients need them most.

STEP 7

Verification

In compliance with U.S. Drug Supply Chain Security Act (DSCSA) requirements, every product shipped from FFF is accompanied by a packing slip that includes information regarding the manufacturer and presentation, as well as the three T's: Transaction Information, Transaction History, and Transaction Statement.

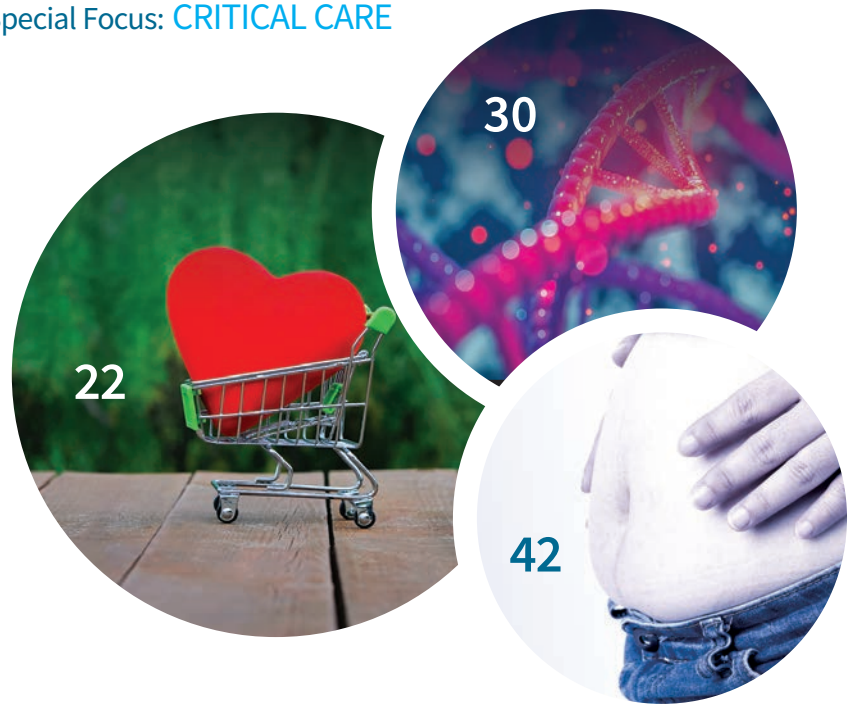
STEP 8

Tracking

To meet DSCSA requirements, FFF provides product traceability information on all packing slips. In addition, Lot-Track® electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

CONTENTS Winter 2022

Special Focus: CRITICAL CARE



Up Front

Features

BioTrends Watch

BioFocus

BioSources

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Shifting to a Wellness Model of Care

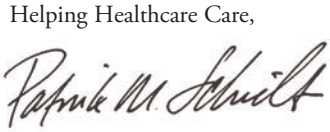
AS THE healthcare industry adapts to an ever-changing landscape, transitioning to a wellness model of care looks to be in its future. That means adjusting to meet an increasing patient demand for care post-pandemic by expanding healthcare staffing, especially in certain sectors; focusing on high-quality care and outcomes by switching from a fee-for-service model to a patient-centered model; acknowledging and meeting the needs of "healthcare consumers;" and embracing new emphasis on preventing disease rather than treating it.

The forces driving this changing landscape are numerous, but most acknowledge the COVID-19 pandemic currently tops the list of contributors. As we highlight in our article "Effects of COVID-19 on Medical Resources" (p.16), these effects stem from staffing and revenue shortages to supply chain management challenges. Declines in patient visits and procedures during the pandemic substantially reduced revenue, with 75 percent of hospitals reporting adverse impacts. Yet, despite the downturn in visits and procedures, adequate staffing continues to be problematic as nurses were already in short supply prior to the pandemic. Recent surveys by several major healthcare organizations show nurses are now leaving their jobs due to forced overtime, burnout and fear of contracting the SARS-CoV-2 virus. And lack of staff isn't limited to nursing. In another study, some 43 percent of physician respondents also reported burnout. Fortunately, the federal government is funding millions of dollars to address these shortages, and many hospitals are starting to report rising revenues. What's more, nursing and medical school enrollment is on the upswing. However, supply chain challenges will continue until the system resolves the issues the pandemic raised.

As concerns over the pandemic diminish, the industry is bracing for a surge in patients due to an aging population and "healthcare consumers," defined as patients engaged in their healthcare through technologies such as electronic health records, telehealth and wearables. An answer to this service gap, according to many, involves retail health centers (RHCs). As reported in our article "Healthcare Disrupted: Transitioning Primary Care, Diagnostics and Chronic Disease Management to the Retail Healthcare Sector" (p.22), while RHCs are not new, their growth is driven by healthcare consumers' desire for more convenient office hours and clear pricing. RHCs provide a growing number of services that are mainly staffed by physician assistants and nurse practitioners, which can result in discord between these facilities and primary care practices. Yet, despite this friction, RHCs appear to be here to stay, and there seems to be no argument that they are serving patients in more convenient locations with hours and pricing that better suit consumer needs.

As always, we hope you enjoy the additional articles addressing the ways in which healthcare is shifting in this issue of *BioSupply Trends Quarterly*, and find them both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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OCR Issues Guidance on HIPAA, COVID-19 Vaccinations and the Workplace

The U.S. Department of Health and Human Services' Office for Civil Rights (OCR) issued guidance to help the public understand when the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule applies to disclosures and requests for information about whether a person has received a COVID-19 vaccine. According to the guidance, the HIPAA Privacy Rule does not apply to employers or employment records because it applies only to HIPAA-covered entities (health plans, healthcare clearinghouses and healthcare providers that conduct standard electronic transactions) and, in some cases, to their business associates.

"We are issuing this guidance to help consumers, businesses and healthcare entities understand when HIPAA applies to disclosures about COVID-19 vaccination status and to ensure that they have the information they need to make informed decisions about protecting themselves and others from COVID-19," said OCR Director Lisa Pino. ❖

OCR Issues Guidance on HIPAA, COVID-19 Vaccinations, and the Workplace. U.S. Department of Health and Human Services press release, Sept. 30, 2021. Accessed at www.hhs.gov/about/news/2021/09/30/ocr-issues-guidance-on-hipaa-covid-19-vaccinations-workplace.html.

HHS Announces the Availability of $25.5 Billion in COVID-19 Provider Funding

The U.S. Department of Health and Human Services (HHS) is making $25.5 billion in new funding available for healthcare providers affected by the COVID-19 pandemic. This funding includes $8.5 billion in American Rescue Plan (ARP) resources for providers who serve rural Medicaid, Children's Health Insurance Program (CHIP) or Medicare patients, and an additional $17 billion for Provider Relief Fund (PRF) Phase 4 for a broad range of providers who can document revenue loss and expenses associated with the pandemic. "This funding critically helps healthcare providers who have endured demanding workloads and significant financial strains amidst the pandemic," said HHS Secretary Xavier Becerra. "The funding will be distributed with an eye toward equity to ensure providers who serve our most vulnerable communities will receive the support they need."

Consistent with the requirements included in the Coronavirus Response and Relief Supplemental Appropriations Act of 2020, PRF Phase 4 payments will be based on providers' lost revenues and expenditures between July 1, 2020, and March 31, 2021. PRF Phase 4 will reimburse smaller providers — who tend to operate on thin margins and often serve vulnerable or isolated communities — for their lost revenues and COVID-19 expenses at a higher rate compared to larger providers. PRF Phase 4 will also include bonus payments for providers who serve Medicaid, CHIP and/or Medicare patients who tend to be lower income and have greater and more complex medical needs. The Health Resources and Services Administration (HRSA) will price bonus payments at the generally higher Medicare rates to ensure equity for those serving low-income children, pregnant women, people with disabilities and seniors.

Similarly, HRSA will make ARP rural payments to providers based on the amount of Medicaid, CHIP and/or Medicare services they provide to patients who live in rural areas as defined by the HHS Federal Office of Rural Health Policy. ARP rural payments will also generally be based on Medicare reimbursement rates. "We know that this funding is critical for healthcare providers across the country, especially as they confront new coronavirus-related challenges and respond to natural disasters," said Acting HRSA Administrator Diana Espinosa. "We are committed to distributing this funding as equitably and transparently as possible to help providers respond to and ultimately defeat this pandemic."

To expedite and streamline the application process and minimize administrative burdens, providers will apply for both programs in a single application. HRSA will use existing Medicaid, CHIP and Medicare claims data in calculating payments. The application portal opened Sept. 29, 2021. To help ensure these provider relief funds are used for patient care, PRF recipients will be required to notify the HHS Secretary of any merger with, or acquisition of, another healthcare provider during the period in which they can use the payments. Providers who report a merger or acquisition may be more likely to be audited to confirm their funds were used for coronavirus-related costs, consistent with an overall risk-based audit strategy. ❖

HHS Announces the Availability of $25.5 Billion in COVID-19 Provider Funding. U.S. Department of Health and Human Services press release, Sept. 10, 2021. Accessed at www.hhs.gov/about/news/2021/09/10/hhs-announces-the-availability-of-25-point-5-billion-in-covid-19-provider-funding.html.

Interim Rule Advances Key Protections Against Surprise Medical Bills

An interim final rule with comment period to further implement the No Surprises Act — a consumer protection law that helps curb the practice of surprise medical billing — details a process that will take patients out of the middle of payment disputes, provides a transparent process to settle out-of-network (OON) rates between providers and payers, and outlines requirements for healthcare cost estimates for uninsured (or self-pay) individuals. Other consumer protections in the rule include a payment dispute resolution process for uninsured or self-pay individuals. It also adds protections in the external review process so individuals with job-based or individual health plans can dispute denied payment for certain claims. "No one should have to go bankrupt over a surprise medical bill," said U.S. Department of Health and Human Services (HHS) Secretary Xavier Becerra. "With today's rule, we continue to deliver on President Biden's Competition Executive Order

by promoting price transparency and exposing inflated healthcare costs. Our goal is simple: giving Americans a better deal from a more competitive healthcare system."

The rule is the third in a series implementing the No Surprises Act, a bipartisan consumer protection law. In early September, a rule was issued to help collect data on the air ambulance provider industry, in addition to a rule in July on consumer protections against surprise billing. Collectively, these rules took effect Jan. 1, 2022, and ban surprise billing for emergency services, as well as certain nonemergency care provided by OON providers at in-network facilities, and limit high OON cost-sharing for emergency and nonemergency services for patients.

"Price transparency is a reality in almost every aspect of our lives except healthcare," said CMS Administrator Chiquita Brooks-LaSure. "The Biden-Harris Administration is committed to changing this. With today's final rule, we are requiring healthcare providers and healthcare facilities to provide uninsured patients with clear, understandable estimates of the charges they can expect for their scheduled healthcare services." ❖

Biden-Harris Administration Advances Key Protections Against Surprise Medical Bills, Giving Peace of Mind to Millions of Consumers Plagued by High Costs. U.S. Department of Health and Human Services press release, Sept. 30, 2021. Accessed at www.hhs.gov/about/news/2021/09/30/biden-harris-administration-advances-key-protections-against-surprise-medical-bills.html.

CMS Launches New Medicare.gov Tool to Compare Nursing Home Vaccination Rates

The Centers for Medicare & Medicaid Services (CMS) is making it easier to check COVID-19 vaccination rates for nursing home staff and residents by making vaccination data available in a user-friendly format. CMS and the Centers for Disease Control and Prevention are also continuing to use this data to monitor vaccine uptake among residents and staff and to identify facilities that may need additional resources or assistance to respond to the pandemic. "CMS wants to empower nursing home residents, their families and caregivers with the information they need when choosing care providers for their loved ones. As we continue to work with our partners to monitor the spread of COVID-19 and keep nursing home residents safe, we want to give people a new tool to visualize this data to help them make informed decisions," said CMS Administrator Chiquita Brooks-LaSure. "CMS knows that nursing home staff want to protect their residents and is calling on them to get vaccinated now. The COVID-19 vaccine is safe, effective and accessible to all at no out-of-pocket cost."

Medicare and Medicaid-certified nursing homes have been required to report weekly COVID-19 vaccination data for both residents and staff since May, and CMS has been posting the information on the CMS COVID-19 Nursing Home Data website at data.cms.gov/covid-19/covid-19-nursing-home-data. The addition of this new consumer-friendly data feature is another valuable tool for patients, residents and families to understand the quality of nursing homes when making healthcare decisions. ❖

CMS Launches New Medicare.gov Tool to Compare Nursing Home Vaccination Rates. Centers for Medicare & Medicaid press release, Sept. 21, 2021. Accessed at www.cms.gov/newsroom/press-releases/cms-launches-new-medicaregov-tool-compare-nursing-home-vaccination-rates.

Interpreting Payment Rule and Revenue Cycle Terminology

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

MANY FIND information concerning payments for drugs, biologicals and radiologicals, vaccines or other products and supplies difficult to understand. Therefore, the goal of this column is to put into perspective some of the terms used in rule sets pertaining to payment for inpatients, which go into effect during the fiscal year effective Oct. 1, as well as outpatient and physician fee services, which go into effect during the calendar year effective Jan. 1.

Coding for Payment

Telling the patient's story accurately and completely in a manner that can be translated into codes is essential. Since all payment transactions are transmitted electronically, the codes chosen must match what actually has occurred during the patient visit/encounter/admission. This series of codes sent to the payer are not only used for payment but also become the clinical record that drives future decisions about treatment and payments.

The basis for transactions includes the disease state(s), problem list and symptoms the patient presents with that are assigned very specific ICD-10 codes representing procedure classifications. In 2022, there are updates to files that need to be incorporated into provider systems to ensure the problem list is accurately represented (www.cms.gov/medicare/icd-10/2022-icd-10-cm). Failure to update will result in a denied payment due to lack of medical necessity.

Drugs, biologicals, vaccines, radiologicals and other products and services are reported to payers as healthcare common procedure coding system (HCPCS) and/or current procedural terminology (CPT) codes, along with national drug codes (NDCs). The list of HCPCS Level II codes and descriptors are approved and maintained jointly by the alphanumeric editorial panel/workgroup whose members represent the Centers for Medicare and Medicaid Services (CMS), America's Health Insurance Plans and Blue Cross and Blue Shield Association. CPT codes and descriptions are copyrighted by the American Medical Association.

Category I CPT codes describe surgical procedures, diagnostic and therapeutic services, and vaccine codes, while Category III CPT codes describe new and emerging technologies, services and procedures. Level II HCPCS codes (also known as alphanumeric codes) identify drugs, devices, ambulance services, durable medical equipment, orthotics, prosthetics, supplies, temporary surgical procedures and medical services not described by CPT codes. Drugs and biologicals are found in sections A, C, J, P and Q. Often, the term "J codes" is used when referring to payment codes. However, looking in only the J section of the table misses listings in all the rest of the coding tables. For example, the most lucrative new pass-through drugs almost exclusively have C codes.

From a CMS outpatient perspective, drugs, biologicals, vaccines and other products are assigned status indicators (SI). These can be found in Addendum B, which is updated quarterly and contains thousands of line items. Pharmacy products are assigned G, K, N and R SIs; pass-through products are assigned SI G; separately payable outpatient drugs based on a daily dollar value threshold ($130 per day based on average sales price [ASP]) are assigned SI K; drugs that will be paid for as part of a bundle/package are assigned SI N; and all blood products are assigned SI R. (See www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates.)

More specifically, pass-through products are assigned a three-year transitional pass-through payment period with additions and expirations updated quarterly. The Medicare, Medicaid and SCHIP Balanced Budget Refinement Act of 1999 (Pub. L. 106-113) provided pass-through payment provisions that require the Department of Health and Human Services make additional payments to hospitals for current orphan drugs as designated under section 526 of the Federal Food, Drug and

ASP Payment Example for 340B Reimbursement

- Quarterly table ASP+6% of product A is $200/billing unit
- ASP+6% of product A is calculated by dividing $200 by 106 and multiplying that result by 100, which equals $188.68/billing unit
- Or, ASP+6% of product A is calculated by multiplying $200 by .943, which equals 188.60/billing unit
- ASP-22.5% of product A is calculated by multiplying the ASP+6% rate by .775 (which is 22.5% less than 100 percent of the product's price): $188.68 x .775 = $146.23/billing unit

Cosmetic Act; current drugs and biologicals and brachytherapy sources used in cancer therapy; and current radiopharmaceutical drugs and biologicals. "Current" refers to those drugs or biologicals that are hospital outpatient services under Medicare Part B for which transitional pass-through payment was made on the first date the hospital outpatient prospective payment system (OPPS) was implemented. Transitional pass-through payments also are provided for certain new drugs and biologicals not being paid for as a hospital outpatient department service as of Dec. 31, 1996, and whose cost is "not insignificant" in relation to OPPS payments for procedures or services associated with the drug or biological. For pass-through payment purposes, radiopharmaceuticals are included as drugs.

All drugs with a SI G designation are paid at ASP+6% regardless of whether a facility is purchasing under the 340B drug program or not. The key is to be aware of the expiration of this G status and plan accordingly because the HCPCS code assigned to the product may change and the new SI may be either K or N. SI K products remain at ASP+6% for non-340B facilities but fall to ASP-22.5% for those purchasing under the 340B program. SI N products are bundled and are no longer eligible for waste billing. An incorrect HCPCS code results in an automatic payment denial.

Average Sales Price (ASP)

ASP is a market-based price that is updated quarterly to reflect the weighted average of all manufacturer sales prices and includes all rebates and discounts privately negotiated between manufacturers and wholesaler/distributor purchasers (with the exception of Medicaid and certain federal discounts and rebates). It should be noted that ASP does not reflect the price a facility pays for the drug, which may be higher. CMS publishes quarterly updated fee schedules that include the 6 percent markup, which will be the amount paid by facilities and practices not using 340B purchasing. Purchasing under 340B requires some simple arithmetic to calculate reimbursement. Remember this applies only to SI K drugs. To determine ASP for SI K drugs, divide the published ASP+6% by 106 and then multiply by 100. Or simply multiple the published ASP+6% by .943. Since 340B-purchased products are paid at ASP-22.5%, deduct 22.5 percent from the ASP just calculated to determine payment (see ASP Payment Example for 340B Reimbursement).

Keep in mind that for all payments regardless of 340B status, CMS pays 80 percent of the amount due, and the patient is responsible for the remaining 20 percent (either personally or through a secondary payer).

These updates are automatically electronically provided to all facilities and practices eligible for CMS payments. Providers can sign up for complimentary online publications of changes and updates (public.govdelivery.com/accounts/USCMS/subscriber/new?pop=t&topic_id=USCMS_7819).

Sequestration

Sequestration is an important concept to understand since it reduced Medicare reimbursement and all other government payment by 2 percent. Currently, sequestration applies to budget limits Congress created in the 2011 Budget Control Act. At that time, there was consensus to use sequester threats to force deficit limit agreements. Sadly, threats didn't work, implementing the sequester to cut spending from 2013 through 2021. Subsequently, expiration dates continue to be extended into the future as each budget deficit looms larger (now into the 2030s).

How do past and present political squabbles affect facilities? The sequestration payment cut implemented in 2013 cut reimbursement by 2 percent for all government payments, including those for healthcare. This 2 percent reduction applies only to the 80 percent Medicare reimburses and not to the 20 percent patient co-pays.

The COVID-19 pandemic paused the sequestration minus 2 percent, which has been extended several times. However, the proposed infrastructure bill discussions maintain a Dec. 31, 2021, expiration with no further extensions of the pause.

Claims Denials Can Be Overcome

The most common reasons for denied claims include incomplete claims and coding errors coupled with failing to justify medical necessity in electronic record documentation or not being medically necessary. Understanding the terms discussed here and ensuring IT departments/providers are compliant will help to prevent these denials. Other payment denial issues include site-of-care shift rulings not recognized by a facility, multiple payers/stakeholders that are not recognized, payer-mandated step therapies and other commercial and Medicare Advantage payer requirements. ❖

BONNIE KIRSCHENBAUM, MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.

Accreditation Can Drive Business Capacity for Healthcare Organizations

By José Domingos

FROM HEALTH Insurance Portability and Accountability Act (HIPAA) laws to the Affordable Care Act, the healthcare industry is highly regulated. In an ever-evolving healthcare landscape, significant regulatory updates occur rapidly and frequently. The COVID-19 pandemic has served to highlight this trend, often requiring organizations to shift focus abruptly, while simultaneously demonstrating compliance in a new, challenging environment.

Now, more than ever, healthcare provider organizations can benefit from leveraging the broad value of accreditation. Many people associate accreditation solely with compliance and the survey experience, but with the right partner, accreditation is the source of a business relationship that can help drive performance improvement, operating efficiencies and risk management — all aspects of a successful business growth strategy — while maintaining ongoing regulatory compliance.

Ongoing Quality Improvement

For any healthcare organization, from a group practice to a corporate entity or hospital system, maintaining performance improvement should be the primary goal in seeking accreditation. Performance improvement is central to sustaining all other objectives — fulfilling legal requirements, attaining higher reimbursement and strengthening competitive advantage.

There is considerable evidence to show accreditation programs improve outcomes across a wide spectrum of clinical conditions.[1] Actively engaging the entire organization — from administrators and practitioners to facility engineers and human resources — in a culture of improvement embeds the practice of accreditation into daily policies and procedures to improve the quality of care and strengthen the organization.

Quality improvement is a pervasive theme across accreditation standards, regardless of setting. The broad issues addressed may be rooted in patient safety and clinical care, but they are also building blocks of a high-performance organization. Elements include:

- Developing a broadly conceived program to touch every area of an organization through data collection activities. Whether employee-based or contracted service, there is very little operationally that cannot be covered by a comprehensive, effective quality improvement program.
- Attaching specific, measurable goals to each service area to establish data-driven, evidence-based protocols. Data for data's sake is not useful. Context makes the data actionable.
- Fully communicating results to ensure engagement and establish accountability spanning from front-line staff through the governing body. At the staff level, quality data are collected and compared with past performance. At the management level, patterns are identified and recommendations are made to maintain a positive trajectory or adjust to correct off-target trends. The executive level holds ultimate responsibility for the quality of services delivered, and as the quality reporting is communicated upward, there is continuing evaluation of whether performance is serving to advance the organization's mission and strategic goals.

In short, the more frequently organizations are thinking about accreditation, the easier it is to integrate the standards into daily, frontline activities and managerial decision-making. For executive leaders who embrace a performance improvement process as the nexus of their operating plan, an accreditation focus brings added value to business operations. Continuous, small course corrections are easier and more sustainable than instituting major overhauls when a survey is approaching. This principle applies equally to standards compliance and management of the business.

Optimizing Efficiencies

With healthcare organizations operating on slim margins, operational efficiency is critical to success. Administrators and

other leaders hold responsibility for compliance with complex federal and state laws, while simultaneously seeking to manage and reduce costs.

For an organization considering expansion, ensuring consistency in quality of care across all services and locations is essential. Whether a home health agency wants to expand into home infusion therapy or a physician group seeks a hospital partner for a joint venture in outpatient surgery, an accreditation resource offering comprehensive service solutions can support sustainable business growth. Taking an integrated approach promotes consistency of practice, optimizing efficiencies across service lines and locations.

Similarly, sharing best practices across service lines and/or facilities is a major benefit for an organization, regardless of size. For a system, a single accreditor facilitates internal benchmarking opportunities. For a smaller setting looking to expand service lines, it streamlines the launch process.

Using an already accredited facility as a template of quality care allows providers to adapt their model of success in other areas. With these best practices established, healthcare organizations also can demonstrate to investors the value of a new operation.

The documented benefits of accreditation are many and include enabling the establishment of better organizational structures and processes, promotion of quality and safety cultures and improvements in patient care.[2] In a survey of health departments that had been accredited for one year, more than 90 percent reported experiencing benefits such as stimulation of quality improvement and performance improvement opportunities, increased accountability and transparency, and improved management processes.[3]

Accreditation standards offer a framework to help organizations develop improved structures and operational excellence. Healthcare leaders should use the accreditation process to inform strategic management and operational decisions.

Differentiating from Competitors

Accreditation status can differentiate a healthcare organization within the community and offers significant competitive advantages. Achieving accreditation assures patients and potential partners that an organization provides the highest quality of care, giving them the confidence to choose your facility over one that is not accredited.

The ideal accreditor provides ongoing, comprehensive guidance and services to meet a range of needs such as recognition for specialties that distinguish facilities from their competitors. For example, a stroke center designation for a hospital means the local EMS can transport the patient to that facility knowing the patient will receive the specialized care necessary for quick assessment and treatment. This type of recognition focuses on the organization's ability to provide a specialized service and stresses to the public the organization is dedicated to meeting the community's need.

While accreditation standards are designed to meet federal and state requirements, healthcare providers should consider an implementation strategy that is customized and tailored to their organization to ensure adequate differentiation and relevant risk management. Ongoing access to accreditation resources, experts and education helps organizations identify high-risk areas and adjust to regulatory changes more smoothly and efficiently.

By using best practices and data collected to meet accreditation requirements, a process is already in place to adjust for risk or update methods and procedures to improve quality of care. This proactive approach to risk management should limit errors and lead to safer processes. As testament, many liability insurers recognize the benefits of accreditation and reduce premiums for accredited organizations.

Accreditation can be a vital tool to optimize and expand your healthcare business. Through ongoing support from an accreditation provider, an organization can realize the value of accreditation beyond the survey. Its optimal impact is achieved when an organization uses quality improvement and risk management to extend accreditation as a capacity-building tool. ❖

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Research

Studies Reveal Antibody Responses of Pregnant Women Infected with SARS-CoV-2

Two recently published studies were effective in determining the antibody responses of pregnant women infected with SARS-CoV-2 and the effect of the fetal sex on those responses. They also found direct clinical implications for COVID-19 infection, as well as future maternal-fetal vaccination strategies.

One of the studies involved a systems serology approach to phenotype the anti-SARS-CoV-2 antibodies in the sera of pregnant, nonpregnant and lactating women following administration of mRNA-1273 or BNT162b2 COVID-19 vaccines. Results indicated pregnant women showed lower SARS-CoV-2 antibody titers, restricted IgG subclass responses and a decreased FcR-binding capacity following the first dose of the vaccine compared to nonpregnant women. However, minimal differences were observed after the second dose between pregnant and lactating women and nonpregnant women. Only in lactating women, increased natural killer (NK) cell-activating antibodies were observed following the second dose of vaccination.

Differences in responses to each mRNA vaccine formulation were also observed in pregnant women. For the mRNA-1237 vaccine, immune responses were enriched for neutrophil and NK cell-recruiting antibodies. In contrast, for the BNT162b2 vaccine, they were more enriched for less specific IgG1 and FcRYIIIa-binding antibodies.

Concerning passive immunity, higher SARS-CoV-2 antibodies were observed in maternal sera compared to cord sera, most likely due to immunization at a later stage of the pregnancy. Additionally, this reduction in transfer may be due to a lower abundance of FcRYIIIa-binding antibodies in pregnant women. However, in lactating women, higher antibodies with greater functional and FcR-binding qualities were observed after vaccination.

The other study investigated the antibody and antiviral interferon responses in COVID-19-infected and -uninfected pregnant women and whether the sex of the fetus had an impact on those responses. To determine the effect of fetal sex on the antibody response, the anti-SARS-CoV-2 antibody titers were quantified along with functions and specificities in maternal and cord blood sera of pregnancies with female and male fetuses.

Results indicated mothers carrying male fetuses had lower titers of IgG antibodies for all SARS-CoV-2-specific antigens. This suggests the fetal sex affects the maternal antibody responses. Furthermore, the transfer ratio of SARS-CoV-2 antibodies was lower in cord blood for male pregnancies compared to female pregnancies.

Placental staining and genome analyses were also conducted to determine whether sex-specific differences in placental FcR expression existed. Results indicated an increased expression of FcRn, FcRYII and FcYRIII, as well as increased co-localization of FcRn and FcRYIII in the male-derived placenta. Glycan profiling revealed that in male pregnancies, higher titers of antibodies were modified by glycosylation and fucosylation. Fucosylated antibodies are less efficiently transferred by the FcRYIIIa-binding that explains the lower IgG transfer in male pregnancies.

According to the researchers, the studies emphasize the need for incorporating pregnant women at different stages of gestation in clinical trials for the development of vaccines. ❖

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Medicines

FDA Approves Avacopan to Treat Rare Autoimmune Disease

The U.S. Food and Drug Administration (FDA) has approved ChemoCentryx Inc.'s Avacopan, sold under the brand name Tavneos, to treat antineutrophil cytoplasmic antibody-associated vasculitides — a group of conditions characterized by destruction and inflammation of small blood vessels and affecting different organs, particularly the kidney. Avacopan works by blocking the activity of a protein called C5a receptor that is responsible for causing numerous inflammatory diseases.

The company received mixed reviews from an expert panel to the FDA in May, with the committee's vote split 9-9 on whether the efficacy data supported the drug's approval. ❖

ChemoCentryx Gets U.S. FDA Nod for Drug to Treat Rare Autoimmune Disease. Reuters, Oct. 8, 2021. Accessed at leaderpost.com/pmn/business-pmn/chemocentryx-gets-u-s-fda-nod-for-drug-to-treat-rare-autoimmune-disease.

Medicines

Kedrion to Market RYPLAZIM to Treat Rare Disease

Kedrion Biopharma, an international biopharmaceutical company specialized in the manufacture and distribution of plasma-derived therapeutic products used in treating rare and serious diseases, is now marketing and distributing RYPLAZIM (plasminogen human-tvmh) in the United States to treat plasminogen deficiency type 1, also known as C-PLGD, an ultra-rare condition affecting less than 2,000 people in the U.S. A lifelong disease, the most severe symptoms of C-PLGD are observed in infants and children. And, given its rarity, the condition is probably underdiagnosed in the U.S.

"The most important mission at Kedrion Biopharma is to improve the lives of people with rare and serious diseases," said Val Romberg, CEO. "As the newest addition to our growing portfolio of products, RYPLAZIM is an excellent example of that dedication. RYPLAZIM meets an urgent unmet medical need for people who face plasminogen deficiency type 1, a potentially devastating, but treatable, medical condition. We are pleased and gratified to be in a position now to help these patients." ❖

Kedrion Biopharma to Commercialize RYPLAZIM® (plasminogen, human-tvmh) in U.S. to Address Unmet Need in Patients with Ultra-Rare Condition: Plasminogen Deficiency Type 1. Kedrion Biopharma press release, Oct. 20, 2021. Accessed at www.biospace.com/article/releases/kedrion-biopharma-to-commercialize-ryplazim-plasminogen-human-tvmh-in-u-s-to-address-unmet-need-in-patients-with-ultra-rare-condition-plasminogen-deficiency-type-1.

Research

IVIG Plus Glucocorticoids Effective for Treating COVID-19 Pediatric Syndrome

A large multicenter clinical trial has found intravenous immune globulin (IVIG) plus glucocorticoids may be better than IVIG alone for treating multisystem inflammatory syndrome in children (MIS-C) caused by COVID-19.

In the study, 596 patients with MIS-C were treated at one of 58 U.S. hospitals, 87 percent (518) of whom were treated with at least one immunomodulatory agent. The median age of the patients was 8.7 years. More than half of the patients (286; 55 percent) had involvement of five or more organ systems, and 196 (38 percent) met the complete or incomplete criteria for Kawasaki disease, a vasculitis of childhood that the investigators noted has some overlapping presentations with MIS-C and responds well to IVIG therapy, the standard of care for the disease.

The primary outcome of the study was cardiovascular dysfunction, a composite of left ventricular dysfunction or shock resulting in the use of vasopressors, on or after day two of therapy. Secondary outcomes included the need for adjunctive treatments such as a glucocorticoid in patients not already receiving them, a biologic or a second dose of IVIG, and a persistent or recurrent fever.

Results showed initial treatment with IVIG plus glucocorticoids (103 patients) was associated with a lower risk for cardiovascular dysfunction on or after day two than IVIG alone (103 patients). The risks of the components of the composite outcome also were lower among those who received IVIG plus glucocorticoids: Left ventricular dysfunction occurred in 8 percent and 17 percent of the patients, respectively. The incidence of shock resulting in vasopressor use also was lower in the IVIG plus glucocorticoid regimen: 13 percent versus 24 percent with IVIG alone. The use of adjunctive therapy was lower among patients who received IVIG plus glucocorticoids than among those who received IVIG alone (34 percent vs. 70 percent), but the risk for fever was unaffected (31 percent and 40 percent).

Methylprednisolone was the most common glucocorticoid prescribed (353 patients; 68 percent), administered at a dose of 2 mg/kg of body weight per day in 284 of the patients (80 percent), and in pulse doses of 10 mg/kg to 30 mg/kg of body weight

per day in 69 patients (20 percent).

The researchers acknowledged earlier studies have shown glucocorticoids and IVIG may be an effective regimen for MIS-C. But in many cases, the studies included fewer patients and less pronounced results. A French study, for example, "suggested" a lower incidence of cardiovascular dysfunction. "In our larger U.S. cohort, we confirmed that cardiovascular function was better, and the incidence of administration of adjunctive treatments was lower" among patients given the combined regimen versus those given IVIG alone. ❖

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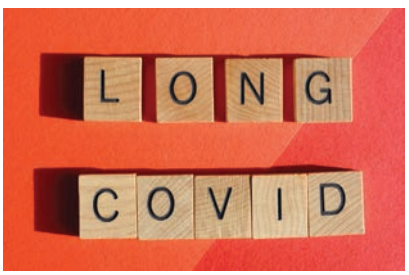
Research

Researchers Theorize Long COVID May Be an Autoimmune Disease



In a study published in September, researchers suggested some people who get COVID-19 develop autoantibodies that attack their own proteins, a hallmark of many autoimmune diseases, which leads to inflammation that could trigger long COVID. Now, the National Institutes of Health is conducting a $470 million study to determine why COVID-19 symptoms persist for so long among many patients.

In the study, the researchers analyzed blood samples from 32 COVID-19 patients who donated plasma to the University of Arkansas, and another 15 who had been hospitalized there. Approximately 81 percent of the plasma donors and 93 percent of the hospitalized patients had developed a particular autoantibody that inhibited their ACE2 enzymes, which serve as ports of entry for the coronavirus to invade the body's cells, but they're also vital to calming the immune system down. When not enough ACE2 is present, the immune system can produce too much inflammation. "It's the inhibition of that ACE2 enzyme that basically is plugging up the system," said John Arthur, MD, PhD, a researcher at the University of Arkansas for Medical Sciences. "It's like if you've got a bunch of hair in the drain and the water starts to accumulate on top."

However, more research is needed to determine whether these ACE2 antibodies cause long COVID. Researchers also aren't sure yet whether severe infections produce more autoantibodies than mild ones. A May study found that to be the case, but Dr. Arthur noted that long COVID is also common among people whose infections were initially mild.

If the theory that long COVID is an autoimmune disease, it would have implications for COVID-19 treatments. Certain blood-pressure medications, for instance, could be used to stifle the harmful cascade of inflammation. And there's already some evidence that vaccines help alleviate long COVID symptoms, perhaps because they help regulate the antibody response. ❖

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Effects of COVID-19 on Medical Resources

The pandemic has left the healthcare system with staffing and revenue shortages, as well as supply chain management challenges, that are expected to extend into the foreseeable future.

By Diane L.M. Cook

THE SARS-COV-2 virus has not only caused more than 44 million cases of illness and over 700,000 deaths[1] in the United States, it wreaked havoc on the nation's healthcare system. Despite extensive pandemic preparedness plans, the healthcare system was completely unprepared for the COVID-19 pandemic that caused widespread adverse effects on medical resources ranging from healthcare, staffing and revenue shortages to supply chain management challenges — all of which hindered the nation's ability to provide specialized care for COVID-19 patients.

These shortages and challenges have cost the healthcare system hundreds of billions of dollars, and costs are expected to continue into the future. According to a recent article, "The pandemic is expected to cause a $3.3 trillion deficit in 2020, which is about 15 percent of the United States' gross domestic product."[2] And,

adds McKinsey & Company, a healthcare system and services management consulting firm, "While the direct impact of COVID-19 has already been substantial, additional layers of delayed or indirect impact have the potential to dwarf the immediate effects. These additional layers of impact related to COVID-19 could result in $125 billion to $200 billion in incremental annual U.S. health system cost."[3]

Declines in Healthcare Visits/ Procedures

Due to fears of contracting the SARS-CoV-2 virus and its more deadly variants such as Delta, many patients decided not to visit hospitals, resulting in delayed or canceled routine or emergency treatments, including surgeries. Coupled with undulating surges of COVID-19 patients at hospitals, this caused extensive healthcare shortages. According to McKinsey & Company, a recent survey it conducted showed U.S. hospital patient volumes moved back to 2019 levels in June 2021.[4] "From March 2020 through July 2021, private sector systems surveyed in the U.S. reported, on average, between a 5 and 15 percent decrease in volumes by site of care compared to 2019 levels. Over this 17-month period, survey respondents reported that procedural volumes were down 13 percent; outpatient visits were down 13 percent; emergency room visits were down 12 percent; and inpatient admissions were down 7 percent," says John Schulz, associate partner at McKinsey & Company.

Staffing Shortages

For several decades, there has been a severe, chronic shortage of nurses in the United States. Unfortunately, the COVID-19 pandemic exacerbated this shortage, and it will continue to do so until it is long over. The reason: Even with substantially reduced patient visits and procedures during the majority of the pandemic in the first, second and third waves, that was not enough to quell the ever-growing nursing shortage, especially during the fourth wave. In fact, countless nurses have left their jobs due to forced overtime, burnout and fear of contracting the SARS-CoV-2 virus.

To understand how serious the nursing shortage is, in August 2021, the American Association of Critical-Care Nurses surveyed 6,000 critical care nurses concerning the pandemic's impact on their careers, 66 percent of whom said their experiences during the pandemic have caused them to consider leaving nursing.[5]

On Sept. 1, 2021, the American Nurses Association (ANA), which represents 4.2 million nurses, urged the U.S. Department of Health and Human Services (HHS) "to declare the current and unsustainable nurse staffing shortage facing our country a national crisis." Included in ANA's letter is a directive that HHS must "convene stakeholders to identify short- and long-term solutions to staffing challenges to face the demand of the COVID-19 pandemic response."[6]

Two weeks later, ANA publicly supported the federal government's "Path Out of the Pandemic: President Biden's COVID-19 Action Plan" announced Sept. 7. "ANA supports the Biden Administration plan to use every lever to increase the number of people vaccinated as the only way to get out of this crisis [pandemic]," said ANA President Ernest Grant, PhD, RN, FAAN.[7] Increasing the number of people getting the COVID-19 vaccine is expected to help ease the current Delta surge being experienced by hospitals and reduce the pressure and stress on nurses who care for COVID-19 patients.

Due to fears of contracting the SARS-CoV-2 virus and its more deadly variants such as Delta, many patients decided not to visit hospitals, resulting in delayed or canceled routine or emergency treatments, including surgeries.

On Oct. 14, 2021, it was announced the Biden Administration would direct $100 million to the National Health Service Corps to help address the healthcare worker shortage. The announcement came after the loss of 17,500 U.S. healthcare employees in September, according to the Bureau of Labor Statistics. In addition, the agency reported the country has lost 524,000 healthcare employees since the start of the pandemic, with the industry's employment sitting at just under 16 million. The biggest job losses in the industry in September occurred in nursing, hospitals and residential care.[8]

In McKinsey & Company's 2021 Future of Work in Nursing survey, it found 22 percent of nurses indicated they might leave their current position of providing direct patient care in the next year, with more than half reporting they were seeking another career path, a nondirect care role or retirement. Gretchen Berlin, a senior partner at McKinsey & Company,

said the July 2021 survey of 100 private sector hospitals found operational leaders reported nursing turnover in the second quarter of 2021 was up 4.7 percentage points, and the nursing vacancy rate was up 3.7 percentage points (Figure).[9]

In addition, said Berlin, research conducted earlier in the pandemic (September 2020) found physicians are also experiencing burnout, which can contribute to shortages: "Almost 43 percent of the respondents reported experiencing burnout to some extent. Physicians reported seeing more medical complications, negative economic impact and higher costs as a result of patients putting off necessary care. A majority of the respondents said they are worried about their practice making it through the COVID-19 pandemic, and about a third of the respondents said that they are more likely to pursue a partnership with a larger organization, preferably with a health system, primarily for financial stability reasons."

On a positive note, the American Association of Colleges of Nursing reported a 5.6 percent increase in 2020 nursing student enrollment.[10] And, the Association of American Medical Colleges reported a 1.7 percent increase in first-year students in the 2020 academic year and an 18 percent increase in medical student enrollment in 2021.[11]

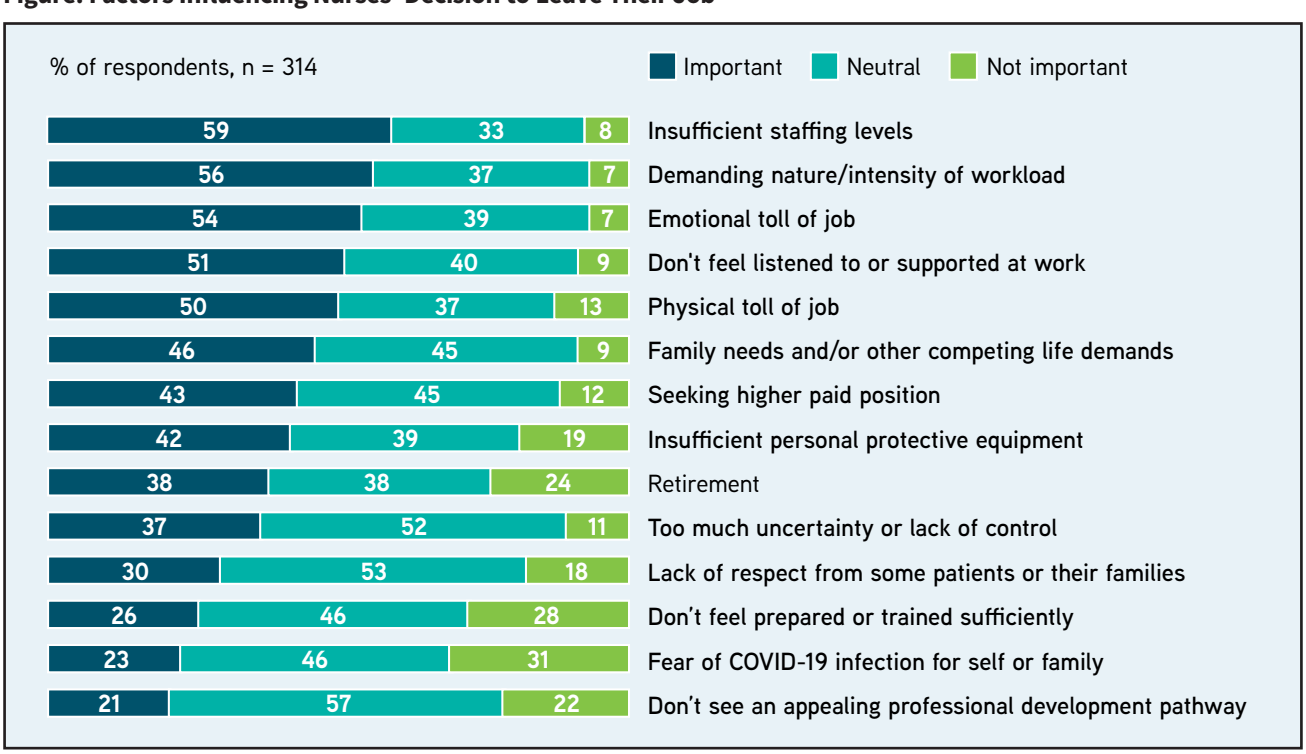
Revenue Shortages

With patient volumes down and hospitals experiencing multiple surges of COVID-19 patients over the previous 18-month period, revenues were understandably down. And although revenues are slowly returning to pre-pandemic levels, the amount of revenue lost during the four waves of the pandemic over a two-year period might never be recovered.

KaufmanHall, a healthcare management consulting firm, released its 2021 Healthcare Performance Improvement Report in October, which found "volumes in many service lines remain below pre-pandemic levels, putting downward pressure on revenues." One highlight of the report was that "75 percent have experienced adverse revenue cycle impacts during the pandemic, including a higher percentage of Medicaid patients and increased rates of denial."[12]

According to two other recent reports from KaufmanHall, "a resurgence of COVID-19 cases from rapid spread of the highly contagious Delta variant is raising new uncertainties for hospitals, health systems and physician practices across the country."[13] The company's September 2021 National Hospital Flash Report, which draws on data from more than 900 hospitals, says the spread of the hyper-transmissible Delta variant continued to

Figure. Factors Influencing Nurses' Decision to Leave Their Job[9]



strain hospitals and healthcare systems nationwide in August.

However, more than a year and a half into the pandemic, even though COVID-19 continues to undermine performance improvement efforts, revenues are starting to rise. "Given the increase in higher acuity cases and yearly rate changes, U.S. hospitals saw revenues increase year-to-date compared to both 2019 and 2020 for a sixth consecutive month," states the report. "Gross operating revenue rose 9.6 percent year-to-date versus 2019 and 16.6 percent year-to-date versus 2020 [not including the Coronavirus Aid, Relief and Economic Security Act]. Outpatient revenue saw the biggest increases at 10 percent year-to-date versus 2019 and 20.3 percent versus 2020, while inpatient revenue was up 5.6 percent year-to-date compared to 2019 and 11.8 percent year-to-date compared to 2020."[14]

In addition, KaufmanHall's August 2021 Physician Flash Report, which draws on data from nearly 100,000 providers representing more than 100 specialties, shows "physician groups across the country saw productivity and revenue improvements in the second quarter compared to the same period in 2020 and to pre-pandemic levels seen in the fourth quarter of 2019. However, significant increases in expenses and continued high levels of physician investment compared to the pre-pandemic period remain areas of concern. The changes are among multiple dramatic swings experienced across key physician performance metrics for the quarter, especially compared to the second quarter of 2020 when nationwide shutdowns and widespread concerns over potential exposure to the virus caused patient visits to plummet at the start of the COVID-19 pandemic."[15]

As of March 1, 2021, HHS's $178 billion provider relief fund gave almost all Medicare-enrolled healthcare providers grants that amounted to at least 2 percent of their previous annual patient revenue, which can be used to cover lost revenue and unreimbursed costs associated with the pandemic.[16] However, the grant is not a full representation of the costs of the pandemic. Additional costs include indirect costs borne across several dimensions, including increased caregiver turnover and clinical costs associated with patients whose medical conditions have exacerbated during the last 18 months. There are also costs from projects that were stalled or revamped due to the pandemic. For example, hospitals in the process of redesigning waiting rooms might have pivoted to allow for more social distancing or screening capabilities. Other hospitals might have reevaluated their need for the number of airborne infection isolation rooms or more air filtration.

"Our healthcare system is still learning the full breadth and scale of these effects of the pandemic, and the overall cost to the healthcare system remains uncertain, especially as additional variants continue to emerge and we gain a greater understanding of complications from the virus, including long-haul patients," says Neil Rao, a partner at McKinsey & Company.

2021 KaufmanHall Hospitals and Healthy Systems Survey Highlights

- 100% of survey respondents face issues with clinical staff, including burnout, difficulty filling vacancies, wage inflation and high turnover rates.
- 99% have experienced challenges in supply procurement, including shortages of key items and significant price increases.
- 92% are having difficulties attracting and retaining support staff, and almost 90% have increased base salaries.
- 75% have experienced adverse revenue cycle impacts during the pandemic, including a higher percentage of Medicaid patients and increased rates of denial.

Source: William H Frey analysis of 2010 U.S. Census and 2020 Census Bureau demographic analysis estimates, released Dec. 15, 2020.

Supply Chain Management Challenges

In addition to patient, staffing and revenue shortages, the healthcare systems also experienced abrupt adverse challenges in its supply chain management system. And, many of these challenges were predicated on how the system operated prior to the pandemic.

One of those challenges is that the United States healthcare system is designed to provide highly individualized healthcare for complex diseases such as cancer or the central nervous system. However, when a pandemic occurs, mass illness of a specific organ system such as respiratory, as is the case with the COVID-19 pandemic, stresses the healthcare system far beyond what it was prepared for.

According to Daniel Moskovic, a partner at McKinsey & Company, the personal protective equipment and ventilator shortages experienced in the COVID-19 pandemic could theoretically have been mitigated by maintaining adequate/more supplies, rapidly introducing new supplies and/or putting into place product utilization and reengineering protocols. "The first two strategies would require substantial investment, which is unfavorable in an overall push to reduce healthcare costs year-to-year;

these would certainly increase costs and, given the infrequency of any given type of pandemic, would likely be viewed unfavorably by taxpayers and consumers [patients]," explained Moskovic. "The latter strategy could potentially be studied and deployed at a far lower cost, but there would be tradeoffs in shifting standards of care and/or redesigning products that likely would be much higher cost."

Additionally, Moskovic said the structure of the payment system incentivizes reduction in unit costs that, like many other industries, leads to a focus on cost minimization by suppliers to remain competitive. Offshoring, just-in-time inventories and specification optimization are all natural outcomes of this type of economic model. "Now that we've experienced the challenges of this type of stress on our healthcare supply chain management system, there will need to be a serious and transparent dialogue about investments we will make — and how those investments will be funded — to determine the tradeoffs we are comfortable with across outcomes, cost and care delivery practices," said Moskovic.

"The financial hit that hospitals and health systems continue to take from the changing utilization patterns caused by COVID's public health and socioeconomic effects is unprecedented. As a result, it's more important than ever for hospital and health system executives to achieve bold and continuous improvements in long-term cost structure to match the decline in patient revenue; build a product portfolio to take advantage of the accelerating movement from fee-for-service to value-based payment; and transform the core delivery business for the truly exceptional clinical and financial performance that is required by a more competitive marketplace," says Kenneth Kaufman, managing director and chair, at KaufmanHall. "The stubbornly persistent effects of this pandemic remind us that the organizational goal in 2021 and beyond is not to find the way back to a pre-COVID comfort zone, but rather to negotiate and navigate toward being the best performing healthcare organization possible within a fast-changing and uncertain post-COVID business environment."

"The financial hit that hospitals and health systems continue to take from the changing utilization patterns caused by COVID's public health and socioeconomic effects is unprecedented."

A Costly Response

It is unfortunate the United States' healthcare system was so unprepared for the COVID-19 pandemic. Even when it was clear that healthcare systems had to pivot quickly to respond to and manage the pandemic, they failed to do so, and this slow response cost hundreds of billions of dollars. Until staffing and revenue issues and supply chain management challenges are adequately addressed to meet the healthcare system's current business model, any future pandemics will likely cause similar adverse effects on the nation's medical resources. ❖

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Healthcare Disrupted:

Transitioning Primary Care, Diagnostics and Chronic Disease Management to the Retail Healthcare Sector

Retail health centers are increasingly offering convenient care at lower prices, but debate surrounds their entry into the primary care arena.

By Amy Scanlin, MS

IN MARCH 2010, the healthcare industry changed when the Affordable Care Act (ACA) was enacted and a flood of newly insured became empowered to seek, consider and choose their own healthcare options. This historic event, coupled with a near simultaneous advancement in healthcare technology (electronic health records [EHRs], telehealth and wearables capable of tracking and reporting data without user intervention) turned the industry on its heels. Ten-plus years later, this newly engaged public has evolved in many respects into a new type of patient: the healthcare consumer.

Healthcare consumers seek simplicity and efficiency; they want convenient office hours and clear pricing. Enter the retail health center (RHC), a growing big-box and stand-alone trend that is filling voids and drawing interest, as well as raising questions. For some healthcare consumers, the lures of an RHC are convenience of location and availability of providers. For others, the lures are simple and more affordable pricing structures.

When RHCs first arrived on the scene in 2000, there were some considerable unknowns. For instance, would they cause care to be fragmented? How would they use EHRs, and would there be compatibility issues with other EHR systems? Yet, despite these unknowns, RHCs have continued to grow, serving an unmet healthcare need, particularly with declining numbers of primary care physicians.

The Doctor (or Physician Assistant/Nurse Practitioner) Will See You Now

Providers must deliver on patient needs. When operating hours and perceived level of care, including scheduling and billing, don't meet patient expectations, the inclinication may be to seek care elsewhere. This is where RHCs are gaining market share.

In turn, traditional healthcare is attempting to meet healthcare consumers' needs by providing extended hours, easier appointment scheduling (including online portals) and improved access to telehealth. But expansion of hours and services isn't always easy, particularly considering the prohibitive cost of staffing and technology. More than half of healthcare visits occur

on weekends and holidays,[1] which RHCs seem better able to offer. "RHCs are not urgent care clinics," stresses Nate Bronstein, COO of the Convenient Care Association (CCA). "We are not replacing doctors; we play an expanded role in the continuum of health."

Originally created to treat limited acute conditions, RHCs have in many cases expanded facilities and services to routine care and management of chronic conditions. In fact, they are often patients' first contact with the healthcare system. Generally, they are located within a 10-mile radius of nearly 50 percent of the population, and approximately 60 percent of their 50 million patients do not have an established primary care provider. According to Tine Hansen-Turton, founding executive administrator director for CCA, about 40 percent to 60 percent of those seeking care in RHCs do so for primary or chronic conditions.

Practice Authority

More than half of U.S. states and the District of Columbia have passed legislation permitting full practice authority for nurse practitioners (NPs), meaning they can evaluate, diagnose, order and interpret diagnostic tests and initiate and manage treatments for patients, including prescribing medications, under the exclusive licensure authority of their state board of nursing. According to the American Academy of Nurse Practitioners (AANP), those states without full practice authority generally see greater geographic healthcare disparities, higher chronic disease burdens, primary care shortages, higher costs of care and lower standings on national health rankings. For example, Bronstein cites Texas and Florida, the two states with the greatest number of RHCs, also have the greatest number of health disparities.

In these more restrictive states, NPs working in RHCs provide care under the remote supervision of an established medical practice, so they are not permitted to see patients and prescribe treatments without physician oversight. According to CCA, the fewer providers available, the more expensive these RHC practices become thanks to increasing collaborative agreement fees, insurance and other needed resources. CCA says the additional overhead could be as much as 5 percent to 10 percent. But, "that hasn't impacted the model," says Bronstein. "There are still more clinics needed." Even so, he says, by granting full NP and physician assistant (PA) practice authority, the U.S. healthcare provider shortage could be reduced by 89 percent.

Out of the Box

But the American Medical Association (AMA) disagrees. AMA takes issue with RHCs as a solution to primary care shortages, particularly in underserved communities.[2] In its opinion, the level of experienced care offered in RHCs is less than that of traditional healthcare facilities.

Originally created to treat limited acute conditions, RHCs have in many cases expanded facilities and services to routine care and management of chronic conditions.

And, while the American Academy of Family Physicians (AAFP) encourages use of RHCs, it does not think it should be at "the expense of the comprehensive, coordinated and longitudinal care available through a medical home." In AAFP's view, chronic care management and comprehensive longitudinal care should be provided by a primary care physician and medical home team, not by a retail clinic. In addition, it says in cases where certain chronic conditions could be managed in retail clinics, care management should only be under a collaborative agreement between the patient's primary care physician and the retail healthcare facility specifying the "guidelines, procedures and protocols to be used to provide such care."[3] Further, AMA urges patients seeking treatment in RHCs to become informed about the qualifications of the staff providing treatment, as well as their limitations in diagnosis and treatment. It also recommends RHCs have an established referral mechanism in the event the scope of care is beyond that of the practitioner or retail clinic.[2]

However, with 89 percent of practicing NPs receiving training in primary care settings, AANP believes NPs play a significant role in providing patients a viable healthcare option. Citing satisfaction surveys that rate NP care equal or superior to physicians for the same problems, NPs make up the most rapidly growing component of the primary care workforce.[4]

CCA agrees NPs and PAs provide valuable primary care roles, and that the establishment of relationships with the larger healthcare community is essential. Citing strong partnerships between member RHCs and hospitals, including RHCs that have been established by healthcare systems, says Hanson-Turton, "we are a national referral service for them."

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ALBUTEIN

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ALBUTEIN FlexBag 5% (albumin [human] U.S.P.)
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Initial U.S. Approval: 1978

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ALBUTEIN 5% is an albumin solution indicated for:
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- Plasma exchange.

----------DOSAGE AND ADMINISTRATION----------

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Dosage and infusion rate should be adjusted to the patient's individual requirements.

Indication	Dose
Hypovolemia	Adults: Initial dose of 20 g (including renal dialysis). For acute liver failure: initial dose of 12 to 25 g.
Cardiopulmonary bypass procedures	Adults: Initial dose of 25 g.
Hypoalbuminemia	Adults: 50 to 75 g For pre- and post-operative hypoproteinemia: 50 to 75 g. For burn therapy after the first 24 h: initial dose of 25 g and dose adjustment to maintain plasma protein concentration of 2.5 g per 100 mL. Third space protein loss due to infection: initial dose of 50 to 100 g.
Plasma exchange	The dose required depends on the volume of plasma removed during the procedure.

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----------DOSAGE FORMS AND STRENGTHS----------

ALBUTEIN 5% is a solution containing 50 g per L of total protein of which at least 95% is human albumin.

----------CONTRAINDICATIONS----------

- Hypersensitivity to albumin preparations or to any of the excipients.
- Severe anemia or cardiac failure with normal or increased intravascular volume.

----------WARNINGS AND PRECAUTIONS----------

- Suspicion of allergic or anaphylactic reactions requires immediate discontinuation of the injection and implementation of appropriate medical treatment.
- Hypervolemia may occur if the dosage and rate of infusion are not adjusted to the patient's volume status. Use with caution in conditions where hypervolemia and its consequences or hemodilution could represent a special risk to the patient.
- Monitor electrolytes, coagulation and hematology parameters, and hemodynamic status when albumin is given.
- Do not dilute with sterile water for injection.
- This product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

---------- ADVERSE REACTIONS ----------

The most common adverse reactions are anaphylactoid type reactions.
To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals LLC at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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ALBUTEIN FlexBag 25% (albumin [human] U.S.P.)
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Initial U.S. Approval: 1978

----------INDICATIONS AND USAGE----------

ALBUTEIN 25% is an albumin solution indicated for:
- Hypovolemia.
- Cardiopulmonary bypass procedures.
- Acute nephrosis.
- Hypoalbuminemia.
- Ovarian hyperstimulation syndrome.
- Neonatal hyperbilirubinemia.
- Adult respiratory distress syndrome (ARDS).
- Prevention of central volume depletion after paracentesis due to cirrhotic ascites.

----------DOSAGE AND ADMINISTRATION----------

For Intravenous Use Only

Dosage and infusion rate should be adjusted to the patient's individual requirements.

Indication	Dose
Hypovolemia	Adults: Initial dose of 25 g (including renal dialysis). For acute liver failure: initial dose of 12 to 25 g.
Cardiopulmonary bypass procedures	Adults: Initial dose of 25 g.
Acute nephrosis	Adults: 25 g together with diuretic once a day for 7 - 10 days.
Hypoalbuminemia	Adults: 50 to 75 g For pre- and post-operative hypoproteinemia: 50 to 75 g. For burn therapy after the first 24 h: initial dose of 25 g and dose adjustment to maintain plasma protein concentration of 2.5 g per 100 mL. Third space protein loss due to infection: initial dose of 50 to 100 g.
Ovarian hyperstimulation syndrome	Adults: 50 g to 100 g over 4 hours and repeated at 4-12 hour intervals as necessary.
Neonatal hyperbilirubinemia	1 g per kilogram body weight prior to or during exchange transfusion.
Adult respiratory distress syndrome (ARDS)	Adults: 25 g over 30 minutes and repeated at 8 hours for 3 days, if necessary.
Prevention of central volume depletion after paracentesis due to cirrhotic ascites	Adults: 8 g for every 1000 mL of ascitic fluid removed.

Do not dilute with sterile water for injection as this may cause hemolysis in recipients.

----------DOSAGE FORMS AND STRENGTHS----------

ALBUTEIN 25% is a solution containing 250 g per L of total protein of which at least 95% is human albumin.

----------CONTRAINDICATIONS----------

- Hypersensitivity to albumin preparations or to any of the excipients.
- Severe anemia or cardiac failure with normal or increased intravascular volume.

----------WARNINGS AND PRECAUTIONS----------

- Suspicion of allergic or anaphylactic reactions requires immediate discontinuation of the injection and implementation of appropriate medical treatment.
- Hypervolemia may occur if the dosage and rate of infusion are not adjusted to the patient's volume status. Use with caution in conditions where hypervolemia and its consequences or hemodilution could represent a special risk to the patient.
- When concentrated albumin is administered, care must be taken to assure adequate hydration of the patient.
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All oversight bodies without question agree on adherence to certain standards governing the setup and operation of RHCs, most importantly regulatory, certification and education requirements specific to the state in which care is being delivered. Currently, standards such as the use of evidence-based guidelines for diagnosing and treating patients, use of appropriate EHRs, evaluation of quality-of-care standards through peer and collaborating physician reviews and patient satisfaction surveys are in some cases law and in others best practice.

Bridging the Gap

For both traditional care settings and RHCs, opportunity can only exist in a proactive relationship in which established primary care patients know where to turn in the event care is needed outside of normal business hours. RHCs must have trusted places to turn when in-depth care is needed or when patients prefer a physician.

Established relationships also reduce the risk of fragmented care. Like the telephone game, the more relay points between a message, the more diluted the message becomes. With patients' consent, the notification and forwarding of records to a primary care provider can be automatic, reducing the risk of information gaps and duplication of treatment protocols. It goes without saying that the mere establishment of relationships is not a panacea for fragmentation. The more access care points, the greater the risk of information lost in transit or translation. Dialogue with the patient and any outside providers are the keys to missing links.

Importantly for the stressed healthcare system, partnerships between hospitals, doctor offices and RHCs can help to reduce hospital readmissions, particularly when patients cannot get in to see their primary care providers. RHCs are also a viable option for patients who have follow-ups within 30 days of hospital release, which result in lower rates of readmission.

Value-Based Care

The movement toward value-based healthcare is resulting in shifting treatment to outpatient settings, reduced costs and improved patient experiences. It is also spurring a trend in consolidation whereby smaller entities are merging with larger entities to improve economies of scale and operational efficiencies. However, these larger entities, thanks to a dearth of competition, may be able to charge patients higher rates to better match insurance reimbursements.

On the other hand, RHCs that are staffed primarily by PAs and NPs offer a lower-cost alternative (in some cases between 30 percent and 80 percent) to traditional healthcare and generally accept most public and private insurance plans. In fact, 60 percent of smaller insurance plans and 73 percent of large plans cover services provided in RHCs, although AMA urges caution against the encouragement of retail clinics to take advantage of lower costs through

reduced or waived copayments. However, it is ACA's position that patients seeking care in RHCs do so predominantly for minor ailments and reassurance that their condition is on the right track. Therefore, in its view, RHCs are potentially "inconsistent with value-based care and payment" because they create "new use" through "improved access." Furthermore, AMA also estimates that were treatment for low-level conditions sought in RHCs versus emergency departments (about 20 percent of total visits), the healthcare system could save $4 billion annually.[2]

Data Concerns

Retailers already collect and analyze a wealth of consumer data. When RHCs are added to the mix, where does customer marketing cross the line into violation of patient privacy?

Adequate use and data protection, including EHRs and telehealth technology, are at the forefront of healthcare. From Health Insurance Portability and Accountability Act (HIPAA) protections, Standards for Privacy of Individually Identifiable Health Information (known as the Privacy Rule) to the Health Information Technology for Economic and Clinical Health Act, numerous laws protect patient information and privacy. Even so, doing the bare minimum legally required may not be sufficient to satisfy healthcare consumers who have become increasingly concerned about privacy in the wake of breaches and poor security measures plaguing all aspects of online industries.

At a time when primary care provider shortages are estimated to grow from 45,000 in 2020 to upwards of 51,000 by 2033, RHCs provide a necessary and viable option for patients seeking care.

This begs a question: Although HIPAA protections prevent the sharing of patient care information to the retailer, what protections are in place when retailers through point-of-sale transactions identify who is being seen or who pays for care in RHCs? As data is collected, customers become viable marketing contacts, particularly when being opted-in or actively opting-in to retailer marketing.

The risks of this information collection came to light in April 2021 when consumer advocates urged District of Columbia Attorney General Karl A. Racine to stop the practice of some retail pharmacies from collecting customer information for marketing purposes as they signed up for COVID-19 vaccinations or inquired about appointment availability.[5] Certainly, a 21st century extension of the Hippocratic oath could reasonably extend to that of patient data privacy, as is required for the ACA.

Here to Stay

At a time when primary care provider shortages are estimated to grow from 45,000 in 2020 to upwards of 51,000 by 2033,[6] RHCs provide a necessary and viable option for patients seeking care. While the debate continues, perhaps with both parties agreeing to disagree on whether these clinics should be used in a primary care context, RHCs are here to stay, offering care and meeting patients and customers where they are: in their communities where they already shop, and with hours and pricing that may better suit their needs.

From a provider standpoint, RHCs offer an opportunity to reach an entirely new patient population, whether as a practicing clinician in an RHC or as part of the referral network for primary or specialty care. Clearly, these alliances between complementary providers have the potential to empower a greater focus on and awareness of health for the benefit of healthcare. As the industry balances the struggle between matching the long-term goals of patient health with short-term accessibility and payment options, it may be that the RHC model provides a key to success. Through RHCs' adherence to established quality and practice standards and their ability to sustain satisfaction metrics while focusing on accessibility, healthcare consumers have every opportunity and every advocate for success. ❖

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GENE THERAPY FOR HEMOGLOBINOPATHIES

By Meredith Whitmore

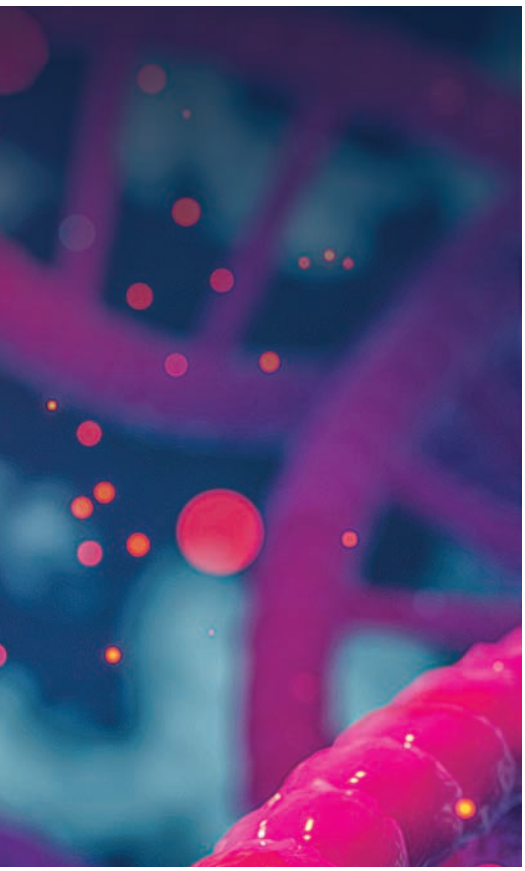
New clinical studies show gene therapy may offer a cure for these chronic and expensive diseases in five to 10 years.

WHILE HEMOGLOBINOPATHIES are not necessarily common in the United States, with only approximately 100,000 adults and children affected, they are more often found in other areas of the world.[1] Approximately 7 percent of the world's population are carriers, and hemoglobinopathies are the most common monogenic diseases, especially widespread in Asia, the Mediterranean and Africa.[2] Today, hemoglobinopathies are spread globally because of increased migration rates.[3] They are also a major health concern, with roughly 330,000 children born with the diseases worldwide every year. In the United States, Hispanic-Americans and Black or African-American populations are more at risk for hemoglobinopathies, and they often carry the autosomal recessive disease (two inherited mutated genes, one from each parent).[4]

Patients living with hemoglobinopathies typically cope with a level of uncertainty or even grief because their lives are so deeply affected by the illnesses. They are often anxious, for example, about their constant need for comprehensive resources to ensure their effective and costly care. And, they are almost invariably concerned about their long-term prognosis.

What Are Hemoglobinopathies?

Hemoglobinopathies are a group of disorders passed down through families in which there is abnormal production or structure of the hemoglobin (the red protein responsible for transporting oxygen in the blood) molecule (Figure). The most common hemoglobinopathies are sickle cell disease (SCD) and thalassemia. SCD, an umbrella group of hemoglobinopathies that includes sickle cell anemia, is an inherited disorder caused by an abnormal form of a protein called beta-globin, which causes red blood cells to become sickle (crescent)-shaped and inflexible.



Thalassemia is an inherited blood disorder caused by a defect in the gene that helps control the production of hemoglobin. There are two main types of thalassemia: alpha and beta, which differ according to which protein is altered. In both cases, people with thalassemia have fewer healthy red blood cells. Two other rare hemoglobinopathies include congenital sideroblastic anemia and congenital dyserythropoietic anemia caused by low levels of functioning red blood cells and often high levels of iron in the body. All types rob the body of adequate blood and oxygen, which damages the kidneys, liver and spleen, among other organs, and can be fatal.[4]

Currently, the only cure for SCD is a blood and bone marrow transplant. Transplants come from a human leukocyte antigen-matched sibling; however, only a small number of people are able and eligible for this treatment. There are other somewhat successful treatments that can reduce symptoms and prolong life, which are relatively available for patients who cannot afford or otherwise access a transplant. Severe cases of thalassemia are sometimes managed by frequent blood transfusions, while milder cases are prescribed folic acid to help treat anemia, typically to augment other therapies. For patients who are unresponsive to such remedies and who are merely managing symptoms, life without an available cure can be devastating.[4]

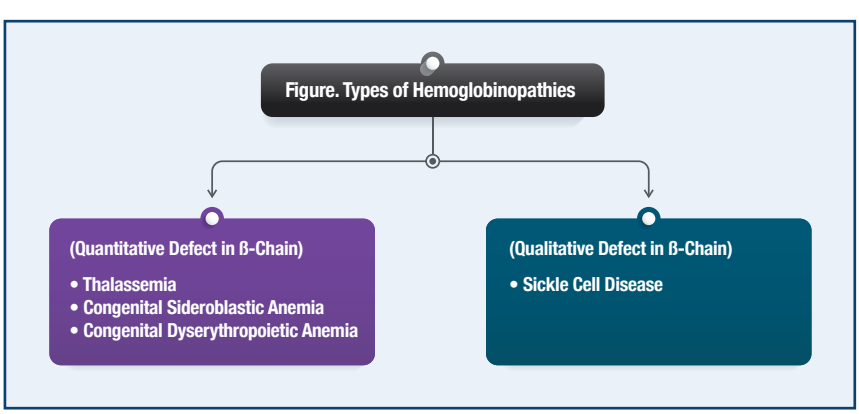
Gene Therapy: A Cure for Hemoglobinopathies?

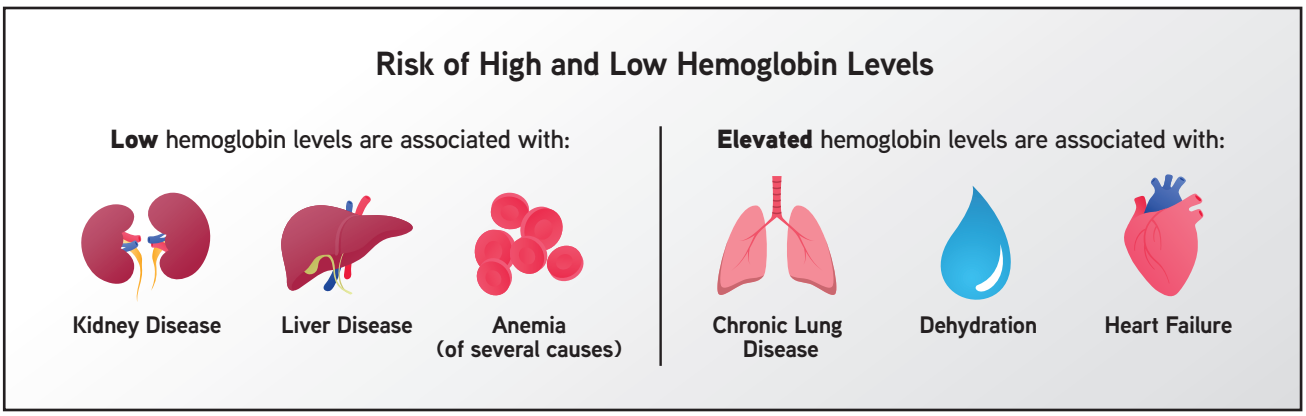
Today, gene therapy is providing a glimmer of optimism for hemoglobinopathy patients, with successful clinical trials pointing to a more accessible cure.

In simplified terms, gene therapy adds modified, functional copies of the beta-globin gene into a patient's hemopoietic stem cells so the body can make functional hemoglobin molecules and, therefore, functional red blood cells. In several ongoing studies, patients with six or more months of follow-up after treatment for SCD had median sickle cell hemoglobin levels reduced to 50 percent or less of total hemoglobin without blood transfusions. And in thalassemia, studies found sufficient hemoglobin production to reduce or eliminate the need for transfusion support. As the first-ever gene therapy for either of the conditions, medical researchers are nearing approval to cure these diseases.[4]

According to the authors of one recent study, "Gene therapy for hemoglobinopathies is now founded on transplantation of autologous hematopoietic stem cells genetically modified with a lentiviral vector expressing a globin gene under the control of globin transcriptional regulatory elements. Preclinical and early clinical studies showed the safety and potential efficacy of this therapeutic approach, as well as the hurdles still limiting its general application. In addition, for both beta-thalassemia and SCD, an altered bone marrow microenvironment reduces the efficiency of stem cell harvesting and engraftment. These hurdles still need to be addressed for gene therapy for hemoglobinopathies to become a clinical reality."[5]

The New England Journal of Medicine has published the work of two groups of researchers who used different types of gene therapy techniques that target the transcription factor BCL11a involved with globin switching, which have improved clinical outcomes in patients





with SCD and thalassemia. According to Mark Walters, MD, a researcher at the University of California's Blood and Bone Marrow Transplant Program, "These trials herald a new generation of broadly applicable curative treatments for hemoglobinopathies." In one clinical trial with two patients, one with thalassemia and the other with SCD, researchers administered CRISPR-Cas9 gene edited hematopoietic stem and progenitor cells (HSPCs) with reduced BCL11A expression in the erythroid lineage. The product, CTX001, had been shown in a preclinical study to restore γ-globulin synthesis and reactivate production of fetal hemoglobin. Both patients underwent busulfan-induced myeloablation prior to receiving the treatment. The researchers suggested the CRISPR-Cas9-based gene-edited product could change the paradigm for patients with these conditions if it is found to successfully and durably graft, produce no "off-target" editing products and, importantly, improve clinical course.[6]

In the second trial, which included six patients with SCD, researchers described results with infusion of gene-modified cells derived from lentivirus insertion of a gene that knocks down BCL11a by encoding an erythroid-specific, inhibitory short-hairpin RNA. They found that at median follow-up of 18 months, all patients had engraftment and a robust and stable HbF induction broadly distributed in red cells. And, clinical manifestations of SCD were reduced or absent during the follow-up period. "The field of autologous gene therapies for hemoglobinopathies is advancing rapidly," lead researcher Erica Esrick, MD, and colleagues reported, "including lentiviral trials of gene addition in which the nonsickling hemoglobin is formed from an exogenous γ-globin or modified ß-globin gene."[6]

Deepa Manwani, MD, director of pediatric hematology at Children's Hospital and professor at Albert Einstein College of Medicine in New York City, maps out other major aspects of hemoglobinopathies in her American Society of Hematology presentation "Moving From Science Fiction to Clinical Reality." In it, she answers key questions regarding the illnesses and their treatment. When asked about the rationale for beta-hemoglobinopathies and SCD, Dr. Manwani says, "These are very common hematologic disorders with a very high cost of care, as well as burden of disease, to the patients. There are limited options for treatment, and specifically for curative treatment. The only curative treatment that's currently approved outside of genetic therapies, most of which are in clinical trials, is stem cell transplantation. [However], since these are genetic disorders, those treatments are available to a minority of patients. Less than 15 percent, for instance, of sickle cell patients will have a matched sibling donor who doesn't have the disease since it's genetic. That's why it's very important that these patients have access to newer therapies that can be accessed by many, many patients."

With regard to recent advances in gene therapies, Dr. Manwani believes it is a "very, very exciting time. Three decades ago, when I decided I would focus my research on beta-hemoglobinopathies, we were talking about gene therapies being a reality in five years, and then we were talking about it every five years like it was going to happen, and it didn't happen." The problem was, she says, that "the gene that's abnormal, the beta-globin gene, is very, very large, and that plagued scientists because they were not able to get it in and be expressed at the right levels. It was challenging technically." But she also states that in the last five years, she and fellow researchers have seen "tremendous improvements," and now the gene can be expressed "through a lentiviral vector." The technology is now easier because the gene "gets into the right place, expressed

at the right level, and these patients are actually on clinical trials doing extremely well. It gives me great hope, and I think that this provides great promise for our patients."

Major challenges in clinical trials versus real world use, according to Dr. Manwani, include treatment expense and the length of treatment. "This is not a therapy that is inexpensive and quick," she says. "It's a commitment on the part of the patient, and it is also extremely expensive. So this is not a therapy that's a pill that can be taken by, for instance, children in Africa where the largest burden of sickle cell disease is. So it will be again, at least initially, available to fewer patients in high-resource settings, but I think that this opens the window to these types of therapies, and this is how we will continue to advance and finally provide those therapies to a wider group of patients at a lower cost.

"One of the biggest problems with the current strategies is it requires what is known as an autologous bone marrow, or stem cell transplantation approach, where the patient's stem cells are actually harvested and modified, but then the patient has to receive chemotherapy to wipe out their bone marrow before these modified stem cells can be given back to the patient, and that's not trivial therapy," explains Dr. Manwani. "For one, it results in infertility. So those types of very toxic, preparative regimens can be a huge problem, especially facing these very difficult decisions about whether to opt for this therapy or not. And I think that researchers are well aware of the urgent need for different ways of preparing the patient's bone marrow to receive the modified stem cells back. There's some very exciting research that's ongoing. And [recently], we've heard about so many wonderful advances, it gives me great hope. I think that we're finally in an era where we're going to continue to move forward, and at a very fast pace. I think in the next five to 10 years, we'll see better and better approaches to delivering this type of care with less toxicity."

Of course, the high cost of this therapy must be overcome, which can be a reality since various organizations and agencies are funding the work. For instance, says Dr. Manwani, in the U.S., the National Heart, Lung and Blood Institute is partnering with the Bill and Melinda Gates Foundation to focus on funding research that will allow this therapy to be delivered more easily without the high cost. One change that might be required to accomplish that, she explains, is called in vivo gene therapy, where the gene therapy can be given as a single shot to correct the abnormal gene without requiring the stem cell transplantation. Given the initial reports with CRISPR/Cas9 and other viral vectors, she believes that is not outside the realm of possibility.

"Even having the high-cost therapy in the high-resource settings is a huge step forward," says Dr. Manwani. "When we talk to our patients, they tell us, 'I know that as doctors and scientists you want everything to be perfect before you move forward, but we want the treatments that are possible now.' I think that the shared decision-making that goes into actually preparing a patient for this type of therapy is going to be very important at this stage."[7]

A Cure May Be Forthcoming

The innovations, medical insights and genetic problem-solving will certainly not end with these studies and advances. As gene therapy for all diseases is developed and honed, patients worldwide who have unbearable, chronic and even life-threatening conditions such as hemoglobinopathies may soon be free of their physical ailments and emotional medical concerns. ❖

Hemoglobinopathy Statistics

- Millions of people are affected by hemoglobinopathies in the world.
- 7% of the world's population are carriers.
- 330,000 children are born with the diseases each year worldwide.
- Approximately 100,000 adults and children are affected in the U.S.
- Since May 1, 2006, all 50 states and the District of Columbia require and provide universal newborn screening for sickle cell disease.
- Screening for other hemoglobinopathies, such as alpha- and beta-thalassemia, is currently performed in only a few states.
- More than 90% of patients currently survive into adulthood.
- Treated patients have a projected life span of 50 years to 60 years.

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Fact or Fiction:
Debunking the Myths Surrounding IG Therapy Improves Patient Outcomes

Experts set the record straight about common misunderstandings regarding IVIG and SCIG products, their administration and possible reactions.

By Luba Sobolevsky, PharmD, IgCP, Rachel Colletta, BSN, CRNI, IgCN, and Amy Clarke, RN, BSN, IgCN

Photo courtesy of EMED Technologies featuring its SCIG60 Infusion System

IMMUNE GLOBULIN (IG) is made from pooled plasma collected from thousands of donors. It contains antibodies against a broad spectrum of bacteria and viruses, and it is used primarily to treat three categories of illnesses: primary immune deficiencies, autoimmune neuromuscular disorders and certain rheumatologic conditions. Historically, the first intravenous IG (IVIG) therapy was approved in 1981 to treat primary humoral immunodeficiency disorders, and in 2006, the first subcutaneous IG (SCIG) therapy was approved. Today, a growing number of patients are treated with IG, and the number of IG products and routes of administration continue to evolve. Yet, while patients treated with IG experience healthier lives, many may have misconceptions about the products, how they are administered and the reactions they can cause.

Myth or Fact?
IG Products Are Interchangeable

Myth: IG products are *not* interchangeable. While all products contain similar amounts of IgG antibodies, the similarities end there. Brands of IG can differ in IgG monomer, dimer and aggregate concentrations. They also differ in concentrations of IgA and IgM (Figure 1). Stabilizers, additives, sodium content, osmolarity and levels of impurities vary from product to product. Because of these differences, IG products cannot be used interchangeably or be mixed together.

Product differences should be considered when choosing the ideal product for each patient. In addition to product differences, patient differences such as comorbidities, tolerability, history of product use and patient lifestyle must be taken into account when choosing a product and route of administration.

Because products are tolerated differently by individuals, first doses of any product should be administered with caution. This is true even when a patient switches from one brand of product to another.

Product differences should be considered when choosing the ideal product for each patient.

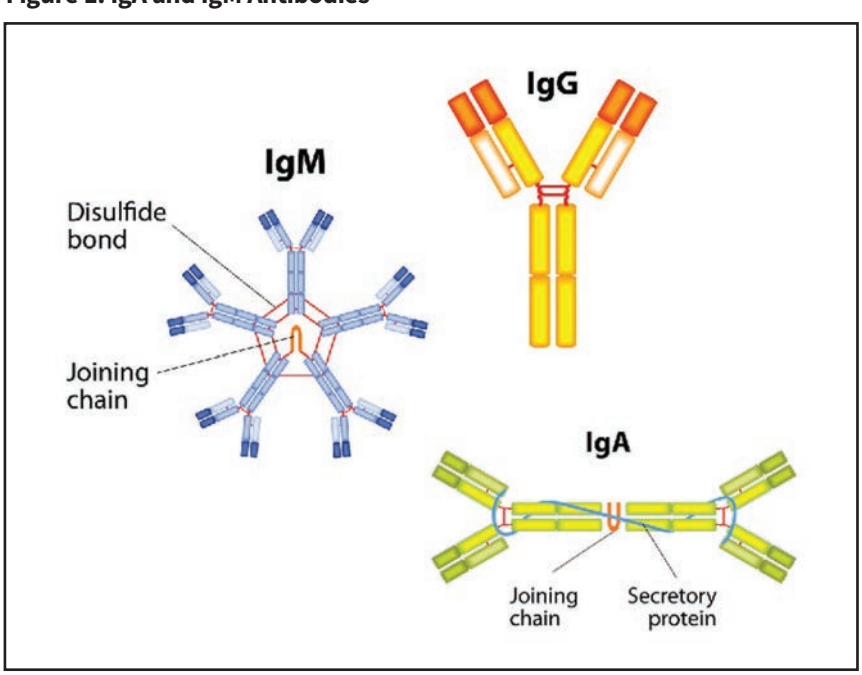
The IG clinician's role is to assess product tolerability and communicate with the healthcare team to ensure the patient has a safe and positive infusion experience.

Potential adverse drug reactions (ADRs) are listed in manufacturers' labeling, which considers both ADRs noted during clinical trials and those seen with all IG products in general.

Overall, IG therapy is safe and well-tolerated in most patients, and clinical efficacy of all products is comparable. However, all IG products contain boxed warnings. IVIG products contain boxed warnings for thrombosis and renal dysfunction/acute renal failure (ARF), whereas SCIG and facilitated SCIG (fSCIG) products contain only boxed warnings for thrombosis (see A History of the Thrombosis Boxed Warning). Therefore, it is imperative a thorough clinical assessment is conducted prior to starting care, and there is astute monitoring during the infusion and post-infusion follow-up.

Thrombosis. Risk factors for thrombosis include advanced age (but not specified); prolonged immobilization; hypercoagulable conditions (easy/excessive

Figure 1. IgA and IgM Antibodies



blood clotting), which may be inherited (e.g., Factor V Leiden) or acquired (e.g., cancer, certain cancer medications, obesity, HIV/AIDS, pregnancy); history of venous or arterial thrombosis; use of estrogen; indwelling vascular catheters; hyperviscosity conditions, including hypergammaglobulinemia markedly increased triglycerides, cryoglobulinemia, paraproteinemia (e.g., macroglobulinemias, monoclonal gammopathy of undetermined significance [MGUS], multiple myeloma); and cardiovascular risk factors. However, thrombosis may occur in the absence of known risk factors.

Mitigation strategies for thrombosis include:

- Administering at the minimum dose feasible (when there is no specific recommendation, large doses can be divided over several days or administered on alternate days)
- Administering at the minimum infusion rate feasible (some brands include no recommendation and other brands recommend 3 mg/kg/minute maximum to 4 mg/kg/minute maximum)
- Ensuring adequate hydration in patients before administration (requirements differ between adult and pediatric patients)

- Monitoring for signs and symptoms of thrombosis (for example, deep vein thrombosis symptoms include lower-leg swelling and pain in knees; pulmonary embolism (PE) symptoms include shortness of breath/pain with breathing and chest pain; myocardial infarction symptoms include chest pain; and transient ischemic attack/cerebrovascular accident symptoms include confusion, slurred speech, drooling and loss of consciousness)
- Assessing blood viscosity in patients at risk for hyperviscosity
- Educating patients about the signs and symptoms of thrombosis

It should be noted that anti-thrombotic therapy concurrent with IVIG should be considered for patients at high risk of thrombosis.

Renal dysfunction and acute renal filure (ARF). Renal dysfunction, ARF, osmotic nephrosis and death may occur with IVIG products in predisposed patients. Renal dysfunction and ARF occur more commonly in patients receiving IVIG products containing sucrose. However, since the last sucrose-containing product was withdrawn from the market in 2018, renal dysfunction and ARF could occur with any brand.

Risk factors for renal dysfunction and ARF include any degree of pre-existing renal insufficiency, diabetes mellitus, age older than 65 years, volume depletion, sepsis, paraproteinemia (e.g., macroglobulinemias, monoclonal gammopathy of undetermined significance, multiple myeloma) and patients receiving known nephrotoxic drugs.

Package insert recommendations for mitigation strategies for renal dysfunction and ARF vary among brands, with some including more instruction than others and some recommendations described outside the boxed warning. Strategies include:

• Administering at the minimum dose feasible (same as thrombosis)

• Administering at the minimum infusion rate feasible (same as thrombosis)

• Administering at the minimum concentration available (this pertains to only two brands)

• Ensuring adequate hydration in patients before administration (same as thrombosis)

• Periodic monitoring of renal function and urine output in patients judged to be at increased risk of developing ARF

• Assessing renal function, including measurement of BUN and serum creatinine, before the initial infusion and at appropriate intervals thereafter

• Considering discontinuation if renal function deteriorates

Myth or Fact? Anaphylaxis Is a Common Occurrence with IG Therapy

Myth: Anaphylaxis is *not* a common occurrence with IG therapy. In fact, true anaphylactic reactions to IG therapy are rare.

All IG brands contain IgA, and it is possible for individuals with IgA deficiency to develop anti-IgA antibodies and anaphylactic reactions after administration of IgA-containing products. Anaphylactic reactions are IgE-mediated and involve the release of mediators from tissue mast cells and peripheral blood basophils. Anaphylactic reactions present as an early onset, acute set of symptoms and are considered medical emergencies.

Anaphylaxis can occur with any IG infusion, so the IG clinician must have clinical expertise in managing these reactions, including the use of epinephrine (intramuscular or subcutaneous), oral or parenteral diphenhydramine (intravenous or intramuscular), corticosteroids, IV solution and supplies (syringes, needle). An anaphylaxis kit should be readily available when every dose is administered, and the patient's vital signs must be monitored. And, since anaphylaxis can occur with *any* infusion no matter how long the patient has been receiving IG therapy, patients should not self-infuse or be left alone for any period of time during the infusion.

After anaphylaxis symptoms resolve, the decision to restart an infusion should be made by the prescriber, patient, nurse and pharmacist. Mitigation strategies to prevent anaphylaxis include pretreatment with an antihistamine and corticosteroid, choosing another IVIG or SCIG brand if it is not IgA autoantibody-related or, if it is IgA autoantibody-related, switching to products containing lower levels of IgA or SCIG therapy.

Much more common than an anaphylactic reaction is an anaphylactoid reaction. Anaphylactoid reactions are similar in presentation to anaphylactic reactions since patients experience shortness of breath and chest tightness. However, these symptoms are much more gradual in onset and severity. Anaphylactoid reactions generally occur within the first half of the infusion and will dissipate with no intervention once the infusion has ended. And, because anaphylactoid reactions are not IgE-mediated, patients will typically experience hypertension rather than hypotension.

Anaphylactoid reactions may be caused by IgG aggregates or impurities not removed during the manufacturing and purification processes; however, the true cause of these reactions remains unknown. It is important for clinicians to understand these differences and be prepared to treat patients accordingly.

Renal dysfunction, ARF, osmotic nephrosis and death may occur with IVIG products in predisposed patients.

Serious ADRs include aseptic meningitis, hemolytic anemia and transfusion-related acute lung injury (TRALI).

Severe aseptic meninigitis generally occurs after an infusion and lasts hours to days. The cause is IG-induced spinal cord inflammation, and it is often described as severe and debilitating. Frequently, it is accompanied by nuchal (nape of the neck) rigidity, drowsiness, photophobia,

History of the Thrombosis Boxed Warning

- 1986: First report in a *Lancet* Letter to the Editor
- 1986-2010: Thromboembolism (TE) reports were consistent with the number of grams sold
- 2010: A small cluster of cases was reported to FDA by a manufacturer
- 2010-2011: There were increased reports of TE with a U.S. brand and a foreign brand of IG
- 2011: Manufacturers implemented thrombogenic testing of products
- 2013: FDA required addition of thrombosis to boxed warning

painful eye movements and nausea (with or without vomiting). Cerebral spinal fluid studies may show increased white blood cell count and protein with a negative culture.

Risk factors for aseptic meningitis include high doses of IG, rapid infusion rate, dehydration and a history of migraines. Pretreatment is generally ineffective; however, there have been some reports of success with IV corticosteroids, IV hydration and antimigraine medication. Treatment may require aggressive pain management.

Mitigation strategies for aseptic meningitis include:

- Reducing the daily dose by dividing over several days
- Alternating days of dosing
- Reducing the maximum infusion rate
- Switching to an IVIG 5% product
- Switching to a different IVIG brand or to SCIG

Hemolytic anemia occurs when there is severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation (a blood clotting disorder) caused by a destruction of red blood cells due to anti-A and anti-B blood type antibodies.

Risk factors for hemolytic anemia include non-O blood types, underlying inflammatory states, immune-mediated disorders and high IVIG doses (e.g., greater than 2 grams/kg, single or divided).

Signs and symptoms of hemolytic anemia generally present within days or weeks and may include fatigue (mild hemolysis), dark urine, jaundice of skin or eyes, heart murmur, increased heart rate and enlarged spleen/liver, which may be life-threatening and require blood transfusions. Therefore, patients should be educated about the signs and symptoms and when to call the prescriber.

Since there is little published evidence about the prevention of hemolytic anemia, mitigation strategies should include:

- Understanding the patient's blood type
- Administering at the slowest rate feasible
- Reducing the daily dose, dividing the dose over several days or alternating days
- Considering an Hgb/HCT test prior to IVIG within approximately 36 hours and in seven days to 10 days if the patient is high risk

TRALI is a rare but potentially fatal complication of receiving blood products. It causes severe respiratory distress, pulmonary edema (non-cardiogenic), hypoxemia (below-normal level of oxygen in the blood), normal left ventricular function and fever. Symptoms typically appear within one hour to six hours following IVIG. It may be managed using oxygen therapy with adequate ventilatory support. There are no particular risk factors or mitigation strategies.

SCIG Therapy Clinical Standards

Pre-Infusion

- Review the patient's documentation.
- If missing clinical information prior to initial visit, perform an assessment.
- Is the patient appropriate for SCIG administration?
- Is the patient or caregiver able to self-infuse?
- Check for the presence of adequate tissue.
- Will adherence be an issue?
- Determine number of sites, volume to infuse, how much volume per site and site location, and then make sure the equipment and supplies are available.
- Assess patient/caregiver's knowledge, provide ongoing education as needed, and document education and training.

During Infusion

- Document vital signs: baseline, rate changes and at completion.
- Document patient tolerance.
- Document infusion issues.
- Document IG brand, dose, lot number(s) and expiration dates.
- Document number of needle sites, gauge, length and flow rate.
- Document location of infusion site(s) used.
- Monitor for ADRs, document ADR management and inform pharmacy and prescriber.

Post-Infusion

- Provide training, education and support:
  - Teach patient/caregiver to log infusions.
  - Encourage independence in self-administration.
  - Explain responses to therapy based on disease state.
  - Explain potential reactions and troubleshooting.
- Know who/how/what to contact should issues arise:
  - Facilitate referrals to community organizations, support groups and financial assistance organizations.

Myth or Fact? ADRs Can't Be Mitigated

Myth: ADRs can be mitigated. These reactions are generally related to factors such as the rate of infusion, the patient's hydration status, patient comorbidities (e.g., history of migraine) and product choice. Whenever possible, the goal should be to prevent ADRs from occurring, which can usually be accomplished by patient education and proper product selection and administration.

Figure 2. SCIG Local Site Reactions

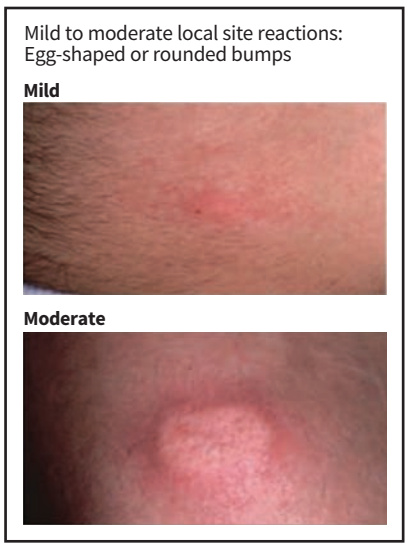


Figure 3. fSCIG Local Site Reactions

Managing ADRs starts with a risk assessment performed by the pharmacist prior to the start of therapy to determine what, if any, comorbidities exist, as well as the patient's history with IG therapy and with previous products.

Product and route selection are the first steps in mitigating ADRs. Patients tolerate products differently, so there is not a one-size-fits-all solution for product selection. Prior history, comorbidities and patient lifestyle factors should be considered.

A well-hydrated patient runs a lower risk of experiencing infusion-related ADRs. Patients should be instructed to begin hydrating one day to two days before the infusion, and hydration should be continued throughout the infusion and into the next day. If patients are not able to consume the amount of fluids needed to fully hydrate, IV hydration may be used as a supplement.

Premedications may be administered as needed, so patients should be assessed for their need for analgesic, antihistamine, antiemetics, etc.

Customizing the infusion rate to patient tolerability is critical. Since most ADRs are related to rate of infusion, a three-step ramping process should be used for every infusion. If ADRs occur, the infusion should be stopped and restarted at the previous infusion rate when symptoms subside. Remember that infusion rates vary from patient to patient and should be reassessed with each infusion.

Effective and frequent communication with the healthcare team is imperative. Patients should be encouraged to report any ADRs so appropriate intervention can be taken. Patients should not have to manage severe ADRs during and after their infusions.

Common mild to moderate IVIG infusion-related reactions include headache (most common) often occurring during the infusion due to mild/moderate blood pressure changes; diarrhea, fatigue, low-grade fever, nausea and other flu-like symptoms, which may last up to 72 hours and can be treated symptomatically; rash/hives; and blood pressure changes. Methods to mitigate these reactions include:

- Stopping the infusion until symptoms resolve, and resuming at a slower rate (recommended)
- Slowing the rate of infusion (may indicate the maximum tolerated rate for the product)
- Repeating ordered antihistamine and analgesic premedications if enough time has passed

A number of factors can contribute to SCIG ADRs. Infusion-related factors include a history of infusion reactions, first infusion, amount of drug infused, rate of infusion and dehydration. Patient-related factors include infection or fever at time of infusion, age, autoimmunity, comorbidities (i.e., diabetes, hypertension, cardiovascular disease) and smoking.

Whenever possible, the goal should be to prevent ADRs from occurring

SCIG ADRs can be local or systemic (Figures 2 and 3). Local reactions are common, occurring in 75 percent of patients. These include immediate swelling and redness at the site of infusion that usually resolves within 24 hours to 48 hours and lessens with subsequent infusions. In fact, occurrence and severity has been shown to decrease over repeated SCIG administrations. Systemic reactions are rare, occurring

in less than 1 percent of patients. These include back pain, migraine, diarrhea, fatigue, nausea, vomiting, rash and arthralgia (joint pain).

When experiencing local site reactions, the following management strategies can be tried:

- If tape sensitivity is suspected, use a skin preparation, different tape or change out the Tegaderm.
- Insert needle using a dry priming technique to decrease redness, itching and site reactions.
- Rotate needle insertion sites.
- Increase activity to help diffuse the product.
- Apply cold compresses 20 minutes on and 20 minutes off.
- Apply a cold topical anesthetic cream to the site, or use a device such as Buzzy.
- Slow or stop the infusion, and restart as the patient tolerates.

There may also be other issues related to SCIG infusions. If there is pain at the site of needle insertion, the needle length should be checked to ensure it is appropriate, and ice, a topical anesthetic or a device such as Buzzy can be used.

If there is leaking at the infusion site, the following should be checked:

- Needle dislodgement
- Needle length
- Subcutaneous tissue (is it adequate to absorb the volume of medication?)
- Infusion rate (is it too fast?)

If the infusion is taking too long, patency of tubing, rate of tubing and needle size should be assessed. Additionally, the site location should be assessed to determine if an additional site is needed. Lastly, the pump should be checked to ensure it is operating correctly.

If there is an acute or delayed infusion reaction (hives, swelling in the mouth or throat, itching, trouble breathing, fainting or dizziness), the infusion should be stopped and the infusion reaction protocol (antinuclear antibody-orders) should be initiated. Also, patients should contact their healthcare provider or emergency medical service if symptoms occur during self-administration.

Importantly, for each infusion, it should be checked and documented that the right drug and dose is being administered to the right patient using the correct route and duration.

The IgNS Standards of Practice published by the Immunoglobulin National Society (IgNS) recommend using a minimum of three rate ramping stages.

Myth or Fact? Maximum Infusion Rates Vary from Patient to Patient

Fact: Maximum infusion rates *do* vary from patient to patient. IG infusions are titrated stepwise to a maximum rate tolerated by the patient and per the prescribing information, prescriber's orders and organizational policies. Other factors that may impact the maximum infusion rate are the patient's hydration status and comorbidities. The IgNS Standards of Practice published by the Immunoglobulin National Society (IgNS) recommend using a minimum of three rate ramping stages. For patients at risk for renal dysfunction and thrombotic events, IG should be administered at the minimum infusion rate feasible and no greater than the maximum rate specified in each manufacturer's current prescribing information. Maximum infusion rates may vary from infusion to infusion based on the patient's state of health on the infusion day.

Similar to finding the patient's ideal product, finding the patient's personal maximum infusion rate is key to providing a positive infusion experience.

Myth or Fact? Long-Term IVIG Patients with No Adverse Reactions Do Not Require a Healthcare Professional to Monitor Infusions

Myth: Anaphylactic reactions can happen with *any* infusion, even in long-term patients with no history of adverse reactions. A patient who is experiencing an anaphylactic reaction will most likely not be able to manage the acute onset of symptoms.

Patient health status and lot-to-lot variability of IG products are a few of the reasons these reactions can occur at any time. IgNS recommends all IVIG infusions be monitored from start to finish by a competent healthcare clinician. ❖

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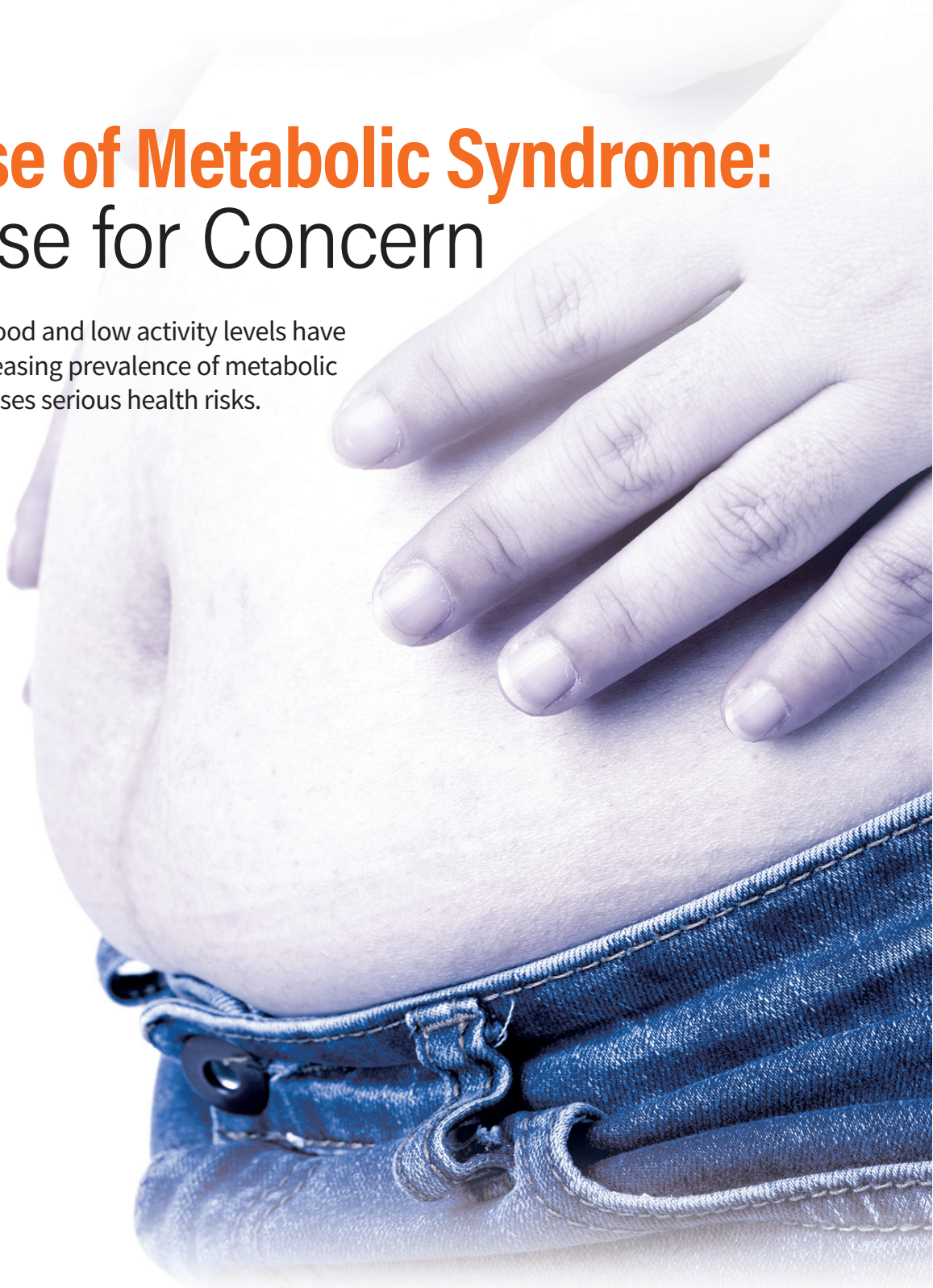
The Rise of Metabolic Syndrome: A Cause for Concern

An abundance of food and low activity levels have resulted in an increasing prevalence of metabolic syndrome that causes serious health risks.

By Jim Trageser



DESPITE CONSIDERABLE technological achievements, the law of unintended consequences still holds sway over human endeavors. Take hunger as an example. For millennia, hunger was the bane of rulers across the globe. Until recently, every society struggled to provide enough sustenance for its people, and at the end of the day, most human beings went to bed hungry. Malnutrition brought with it a host of medical issues, including rickets, stunted growth, anemia, etc., and physicians were well-accustomed to treating them.

But by the late 1700s, the Industrial Revolution brought forth new planting and harvesting machines that allowed

farmers to grow more food on the same acreage. Over the ensuing decades, better understanding of irrigation and crop rotation also contributed to increasing yields, as did selective crossbreeding of crops. The arrival of rail and steamships coupled with modern refrigeration allowed for the development of vast new distribution networks that could bring food from the farm to cities quickly. Automated canning factories and the development of quick-freezing methods combined with the earlier developments ensured most Americans (and soon, others around the world) had access to more food than their parents and grandparents could ever have imagined. Moreover, it was more varied and more affordable than had been enjoyed by royalty a century earlier.

All these advances greatly reduced the incidence of mass starvation across the globe. But as the law of unintended consequences kicked in, two developments arose out of the sudden, unexpected bounty of cheap, available foodstuffs:

1) The newly efficient agricultural sector needed far fewer farm workers to harvest the additional food, leading to a mass exodus from the countryside and into cities (a process still occurring in parts of India, China and Africa). And, these new city dwellers found themselves with jobs that were far less physically strenuous than the farmwork in which their parents and grandparents had engaged. Plus, the advent of radio and television also led to many people's leisure hours being spent sitting passively.

2) Cheap, available food led to a dramatic rise in the average daily caloric intake of most people. It turned out that when food was plentiful and affordable, people consumed more than their bodies needed.

This combination of too much food and too little physical activity has led to what is an unprecedented outbreak of diseases formerly associated with wealth: obesity, cardiovascular disease and type 2 diabetes. Today, these conditions affect people from all demographics in the West. In fact, the poor are more likely to suffer from some of these than are the wealthy.

Metabolic syndrome is one condition associated with overnutrition and a sedentary lifestyle, another unexpected development from the successful effort to reduce mass starvation. And it is affecting more people than ever before — more than a third of all U.S. adults.[1]

What is Metabolic Syndrome?

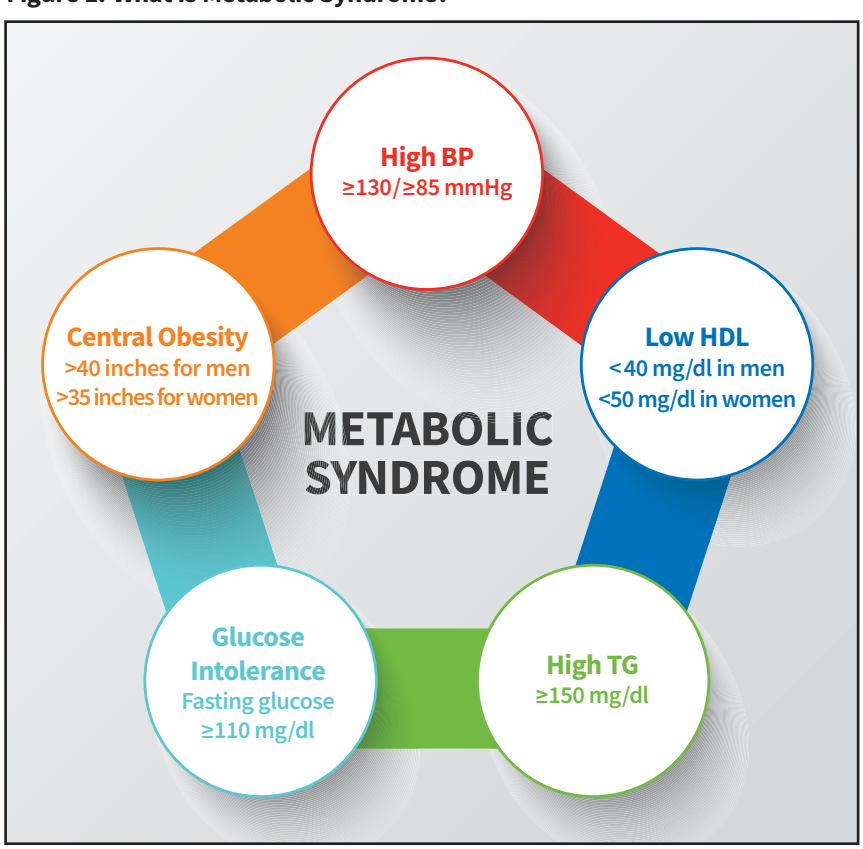
Metabolic syndrome is the name given to a collection of risk factors that heighten the chance of developing heart disease, stroke and/or type 2 diabetes.[2] The National Institutes for Health lists these risk factors as (Figure 1):[3]

- A large waistline (35 inches or greater for women, 40 inches or greater for men)
- A high triglyceride level
- A low HDL cholesterol level
- High blood pressure
- High fasting blood sugar

Having three or more of these indicators generally leads to a diagnosis of metabolic syndrome.

What is now referred to as metabolic syndrome was first described in 1966 by French physician Jean-Pierre Camus, although he referred to it as a "metabolic trisyndrome."[4] Twenty-two years later, Gerald Reaven, MD, referred to this cluster of factors as "Syndrome X" in a talk at the American Diabetes Association

Figure 1. What Is Metabolic Syndrome?



national meeting,[5] which led to a flurry of interest in this condition. Studies and papers about it accelerated as researchers realized this was a growing problem associated with the abundance of food and a growing amount of highly processed foods heavy in sugars in the average diet.

At one time, metabolic syndrome was considered the same condition known as insulin resistance, which occurs when the body's cells don't react normally to insulin, preventing glucose from being absorbed into cells.[6] However, while there remains a high correlation between metabolic syndrome and insulin resistance, they are generally now viewed as two distinct albeit related conditions.[7]

As the name metabolic syndrome indicates, researchers believe this collection of risk factors is likely caused by an underlying "abnormal carbohydrate and lipid metabolism."[8]

Smoking, high alcohol intake and high levels of stress also seem to have a correlative relationship.[7] Other possible contributing factors include sleep apnea, gallstones and ovarian cysts.[3]

Health Risks Associated with Metabolic Syndrome

Individuals with metabolic syndrome are already suffering damage to their cardiovascular system, as well as their ability to process nutrients at the cellular level. Hence, they are at elevated risk for developing full-blown heart disease and type 2 diabetes.

Recent research suggests the long-term systemic inflammation caused by obesity is the driving factor in developing metabolic syndrome,[9] with patients having a high correlation for high-sensitivity C-reactive protein, a marker for systemic inflammation. Other inflammation markers found in higher-than-normal levels in patients diagnosed with metabolic syndrome include tumor necrosis factor-alpha, interleukin (IL)-6 , IL-18 and oxidation of LDL.[8]

The reality is while there are genetic factors at work in triggering metabolic syndrome, it is largely driven by behavior.

Causes of Metabolic Syndrome

While researchers are fairly certain obesity and low activity levels are the cause of metabolic syndrome, the specific triggers that cause the body's metabolism to change are not fully understood.[7] And, while some people who suffer from obesity never develop metabolic syndrome, not all people who have metabolic syndrome are obese.

In addition to obesity and a sedentary lifestyle, other significant risk factors are age and genetics. The risk of developing metabolic syndrome increases as people age, and those with a family history of diabetes seem more likely to develop it.

In fact, the serious bodily damage caused by metabolic syndrome has led the American Heart Association to predict it will soon eclipse smoking as the main cause of heart disease.[7]

Prevalence of Metabolic Syndrome

A major study conducted a decade ago found the incidence of metabolic syndrome among adults in the United States increased from 25.3 percent in 1994 to 34.2 percent in 2012.[10] The researchers noted the correlation between the increase in the percentage of adults with metabolic syndrome and the percentage of adults who are overweight or obese, which now tops two-thirds of the population in the United States. (Even in Kazakhstan, which is not yet as developed as the United States, more than 20 percent of the population was obese as of 2017.[11])

Among the clinically obese, 61.6 percent suffer from metabolic syndrome, according to one recent study. But even 8.6 percent of American adults at a healthy weight had metabolic syndrome.[12]

More troubling than the increase in the percentage of adults developing metabolic syndrome, though, are recent signs that children are also now suffering the effects of a high-fat, nutrient-poor diet combined with a lack of physical activity. A 2017 study in Chile found 18 percent of children had early onset obesity, and half of those remained obese into their teens and had a high-risk factor for metabolic syndrome.[13]

Considering the troubling worldwide numbers, it is easy to see why the American Heart Association has labeled metabolic syndrome as the greatest future threat to cardiovascular health in the United States.

Metabolic Syndrome and Expected Life Span

While metabolic syndrome obviously increases the chances of developing life-threatening conditions such as arteriosclerosis or suffering a stroke, research indicates that charting a clear mortality risk from the diagnosis remains fuzzy. Numerous studies have shown patients with metabolic syndrome have a higher mortality rate than those without it, but nearly all of these studies caution against trying to determine a quantitative value.[14] In fact, researchers pointed

out that other underlying conditions also contribute to mortality and trying to assign mortality rates to what are overlapping conditions is impossible.

Best Practices

The reality is while there are genetic factors at work in triggering metabolic syndrome, it is largely driven by behavior. The most effective way to reverse a diagnosis is weight loss and an increase in physical activity. When these are both achieved, even at modest levels, blood pressure generally improves, and weight loss also lowers the systemic inflammation associated with obesity. However, changing behavior in human beings is one of the most challenging tasks (and attempting to do so undoubtedly contributes significant stress to the professional lives of physicians).

Controlling blood pressure with medication will not reverse a diagnosis of metabolic syndrome, but it will significantly reduce the risk of cardiovascular damage. Controlling triglyceride levels and cholesterol are also effective methods of lowering the long-term health risks of metabolic syndrome.

One recent study recommended a treatment blending lifestyle changes with proven medications to lower risks while pursuing longer-term improvements. According to the researchers, "While therapeutic lifestyle changes (TLCs) should be strongly recommended, clinicians should not let the perfect be the enemy of the possible. Evidence-based doses of statins, aspirin and angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers, should be prescribed as adjuncts, not alternatives, to TLCs."[15]

Looking Ahead

Humans spent millions of years honing the skills necessary to find enough food to sustain another day. So, adjusting to the influx of an overabundance of food is likely to take some time to adjust to. Individuals are programmed by nature to seek out high-calorie foods, and overcoming that innate drive that allowed our ancestors to survive is difficult for most. This explains why recent studies show the prevalence of metabolic syndrome continues to rise. And, as more nations raise the standard of living for their people, metabolic syndrome will undoubtedly increase in those societies as well.

While new treatments and medications to assist with control of symptoms or assisting with weight loss will undoubtedly come to market, it is unlikely there will ever be a magic pill that allows people to simply undo the effects of poor eating habits. Consequently, for the foreseeable future, the only effective treatment for metabolic syndrome will consist of working with patients to establish healthy eating and exercise regimens, augmented with medications to regulate blood pressure, triglycerides and cholesterol.

As one of the greatest public health crises of the next generation, it is a challenge that will likely be met in clinical settings rather than in research laboratories. ❖

How to Prevent Metabolic Syndrome

- **Know your genetics:**
  - Understand what to work against
- **Keep stress levels low:**
  - Exercise
  - Meditation
  - Talk with family or friends
  - Visit a mental health professional
- **Avoid too much inactivity**
  - Avoid sitting all day
  - Engage in moderate to vigorous exercise several times a week
  - Expend at least 1,000 calories a week during exercise
- **Eat a heart-healthy diet:**
  - Fruit
  - Vegetables
  - Whole grains
  - Soy products
  - Soluble fiber
  - Omega-3 fatty acids
- **Limit consumption of:**
  - Alcohol
  - Sodium
  - Saturated fats
  - Refined carbohydrates

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Universal Flu Vaccines Advance from Concept to Clinical Trials

By Keith Berman, MPH, MBA

"Scientists have identified components of the influenza virus that do not really change much at all. The critical challenge is getting a vaccine to induce a response to those components."
— Anthony Fauci, MD, Director, National Institute of Allergy and Infectious Diseases

YEAR AFTER YEAR, the extraordinary mutability of influenza (flu) viruses that enables their progeny to escape immune detection to reinfect us translates into more than 450,000 hospitalizations and more than 40,000 flu-related deaths annually.[1] If this were not enough, the ongoing COVID-19 pandemic serves as a harsh reminder that we may someday face an influenza pandemic to rival the catastrophic 1918 pandemic that claimed more than 650,000 U.S. lives — at a time when our population was less than one-third the size it is today.

This ability of influenza viruses to continually reinvent themselves has another important ramification. Those spontaneous RNA mutations in the large mushroom-like head region of the hemagglutinin protein that decorates the viral membrane surface necessitates a complex, costly global effort each year to isolate and produce new vaccines against emergent influenza strains believed most likely to circulate in the upcoming flu season.

Adding to the fact that selecting the eventual epidemic strains is an imperfect art, ongoing genetic drift of the selected A and B strains over the months that elapse before availability of mass-produced vaccines can enable them to evade antibody-mediated immunity induced by the inactivated whole-virus or synthetic antigen vaccine. As a consequence, the effectiveness of seasonal flu vaccines can differ widely from one year to the next; over the last decade, it has ranged from about 50 percent to as low as 20 percent.[2] This in turn partly accounts for why more than one-half of U.S. adults don't elect to get the annual flu shot.[3]

For decades, virologists and public health experts have touted the concept of "universal" flu vaccines capable of inducing broad immune protection against both seasonal and pandemic influenza outbreaks. Ideally, such vaccines would eliminate the need for annual vaccination, and provide at least some degree of herd immunity to help reduce infection risk in those who fail to get immunized. The National Institute of Allergy and Infectious Diseases (NIAID) has defined several criteria for any universal influenza vaccine, including the ability to:

- Be at least 75 percent effective;
- Protect against both group I and II influenza A viruses;
- Provide durable protection that lasts at least one year; and
- Be suitable for all age groups.

Advances over the last decade in virology and molecular genetics have enabled academic, government and industry scientists to design, produce and

test a diverse spectrum of universal flu vaccine candidates. Today, more than 100 university and private sector-based laboratories are working on novel universal flu vaccines of one type or another, at least 16 of which are currently in clinical-stage development (Table).[4]

The strategy behind all of these candidate vaccines essentially amounts to eliciting a robust host immune response to one or more viral proteins — the hemagglutinin (HA) stem domain, matrix proteins M1 and M2, nucleoprotein (NP) and neuraminidase (NM) — that are highly conserved across different influenza strains and subtypes. But the vaccines themselves and the technology platforms used to produce them broadly fall into six distinct categories (Table):

- Nucleic acid-based vaccines
- Recombinant influenza virus-based vaccines
- Recombinant protein vaccines
- Virus-vectored vaccines
- Virus-like particle (VLP) vaccines
- Non-VLP nanoparticle vaccines

Several vaccine candidates in each of these categories have currently advanced to human trials, and numerous others are being tested in animal models to characterize their safety, immunogenicity and tolerability.

Nucleic Acid-Based Vaccines

Population-based experience over this last year of the COVID-19 pandemic has proven that messenger RNA (mRNA) vaccines are safe and highly protective against multiple strains of SARS-CoV-2. mRNA vaccines can direct expression of virtually any membrane-bound or soluble target antigen, thus mimicking antigen expression that occurs in a natural infection. The ability to be rapidly formulated and manufactured on a large scale can additionally help avert antigenic drift over the multiple months required for egg-based vaccine production.

mRNA lipid nanoparticle vaccines (Moderna). In essence, mRNA is a temporary set of instructions that directs cells to make a protein. This may include virtually any membrane-bound or soluble viral antigen, mimicking the antigen expression that occurs in a natural infection. A particularly strong appeal of mRNA influenza vaccines is the ability to rapidly formulate and manufacture them on a large scale, helping to avert the problem of antigenic drift that occurs over the roughly six months between early identification of anticipated circulating strains and large-scale production of whole-virus influenza vaccines in chicken eggs or mammalian cells.

Over the five years prior to the COVID-19 pandemic, Moderna had already been developing mRNA vaccines targeting a number of viral infections, including seasonal and pandemic influenza. The company recently completed a pair of Phase I dose-ranging studies evaluating lipid nanoparticle-encapsulated mRNA vaccines directed against potentially pandemic avian H10N8 and H7N9 influenza viruses.[5] Both vaccines were well-tolerated and elicited robust humoral immune responses in healthy adult volunteers, as measured both by hemagglutinin inhibition (HAI) and microneutralization assays.

Modified mRNA vaccines (Pfizer/BioNTech). In September 2021, Pfizer announced the first study participants had received a single dose of monovalent

Table. Universal Influenza Vaccine Candidates in Preclinical and Clinical Development

Platform	Preclinical	Phase I clinical trials	Phase II clinical trials	Phase III clinical trials
Virus-like particle (VLP) vaccines	17 vaccines	**M2e-based VLPs** (Sanofi)		**Quadrivalent VLP** (Medicago)
Non-VLP nanoparticle vaccines	18 vaccines	**Stabilized headless HA stem nanoparticles** (NIAID/Sanofi) **FluMos-v1** (NIAID)	**OVX836** (Osivax)	**NanoFlu** (Novavax)
Nucleic acid vaccines	14 vaccines	**mRNA lipid nanoparticles** (Moderna) **Modified mRNA vaccine** (Pfizer) **Micro-consensus DNA vaccine** (Inovio/Wistar Institute)		
Recombinant flu virus vaccines	8 vaccines	**cHA-based LAIV combinations** (Icahn/Mount Sinai) **Codagenix** (CodaVax)	**deltaFLU** (Vivaldi Biosciences) **RedeeFlu M2SR** (FluGen)	
Recombinant protein vaccines	22 vaccines	**M2e-based recombinant fusion proteins** (VA Pharma)	**FLU-v** (Imutex/SEEK)	
Virus-vectored vaccines	14 vaccines	**NasoVAX** (Altimmune)	**MVA-NP+M1** (Vaccitech)	

or bivalent investigational quadrivalent mRNA influenza vaccines.[6] This Phase I trial in more than 600 healthy adults aged 65 years to 85 years will assess the safety, tolerability and immunogenicity against an FDA-approved standard quadrivalent influenza vaccine used as a control. While it is a seasonal mRNA flu vaccine, its performance in this and later efficacy studies is an important first step toward gauging the potential utility of a pandemic mRNA flu vaccine.

Numerous other novel mRNA and DNA-based vaccine candidates are currently in preclinical development. For example, collaborators at the University of Pennsylvania and the Icahn School of Medicine have shown that a single intradermal dose of their modified mRNA-lipid nanoparticle vaccine targeting a combination of conserved influenza virus antigens (HA stem, NM, NP) induced a strong immune response and was provided protection from challenge with pandemic H1N1 virus at 500 times the lethal dose in a murine model.[7] Strong immunogenicity and broad protection against pandemic viruses was also shown in ferrets immunized with Denmark-based Statens Serum Institute's polyvalent influenza A DNA vaccine, which encodes HA and NA proteins derived from the pandemic 2009 H1N1 and 1968 H3N2 virus strains, as well as matrix proteins from the pandemic 1918 strain.[8]

Recombinant Influenza Virus-Based Vaccines

Two of four recombinant virus-based universal flu vaccines currently in clinical development have advanced to Phase II testing: live attenuated influenza virus (LAIV) vaccines developed by FluGen in Madison, Wis., and Austria-based Vivaldi Biosciences.

Single-replication (SR) recombinant live influenza vaccine (FluGen). Licensed from the University of Wisconsin, FluGen's novel M2SR vaccine contains genetically engineered influenza viruses in which a portion of the M2 gene has been deleted. Delivered intranasally like another licensed LAIV, FluMist, M2SR can infect cells and express the entire spectrum of influenza RNA and proteins, but cannot produce any infectious virus particles or cause any pathological signs of infection. Further, the M2SR vaccine can be engineered to express HA and neuraminidase antigens common to different influenza virus strains.

Healthy adults enrolled in a Phase II human challenge study received a single low intranasal dose of the "supra-seasonal" M2SR vaccine constructed with the H3N2 virus Bris2007, then were challenged with an H3N2 influenza strain seven years drifted from the vaccine. Despite the mismatch of vaccine and challenge strains, the subset of subjects with a neutralizing antibody response had significantly reduced rates of infection after challenge and reduced illness.[9] A dose-escalation study has shown that up to 10-fold higher doses of M2SR induce protective immune response in a higher proportion of recipients. In May 2021 with support from NIAID, FluGen initiated the first placebo-controlled study of M2SR in older adults aged 65 years to 85 years who are most vulnerable to serious complications and death from the flu.

Replication-deficient LAIV vaccine (Vivaldi Biosciences). Austria-based Vivaldi recently completed Phase I and II clinical testing of DeltaFLU, another intranasally administered LAIV universal influenza vaccine missing a specific viral protein that prevents viral replication. According to the company, findings indicate that DeltaFLU "shows potential for universal protection against all influenza A and B virus strains, including drifted seasonal influenza strains and emerging pandemic strains."[10]

Vivaldi has also announced positive preclinical data that supports further development of a novel intranasal combination vaccine called Delta-19, which is designed to confer protection against both COVID-19 and all influenza strains.

Chimeric hemagglutinin (cHA)-based LAIV vaccine (Icahn/Mount Sinai). This research team has developed a sequential chimeric HA vaccination strategy that combines the highly conserved stem domain with immunodominant head domains from avian influenza virus subtypes. Boosting with a cHA construct that contains the same stem but a different head induces a stronger recall response against the stem than the initial low-level "immune priming" response.

A Phase I study in healthy 18- to 39-year old subjects documented a strong, durable and functional immune response

> Over the five years prior to the COVID-19 pandemic, Moderna had already been developing mRNA vaccines targeting a number of viral infections, including seasonal and pandemic influenza.

targeting the conserved HA stem domain, suggesting that "chimeric hemagglutinins have the potential to be developed as universal vaccines that protect broadly against influenza viruses."[11]

Recombinant Protein Vaccines

A number of laboratories have developed recombinant peptide vaccines that match conserved antigens present in specific internal or external viral proteins. Among the leading efforts is a collaboration between UK-based Imutex and NIAID to conduct Phase IIb clinical studies of FLU-v, a mixture of four recombinant peptides that originate from highly conserved internal proteins (M1, M2 and NP) common to all influenza A and B viruses.

A pair of recently completed Phase II studies found healthy adults who received a single dose of an adjuvanted version of FLU-v mounted a protective T cell-mediated response and were significantly less likely than control subjects to develop mild-to-moderate flu following intranasal challenge with a single H1N1 strain.[12,13]

In addition to the potential for FLU-v to confer protective immunity against any influenza strain, the selective cellular immune response could be of particular benefit for the 10 percent to 20 percent in the general population who fail to mount a good antibody response against the exposed HA region of the virus.

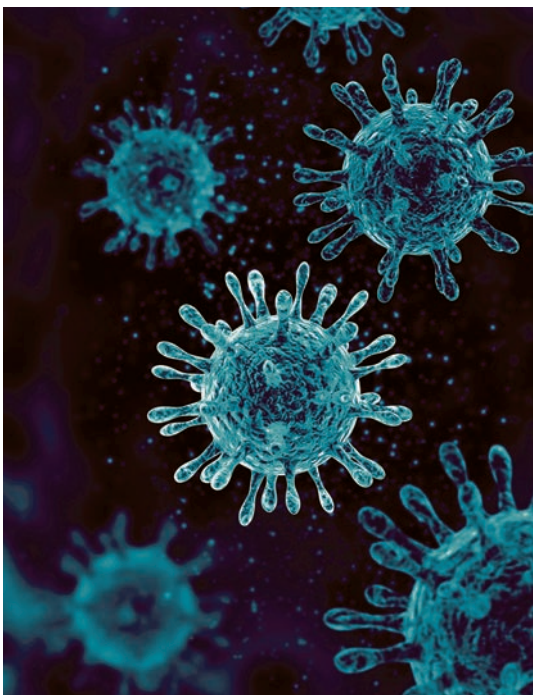
Numerous other laboratories across the globe are currently in preclinical development with their own universal recombinant protein vaccines to try to induce T cell and humoral immunity directed against conserved epitopes on the viral HA stem, M1, M2 and NP proteins. But several of the most advanced candidate vaccines have failed in clinical testing, most disappointingly BiondVax Pharmaceuticals' M-001 vaccine comprising nine highly conserved HA head domain epitopes common to some 40,000 isolated influenza virus strains. After 15 years of largely encouraging preclinical and clinical findings, the company announced in late 2020 that data from a pivotal Phase III trial of M-001 failed to show a significant difference in flu illness or severity in more than 12,000 adult subjects (half of whom were age 65 and older) over the 2018-2019 flu season.[14]

Virus-Vectored Vaccines

Similar to how gene therapy uses viral vectors to carry genetic instructions to host cells to express key missing functional proteins, novel vaccines are being developed to induce our cells to express influenza virus proteins that are largely conserved across strains and subtypes.

Of more than a dozen initiatives in progress, Vaccitech's modified vaccinia Ankara (MVA)-vectored construct expressing influenza A-derived NP and M1 protein has completed a Phase IIb safety and immunogenicity study in 846 adults aged 65 years and older. While this VMA-NP+M1 vaccine induced a substantial M1-specific T cell response,[15] the study sample was too small to draw any conclusions about potential efficacy endpoints such as incidence and duration of influenza-like illness (ILI) or number of days with moderate or severe symptoms during an ILI episode.[16]

Other promising virus-vectored influenza vaccines have reached Phase II clinical development. In particular, a single dose of Altimmune's intranasally delivered replication-deficient adenovirus-based vaccine, NasoVax, mediates expression of the HA protein found on a targeted flu virus strain, and elicits robust mucosal and systemic immune responses. However, it is



strain-specific and therefore is not designed to confer broad protection against other flu strains and subtypes.[17]

Virus-Like Particle Vaccines

Comprising one or more viral structural proteins, virus-like particles (VLPs) are molecules that closely resemble their live virus counterparts, but are noninfectious because they contain no viral generic material. More than a decade ago, intranasal immunization of mice with recombinant VLPs generated from structural proteins of the pandemic 1918 H1N1 virus were first shown to be protective against a lethal challenge with both the 1918 virus and a highly pathogenic avian H5N1 virus.[18]

Furthest along among nearly 20 influenza VLP development programs is Medicago, a privately held Canadian firm whose investigational HA-bearing quadrivalent VLP (QVLP) vaccine is produced in a relative of the tobacco

plant. In a large-scale multinational study in elderly participants covering two influenza seasons between 2017 and 2019, the QVLP vaccine met its primary noninferiority endpoint relative to standard quadrivalent influenza vaccine for the prevention of ILI caused by any strain.[19]

20 HA antigens arranged in repeated patterns, sending a strong "danger" signal to the immune system that prompts a vigorous antibody response.[21] Dubbed FluMos-v1, this universal flu vaccine candidate began Phase I clinical testing in May 2021.

A number of laboratories have developed recombinant peptide vaccines that match conserved antigens present in specific internal or external viral proteins.

Non-VLP Nanoparticle Vaccines

Perhaps most exotic of all are the nanoparticle vaccines, which are novel constructs of conserved viral antigens displayed on a nonviral nanoparticle. A prime example is a stabilized leadless HA stem nanoparticle vaccine being co-developed by Sanofi Pasteur and NIAID. Numerous HA stem portion "spikes" are presented on the surface of a microscopic nonhuman ferritin nanoparticle, mimicking the natural organization of HA on the influenza virus.

While HA stem antigens were derived from an H1N1 flu virus, this candidate vaccine protected both mice and ferrets against a lethal H5N1 flu virus, despite the fact that H5N1 is an entirely different viral subtype.[20] This vaccine has also elicited broadly neutralizing antibody responses to diverse H1 and H3 viruses in nonhuman primates. NIAID completed a safety, tolerability and immunogenicity study earlier this year, and findings are currently being analyzed.

Another non-VLP nanoparticle vaccine showing promise is NIAID's "mosaic" quadrivalent flu vaccine that displays

Many Candidate Vaccines Boost Prospects

"Our ultimate aspirational goal is to have vaccines that you can give relatively infrequently — maybe every five or 10 years — that provide protection against the broad array of influenza viruses that we encounter," NIAID Director Anthony Fauci, MD, recently noted.[22] But he cautioned that effective universal flu vaccines could arrive in a stepwise fashion, with successive iterations providing protection against increasing portions of the numerous influenza subtypes and groups.

Time will tell, but the many novel universal flu vaccine candidates entering the pipeline and advancing from preclinical development to human testing offer new hope that the realization of a decades-old dream is not far off. ❖

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KEITH BERMAN, MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. He also serves as editor of *International Blood/Plasma News*, a blood products industry newsletter.

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Mary Hettinger, who has a family history of osteoporosis, knew the seriousness of getting regular bone density screenings, and since her diagnosis at age 61, she has made lifestyle changes to decrease her risk of bone breaks.

Osteoporosis: *A Patient's Perspective*

By Trudie Mitschang

WHEN MARY Hettinger was diagnosed with osteoporosis in 2019 at age 61, the news came as no surprise. Six years earlier, Mary tested positive for osteopenia, a condition that indicates an overall weakening of the bones and is often a precursor to osteoporosis. Because Mary's mother also had osteoporosis, Mary says she knew her risk factor was higher than average. "My mom suffered from the disease and had that telltale hunch in her back," she recalls. "I started getting bone density screenings early because I knew osteoporosis can be present long before symptoms appear."

The word "osteoporosis" literally means "porous bone." It's a disease that weakens bones and puts those who suffer from it at increased risk for bone fractures due to diminished bone mass and strength. According to the National Osteoporosis Foundation, approximately 10 million Americans have osteoporosis and another 44 million have low bone density, placing them at increased risk for developing osteoporosis later in life.[1] The condition is more common in women than men, affecting almost one in five women aged 50 and older. And, while genetics plays a factor (as was the case with Mary), decreased estrogen levels after menopause, a diet low in calcium, a sedentary lifestyle, caffeine consumption and smoking tobacco can all contribute to bone mass loss as people age.

Because many people with osteoporosis do not know they have it until they break a bone, regular bone density screenings are one of the best ways to obtain an early diagnosis and begin potential interventions. "After my doctor told me I had osteopenia, I did make some small lifestyle adjustments, like giving up caffeine," says Mary. "I was already fairly active and embraced a healthy diet overall, but since my osteoporosis diagnosis, I have made exercise an even higher priority."

Mary works full time as a management consultant, a career that includes large chunks of time spent in front of a computer screen. Since her job is primarily sedentary, Mary blocks time on her calendar to go to the gym three to four times a week, where she combines strength training with aerobic classes to keep herself strong and limber. "I do weight-bearing routines at least twice a week, including a group exercise class that uses barbells," she says. "We also have a home gym with weights in our basement in case I miss a class."

After her diagnosis, Mary's doctor also recommended she include more calcium-rich foods in her diet and prescribed a generic alendronate, a medication that has been shown to slow the progression of bone loss. In addition to her prescription that is a pill taken once-weekly, Mary takes a twice-daily calcium and vitamin D supplement.

Statistics show people who suffer osteoporotic bone breaks are most likely to have them occur in the hip, spine or wrist, so Mary (whose osteoporosis is currently limited to her spine) is careful to avoid high-risk activities like skiing or softball. In terms of her overall health, Mary says she considers herself fortunate to have caught the disease early enough to treat it. At the time of this writing, her next bone density screening was in December 2021, and she is hopeful the medication and lifestyle adjustments she's made are making a positive difference. "I am a big believer in screenings," says Mary. "If you have any family history of low bone density or other risk factors, tell your doctor and do your research. I know doctors don't always love it when patients do Internet research and, of course, there is misinformation out there, but I felt more empowered when I learned all the facts about this condition." ❖

Reference

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Osteoporosis Fast Facts[1]

- Osteoporosis is often called a "silent disease" because individuals cannot feel their bones getting weaker; they may not even know they have it until after they break a bone.
- Osteoporosis-related bone breaks cost patients, their families and the healthcare system $19 billion annually.
- By 2025, experts predict osteoporosis will be responsible for three million fractures resulting in $25.3 billion in costs.
- Osteoporosis is preventable. Studies show building strong bones during childhood and adolescence can help prevent osteoporosis later in life.
- Osteoporosis is manageable. Eating a healthy diet and exercising regularly can help slow or stop the loss of bone mass and help prevent fractures from occurring.

Dr. Sarah Berry is at the forefront of osteoporosis research, studying modifiable risk factors for falls.

Osteoporosis: *A Physician's Perspective*

SARAH BERRY, MD, MPH, has dedicated her life to the study of bone health. She is the associate director at the Musculoskeletal Research Center, associate scientist at the Hinda and Arthur Marcus Institute for Aging Research and associate professor of medicine at Harvard Medical School, Beth Israel Deaconess Medical Center. Dr. Berry's primary research has focused on outcomes following hip fractures both in the community and nursing homes. Given the strong link between falls and fractures, she is also interested in studying novel and modifiable risk factors for falls and is at the forefront of osteoporosis research.

BSTQ: Have you seen or been involved in any promising research for how to effectively treat or manage osteoporosis?

Dr. Berry: Currently, I am participating in a multisite study to test the effects of low-dose testosterone combined with exercise in older women recovering from a hip fracture. We don't yet know the results of the trial and whether the testosterone will be helpful, but it is exciting to consider and learn about new approaches.

BSTQ: What dietary changes can help prevent osteoporosis?

Dr. Berry: Dairy foods are high in calcium, which is important to maintain bone health. It is particularly important that children and teenagers consume enough calcium since this is a period of rapid bone growth. There is some evidence to support adequate protein intake is also important to maintain bone health.

BSTQ: What is a little-known fact about osteoporosis?

Dr. Berry: Osteoporosis is a silent disease. Typically, people don't realize they have weak bones until they have a fracture. Because of that, it's better to focus on preventing osteoporosis rather than waiting to find out you have it.

BSTQ: At what age should someone request a bone density screening?

Dr. Berry: Women should get screened beginning at age 65, and men beginning at age 70. However, if a man or woman has risk factors such as paralysis or a history of adult fracture, they should get screened earlier.

BSTQ: How do you screen for osteoporosis?

Dr. Berry: A bone density test is similar to an X-ray (but with less radiation than a chest X-ray). It measures how tough your bones are. Another option is to use the FRAX model, an online tool developed by the World Health Organization that assesses the risk of osteoporosis over a 10-year period based on age, weight, family health history and other factors.

BSTQ: Is it ever too late to "grow" new bones?

Dr. Berry: Your skeleton turns over every 10 years. After age 30, the rate of bone loss outpaces the rate of bone growth. Bone loss also increases in women after menopause. However, it is possible to rebuild bone and increase bone strength.

BSTQ: What advice do you have for patients with high-risk factors for osteoporosis?

Dr. Berry: I recommend speaking with your doctor. Exercise, especially weight-bearing exercise like walking and dancing, is helpful to strengthen bones.

BSTQ: What factors make osteoporosis a life-threatening disease?

Dr. Berry: Most people don't realize it can be deadly because of common complications such as infections, blood clots and loss of mobility. Pain medications can affect cognition and cause confusion. Twenty percent of people with hip fractures die within a year, while another 20 percent end up needing long-term care.

BSTQ: Your research encompasses risk factors for falls. Tell us more about that.

Dr. Berry: Prescription medications are one of the most common risk factors for falls because so many cause side effects. It's important for patients to speak with their doctor regularly about their medicines and ask about the lowest dose available that still works for them.

BSTQ: What lifestyle adjustments can people make to strengthen their bones and prevent osteoporosis?

Dr. Berry: It is so important to exercise because it strengthens the bones, which can prevent falls. Talk to your doctor to see if you are getting enough calcium and vitamin D or if you need to be taking a prescription medication to prevent fractures. Understand the indication for all your medications, and work with your doctor to use the lowest dose effective for you. It's important to lay the foundation for strong bones now, no matter your age. By incorporating good healthy habits, you can reduce the risk of fracture later. ❖

TRUDIE MITSCHANG is a contributing writer for *BioSupply Trends Quarterly* magazine.

Medical Terminology: A Quick & Easy Reference Book — Basics of Terminology, Anatomy, and Abbreviations

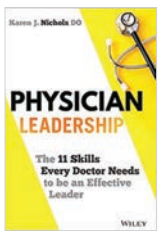
Author: Medical Resources Team

This companion to medical study guides includes information related to CPC billing and coding, nursing entrance exams such as TEAS and HESI A2, NCLEX, MCAT, certified medical assistants, nursing assistants/aides and more. In addition, the book covers all facets of medical terminology for health professionals, including a refresher course on Greek and Latin affixes, all affixes listed alphabetically and by body system, a full list of common medical abbreviations and a list of body positions and anatomical reference terms.

www.amazon.com/MEDICAL-TERMINOLOGY-Reference-Terminology-Abbreviations/dp/B0851LZNQS

Physician Leadership: The 11 Skills Every Doctor Needs to Be an Effective Leader, 1st Edition

Author: Karen J. Nichols, DO



This book is a concise guide for busy physicians doing their best to successfully lead people and organizations. It covers foundational leadership essentials every physician needs to master to transform themselves from a highly motivated novice leader into an effective, skilled and productive leader. Each chapter offers readers a summary of the crucial points found within, sample questions, exercises and a bibliography of the relevant academic literature for further study. Actionable, real-world advice for practicing and aspiring physicians is provided, including a thorough introduction to personal approach and style when interacting with patients, managers, boards and committees; an exploration of how to employ the principles of effective communication to achieve desired results and practical techniques for implementing those principles; practical discussions of the role perspectives play in shaping an organization's culture and how those perspectives affect leadership efficacy; and in-depth examinations of approaches to decision-making that get buy-in from others and achieve results.

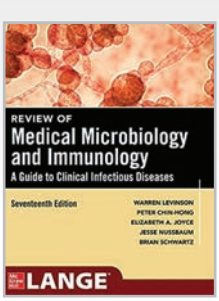
www.amazon.com/Physician-Leadership-Skills-Doctor-Effective/dp/1119817544

The Resilient Healthcare Organization: How to Reduce Physician and Healthcare Worker Burnout, 1st Edition

Author: George Mayzell, MD, MBA

The Resilient Healthcare Organization focuses on physicians' and healthcare professionals' experiences and how they overcame a loss of enthusiasm for work, feelings of cynicism and a low sense of personal accomplishment. The feelings of emotional exhaustion are characterized by depersonalization and perceived ineffectiveness — the cardinal features that define "burnout" and affect almost 50 percent of physicians and 30 percent to 70 percent of nurses. Addressed are why burnout is viewed as a threat and how it can be fought. Included is a discussion of the contributing factors and solutions at the health system and societal levels. Additionally, the book explores the current and future etiology and impacts on physicians and healthcare professionals, with a significant emphasis on solutions at both the individual and system levels.

www.amazon.com/Resilient-Healthcare-Organization-Physician-Burnout/dp/1032173025



Review of Medical Microbiology and Immunology, 17th Edition

Authors: Warren E. Levinson, Peter Chin-Hong, Elizabeth A. Joyce, Jesse Nussbaum and Brian Schwartz

This book covers both basic and clinical aspects of bacteriology, virology, mycology, parasitology and immunology. Important infectious diseases are discussed using an organ system approach using a mix of narrative text, color images, tables, figures, Q&As and clinical vignettes. This updated edition reflects the latest research, treatment and developments, as well as a chapter on COVID-19 with images.

www.amazon.com/Review-Medical-Microbiology-Immunology-17th-ebook/dp/B09H3NB6RL

Transition from Clinic- to Home-Based IVIG/SCIG Is Successful to Decrease Exposure to COVID-19

A recent study shows transition of clinic-based to home-based intravenous immune globulin (IVIG)/subcutaneous IG (SCIG) infusion can be successfully done to decrease potential exposure during a pandemic in a high-risk immunosuppressed population, with no impact on patient satisfaction, adherence or efficacy. In addition, home-based infusions were associated with a reduction in costs to patients and an increase in available chair time in the infusion clinic.

In the study, criteria were developed to identify high-risk immunosuppressed patients who would be appropriate candidates for potential conversion to home-based IVIG infusions. Data were collected via chart review, and cost analysis was performed using Medicare Part B reimbursement data. A patient outcome questionnaire was developed for administration through follow-up phone calls.

From March 2020 to May 2020, 45 patients met criteria for home-based infusion, with 27 patients (60 percent) agreeing to it. Posttransition patient outcomes assessment, conducted in 26 patients (96 percent), demonstrated good patient understanding of the home-based infusion process. No infusion-related complications were reported, and 24 patients (92 percent) had no concerns about receiving future IVIG and/or SCIG doses at home. No patient tested positive for COVID-19 during the study period. Clinic infusion visits decreased by 26.6 visits per month, resulting in a total of 106 hours of additional available infusion chair time per month and associated cost savings of $12,877.

Perreault S, Schiffer M, Clinchy-Jarmoszko V, et al. Mitigating the risk of COVID-19 exposure by transitioning from clinic-based to home-based immune globulin infusion. *Am J Health Syst Pharm* 2021 Jun 7;78(12):1112-1117.

Study Shows COVID-19 Infection Correlates with Autoimmune Markers

A new study demonstrates how severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) infection could be associated with an autoimmune response and development of autoantibodies.

In the study, the researchers elucidated whether SARS-CoV-2 stimulates autoantibody production and contributes to autoimmunity activation. Forty adult patients (66.8 years mean age) were enrolled and admitted to Alessandria Hospital between March 2020 and April 2020. All patients had a confirmed COVID-19 diagnosis and no previous clinical record of autoimmune disease. Forty blood donors were analyzed for the same markers and considered as healthy controls. The patients had high levels of common inflammatory markers such as C reactive protein, lactate dehydrogenase, ferritin and creatinine. Interleukin-6 concentrations were also increased, supporting the major role of this interleukin during COVID-19 infection. Lymphocyte numbers were generally lower compared with healthy individuals. All patients were also screened for the most common autoantibodies.

Results showed a significant prevalence of antinuclear antibodies, antineutrophil cytoplasmic antibodies and ASCA immunoglobulin A antibodies. Patients having a de novo autoimmune response had the worst acute viral disease prognosis and outcome. According to the researchers, the results sustain the hypothesis that

COVID-19 infection correlates with the autoimmunity markers. However, they concluded other investigations are necessary to define the possible link between SARS-CoV-2 infection and autoimmune disease onset.

Sacchi MC, Tamiazzo S, Stobbione P, et al. SARS-CoV-2 infection as a trigger of autoimmune response. *Clin Transl Sci* 2021 May;14(3):898-907.

Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2022, through March 31, 2022

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$963.54	$948.09
	BIVIGAM	ADMA Biologics	J1556	$140.98	$138.72
	FLEBOGAMMA DIF	Grifols	J1572	$71.79	$70.63
	GAMMAGARD SD	Takeda	J1566	$139.18	$136.95
	GAMMAPLEX	BPL	J1557	$101.61	$99.98
	OCTAGAM	Octapharma	J1568	$83.23	$81.89
	PANZYGA	Octapharma/Pfizer	90283/J1599	$130.09	$128.01
	PRIVIGEN	CSL Behring	J1459	$90.02	$88.57
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$93.33	$91.84
	GAMMAKED	Kedrion	J1561	$93.02	$91.53
	GAMUNEX-C	Grifols	J1561	$93.02	$91.53
SCIG	CUTAQUIG	Octapharma	90284/J3590	$135.26	$133.09
	CUVITRU	Takeda	J1555	$147.48	$145.11
	HIZENTRA	CSL Behring	J1559	$117.85	$115.96
	HYQVIA	Takeda	J1575	$154.19	$151.72
	XEMBIFY	Grifols	J1558	$132.96	$130.83

*ASP + 4.3% applies only after April 1, 2022, after which a 1% reduction in payment will apply until July 1, 2022, unless further Congressional action is taken to extend the moratorium.

Calculate your reimbursement online at www.FFEnterprises.com.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	0.5 g, 2.5 g, 5 g, 10 g, 20 g
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	2.5 g, 5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	2.5 g, 5 g, 10 g, 20 g
	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g, 25 g
	OCTAGAM Liquid, 10%	Octapharma	ITP, DM	2 g, 5 g, 10 g, 20 g, 30 g
	PANZYGA Liquid, 10%	Octapharma/Pfizer	PI, ITP, CIDP	2.5 g, 5 g, 10 g, 20 g, 30 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	IVIG: PI, MMN	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
			SCIG: PI	
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g
			SCIG: PI	
	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma	PI	1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g, 10 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g 1 g PFS, 2 g PFS, 4 g PFS
	HYQVIA Liquid, 10%	Takeda	PI	2.5 g, 5 g, 10 g, 20 g, 30 g
	XEMBIFY Liquid, 20%	Grifols	PI	1 g, 2 g, 4 g, 10 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
DM Dermatomyositis
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease
PFS Prefilled syringes

2021-2022 Influenza Vaccine

Administration Codes: G0008 (Medicare plans)
Diagnosis Code: V04.81

Product	Manufacturer	Presentation	Age Group	Code
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90688
AFLURIA PEDIATRIC (IIV4)	SEQIRUS	0.25 mL PFS 10-BX	6-35 months	90685/90687
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694/90654
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	2 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	2 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662

ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray

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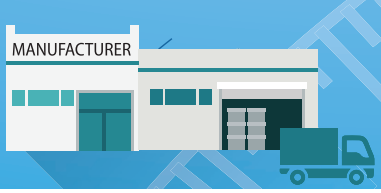

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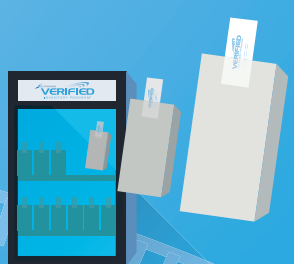

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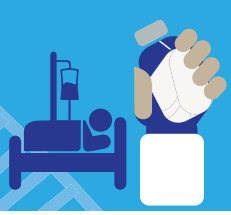

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