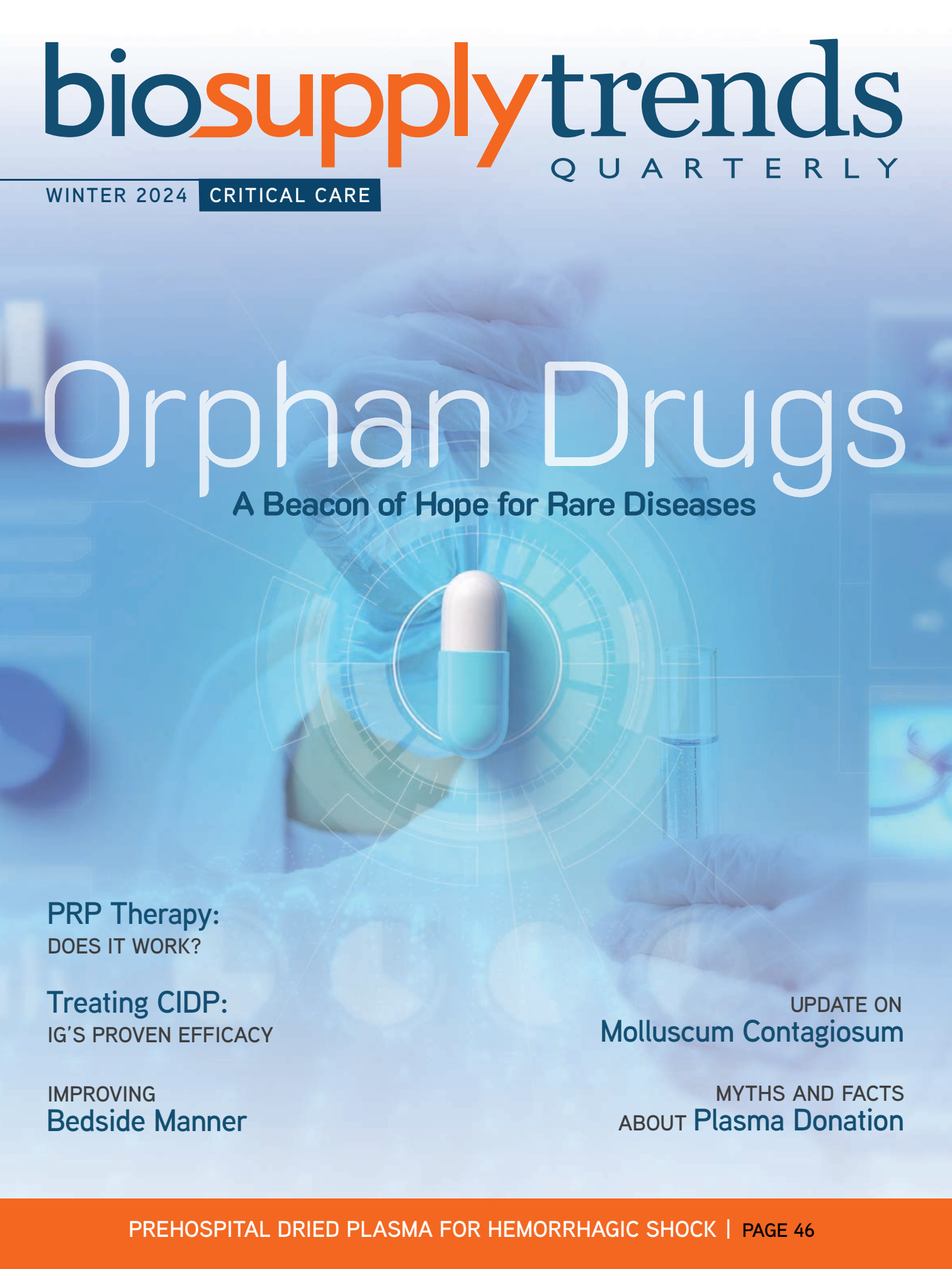
biosupplytrends QUARTERLY

WINTER 2024 CRITICAL CARE

Orphan Drugs

A Beacon of Hope for Rare Diseases



PRP Therapy:
DOES IT WORK?

Treating CIDP:
IG'S PROVEN EFFICACY

IMPROVING
Bedside Manner

UPDATE ON
Molluscum Contagiosum

MYTHS AND FACTS
ABOUT Plasma Donation

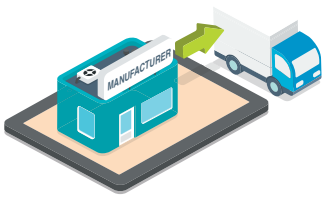
PREHOSPITAL DRIED PLASMA FOR HEMORRHAGIC SHOCK | PAGE 46

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

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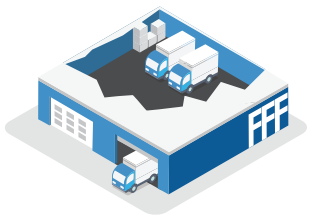

STEP 3

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STEP 4

Interactive Allocation

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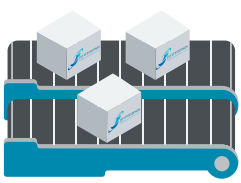

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

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STEP 5

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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.

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About BioSupply Trends Quarterly
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Innovative Therapies Continue to Advance Treatment Efficacy

SCIENTIFIC ADVANCEMENTS are moving the healthcare industry forward. New, innovative tools and therapy options are helping providers accurately diagnose and treat myriad conditions, from common illnesses to rare diseases. For the millions suffering from all kinds of ailments, the changes are welcome, as they are increasingly opening doors to treatment options that can significantly improve quality of life. However, there are both significant opportunities and considerable challenges to meeting patient needs.

Treatments for rare diseases were historically few and far between, as their development was hindered by low potential return on investment. However, orphan drugs (pharmaceuticals that target only a very small population of people with rare diseases) now account for 50 percent of new drugs approved by the U.S. Food and Drug Administration. As we explain in our article "The Future of Orphan Drugs: Advancements, Challenges and Hope" (p.18), scientific breakthroughs combined with patient advocacy and regulatory incentives led to this growth. Today, orphan drugs are increasingly improving the quality of life for the patients they serve.

The hope of an improved quality of life is often enough for a patient to choose experimental and sometimes even controversial therapies. We delve into one such treatment option in our article "Platelet Rich Plasma Therapy: The Future of Healing?" (p.22). Platelet rich plasma (PRP) therapy is a unique method of using a patient's own plasma to stimulate healing. PRP is used primarily to help ease chronic pain, and clinical evidence appears to be favorable for treatment of inflammatory responses associated with osteoarthritis of the knee. Although PRP has been available for nearly 30 years, regulations, protocols and dosing standards vary, and it lacks definitive studies confirming its efficacy. Still, demand for the controversial treatment continues to grow even as providers aren't certain how to counsel patients about its risks versus reward.

Uncertainty in healthcare leaves both patients and providers frustrated. Chronic inflammatory demyelinating polyneuropathy (CIDP) is a case in point: This rare autoimmune disorder puzzles providers, since it affects relatively few people and hides behind symptoms common among many other rare neurological conditions. As we explain in our article "The Proven Success of Immune Globulin Therapy to Treat Chronic Inflammatory Demyelinating Polyneuropathy" (p.26), the path to appropriately treating CIDP isn't an easy one, but in many cases, patients are seeing their quality of life increase with the proven use of immune globulin therapy.

As always, we hope you enjoy the additional articles 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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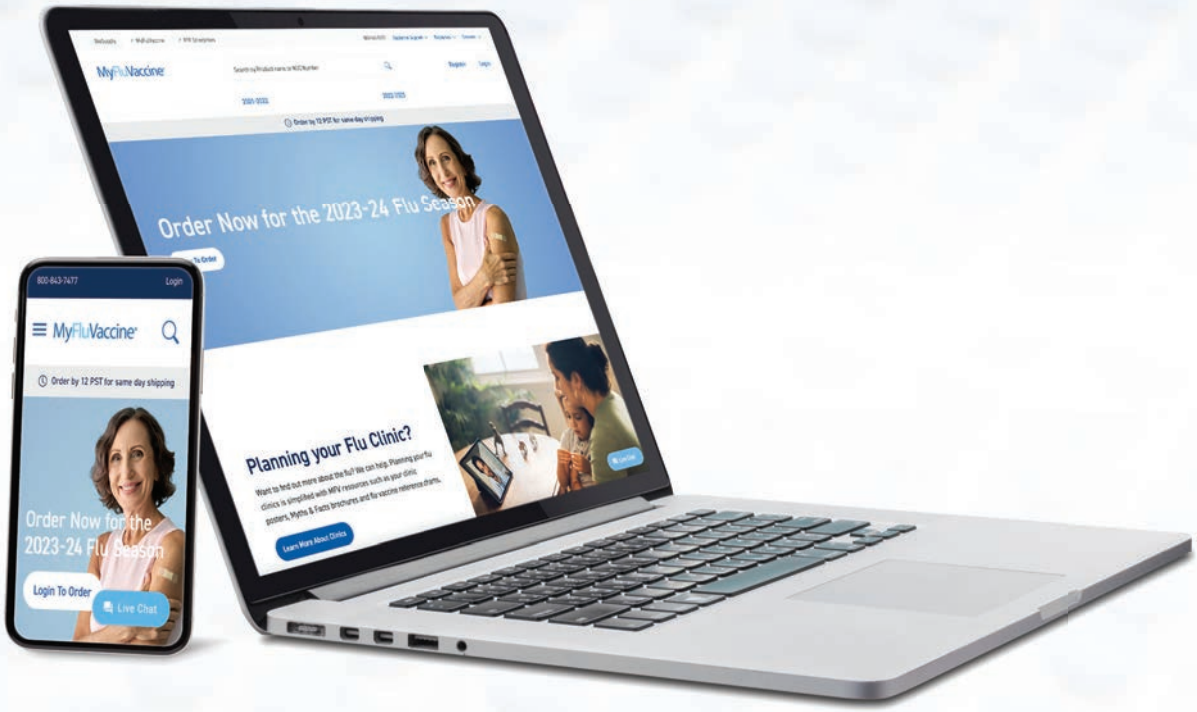

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OCR Issues Resources to Educate Patients about Telehealth and the Privacy and Security of Protected Health Information

The Office for Civil Rights (OCR) at the U.S. Department of Health and Human Services has issued two resource documents to help explain to patients the privacy and security risks to their protected health information (PHI) when using telehealth services and ways to reduce these risks.

The first resource is for healthcare providers titled "Educating Patients about Privacy and Security Risks to Protected Health Information when Using Remote Communication Technologies for Telehealth." Although healthcare providers are not required by the HIPAA Rules to provide this education, the resource supports the continued and increased use of telehealth by providing information to help healthcare providers who choose to discuss telehealth privacy and security with patients. The resource provides suggestions for discussing telehealth options offered; risks to PHI when using remote communications technologies; privacy and security practices of remote communication technology vendors; and applicability of civil rights laws.

OCR also issued a resource for patients titled "Telehealth Privacy and Security Tips for Patients," which provides recommendations that patients can implement to protect and secure their health information such as conducting a telehealth appointment in a private location; turning on multi-factor authentication if available; using encryption when available; and avoiding public Wi-Fi networks.

"Telehealth is a wonderful tool that can increase patients' access to healthcare and improve healthcare outcomes," said OCR Director Melanie Fontes Rainer. "Healthcare providers can support telehealth by helping patients understand privacy and security risks and effective cybersecurity practices so patients are confident that their health information remains private."

The guidance on Educating Patients about Privacy and Security Risks to Protected Health Information when Using Remote Communication Technologies for Telehealth can be accessed at www.hhs.gov/hipaa/for-professionals/privacy/guidance/resource-health-care-providers-educating-patients/index.html.

The guidance on Telehealth Privacy and Security Tips for Patients can be accessed at www.hhs.gov/hipaa/for-professionals/privacy/guidance/telehealth-privacy-security/index.html. ❖

HHS Office for Civil Rights Issues Resources for Health Care Providers and Patients to Help Educate Patients about Telehealth and the Privacy and Security of Protected Health Information. U.S. Department of Health and Human Services press release, Oct. 18, 2023. Accessed at www.hhs.gov/about/news/2023/10/18/civil-rights-issues-resources-help-educate-patients-telehealth-privacy-security-protected-health-information.html.

First Drugs Selected for Medicare Drug Price Negotiation

The U.S. Department of Health and Human Services (HHS), through the Centers for Medicare and Medicaid Services (CMS), announced the first 10 drugs covered under Medicare Part D selected for negotiation as part of the Inflation Reduction Act. The negotiations with participating drug companies will occur in 2023 and 2024, and any negotiated prices will become effective beginning in 2026. Medicare enrollees taking the 10 drugs covered under Part D selected for negotiation paid a total of $3.4 billion in out-of-pocket costs in 2022 for these drugs.

The selected drug list for the first round of negotiation is Eliquis, Jardiance, Xarelto, Januvia, Farxiga, Entresto, Enbrel, Imbruvica, Stelara and Fiasp (Fiasp FlexTouch; Fiasp PenFill; NovoLog; NovoLog FlexPen; NovoLog PenFill). These selected drugs accounted for $50.5 billion, or about 20 percent, of total Part D gross covered prescription drug costs between June 1, 2022, and May 31, 2023, which is the time period used to determine which drugs were eligible for negotiation. CMS will publish any agreed-upon negotiated prices for the selected drugs by Sept. 1, 2024; those prices will come into effect starting Jan. 1, 2026. In future years, CMS will select for negotiation up to 15 more drugs covered under Part D for 2027, up to 15 more drugs for 2028 (including drugs covered under Part B and Part D) and up to 20 more drugs for each year after that.

"For far too long, pharmaceutical companies have made record profits while American families were saddled with record prices and unable to afford lifesaving prescription drugs," said HHS Secretary Xavier Becerra. "Although drug companies are attempting to block Medicare from being able to negotiate for better drug prices, we will not be deterred." ❖

HHS Selects the First Drugs for Medicare Drug Price Negotiation. U.S. Department of Health and Human Services press release, Aug. 29, 2023. Accessed at www.hhs.gov/about/news/2023/08/29/hhs-selects-the-first-drugs-for-medicare-drug-price-negotiation.html.

Evidence-Based Teen Pregnancy Prevention Programs Receive HHS Awards

The U.S. Department of Health and Human Services (HHS), through the Office of Population Affairs (OPA), announced approximately $23 million in funding to foster innovation, provide new research and expand the evidence to support and advance equity in the Teen Pregnancy Prevention (TPP) program. The TPP program is a national, competitive program that provides funding to replicate and scale evidence-based programs and develop and evaluate new and innovative approaches to prevent unintentional teen pregnancy and sexually transmitted infections among adolescents, promote positive youth development and advance equity in adolescent health.

Through the TPP program, HHS seeks to advance equity in adolescent health by supporting projects that create, identify and scale effective approaches in communities and populations with the greatest needs and facing significant disparities across the country to improve adolescent health and well-being. Collectively, 18 new Tier 2 projects, along with the 53 new Tier 1 projects announced in June 2023, demonstrate how the TPP program is responsive to the needs of youth, their families and communities.

"All the new interventions address gaps in the current evidence base and have the potential to contribute new evidence-based interventions for future implementation to scale through OPA's TPP program," said Jessica Swafford Marcella, HHS deputy assistant secretary for population affairs. ❖

HHS Awards $23 Million to Support Evidence-Based Teen Pregnancy Prevention Programs. U.S. Department of Health and Human Services press release, Aug. 25, 2023. Accessed at www.hhs.gov/about/news/2023/08/25/hhs-awards-23-million-support-evidence-based-teen-pregnancy-prevention.html.

HHS Awards $45 Million in Grants to Expand Access to Care for People with Long COVID

The U.S. Department of Health and Human Services (HHS), through the Agency for Healthcare Research and Quality (AHRQ), has announced nine grant awards of $1 million each for up to five years to support existing multidisciplinary Long COVID clinics across the country to expand access to comprehensive, coordinated and person-centered care for people with Long COVID, particularly underserved, rural, vulnerable and minority populations that are disproportionately impacted by the effects of Long COVID. The grants are designed to expand access and care, develop and implement new or improved care delivery models, foster best practices for Long COVID management and support the primary care community in Long COVID education.

The AHRQ-funded Long COVID clinics will focus on increasing access to care, improving person-centered care coordination, expanding multidisciplinary networks and behavioral health support, and expanding social support services for adult, pediatric and priority populations through strategies such as:

- Increasing Long COVID care access by expanding in-person and virtual visit capacity, establishing new satellite clinics and growing provider-based referrals through a coordinated education series;
- Adding dedicated care coordination, social services, language interpretive staff and group programs for people with Long COVID; and
- Integrating dedicated behavioral health staff and implementing behavioral health and rehabilitation group support programs.

"These nine grants have strong potential to serve as a roadmap for developing improved care models for primary care and specialty clinics serving populations disproportionately impacted by the effects of Long COVID," said AHRQ Director Robert Otto Valdez, PhD, MHSA. "We look forward to sharing actionable knowledge from AHRQ grantees with other healthcare providers to support high-quality care for vulnerable patients with Long COVID." ❖

HHS Awards $45 Million in Grants to Expand Access to Care for People with Long COVID. U.S. Department of Health and Human Services press release, Sept. 20, 2023. Accessed at www.hhs.gov/about/news/2023/09/20/hhs-awards-45-million-grants-expand-access-care-people-long-covid.html.

Using Modifiers to Untangle Billing for Waste

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

TELLING A patient's story accurately, completely and in a codable fashion is essential when submitting payment claims to payers, whether it is a commercial, Medicaid, Medicare or Medicare Advantage plan. Virtually all of the verbiage in the electronic health record (EHR) is converted into codes that are electronically transmitted to payers. Disease states, presenting conditions and reason for the visit fall into the International Classification of Diseases-10 series; procedures and tests are covered by Current Procedural Terminology codes; and all products, including drugs and biologicals, are given designated Healthcare Common Procedure Coding System codes. Medicare then identifies payment possibilities by assigning status indicators.

Modifiers are alpha character designations that add details or clarifying facts or differentiate between actions/events to indicate a service or procedure performed has been altered by some specific circumstance, but not changed in its definition or code.

Implementation of JW and JZ Modifiers

Even with all these coding sets, it is sometimes necessary to increase the specificity of the data or to add a contingency of payment by adding modifiers. This is because payers, including Medicare, may want to capture particular types of data or use payment information for policy planning or implementation purposes. Modifiers are alpha character designations that add details or clarifying facts or differentiate between actions/events to indicate a service or procedure performed has been altered by some specific circumstance, but not changed in its definition or code. They are used to add information or change the description of service to improve accuracy or specificity.

Modifiers play a specific role in waste billing. Medicare created the ability to bill for expensive waste in the outpatient area shortly after moving to the concept of "billing units representing actual dose given" for reimbursement, away from the "whole vial" method of billing under the Outpatient Prospective Payment System. Medicare does not mandate billing for waste, but makes it possible to recoup some lost dollars if facilities choose to bill for them. However, it does mandate the use of the JW modifier to differentiate the billing units for waste from the billing units for the dose administered. As of Jan. 1, 2017, the Centers for Medicare and Medicaid (CMS) established a consistent policy among all Medicare administrative contractor jurisdictions to use the JW modifier billing for waste for discarded amounts of drugs from single-dose containers. CMS encourages physicians, hospitals and other providers and suppliers to care for and administer drugs and biologicals to patients in such a way that they can use drugs or biologicals most efficiently and in a clinically appropriate manner. Overfill in vials is not considered either as a billable administered drug or as potential drug waste. Rather, all calculations are based on the labeled amount of the container.

Implementation of the Infrastructure Act

Unfortunately, use of the JW modifier has not been particularly successful. Observed low compliance with the use of the JW modifier has led to incomplete JW modifier data, as well as lack of data integrity in billing for waste.[1] This has caused a major problem with the recently passed Waste Refund Act (Section 90004 of the Infrastructure Investment and Jobs Act [Pub. L. 117-9, Nov. 15, 2021], hereafter the Infrastructure Act, amended section 1847A of the Act). The goal of the Act is for CMS to obtain rebates from manufacturers for the value of the amount of drug wasted. The bill requires drug companies/manufacturers to reimburse Medicare for certain wasted medications, although some exclusions apply. Specifically, the Act states that those administering certain single-dose container or single-use package drugs payable under Medicare Part B will provide refunds with respect to discarded amounts of such drugs. Wasted medications include leftover portions of drugs packaged in single-use containers. To ensure accurate rebate transactions, it

became necessary to differentiate between each single-dose package sold that had some CMS-billable waste (identified with the JW modifier) versus those that did not have any waste billed to CMS. Hence, on July 1, 2023, a second modifier, JZ, was initiated to be included on claims for single-dose container drugs to attest when there were no discarded amounts. This is because the JW modifier relies on the discarded drug refund data for audit purposes. Use of the JZ modifier was made mandatory effective Oct. 1, 2023.

Claims for drugs with discarded amounts furnished on or after Jan. 12, 2017, to June, 30, 2023, that have not used the JW modifier correctly may be subject to review. Those billed on or after July 1, 2023, that do not report the JW or JZ modifier may be subject to provider audits. In addition, claims not reporting the modifiers as appropriate on or after Oct. 1, 2023, may be returned as unprocessable until claims are properly resubmitted.

Further provisions require the Department of Health and Human Services (HHS) to quarterly aggregate the total amount of discarded Part B drugs using Medicare Part B claims and to calculate refunds using the average wholesale price (ASP) (or wholesale acquisition cost if ASP is not available). Drug manufacturers will be required to provide a rebate to HHS for the total amount of discarded medication recorded, above a 10 percent low-volume threshold. Noncompliance of providing a timely rebate could incur civil monetary penalties under this Act.

The Act applies to the following settings:

1) All providers and suppliers who buy and bill status indicator G and K separately payable drugs under Medicare Part B (These are mostly physician's office and hospital outpatient settings for beneficiaries who receive drugs incident to physicians' services.)

2) Critical access hospitals (CAHs), since drugs are separately payable in the CAH setting

3) Non-renal dialysis service drugs and biological products administered in end-stage renal disease

JW and JZ modifiers do not apply to drugs administered in rural health clinics (RHC) or federally qualified health centers (FQHC) because drugs administered are generally not separately payable under Part B. Instead, their payment is included in the RHC's all-inclusive rate or the FQHC's prospective payment system rate for the patient's visit. JW and JZ modifiers are also not intended for use in claims for hospital inpatient admissions billed under the inpatient prospective payment system.

Logistics of Reporting JW and JZ Modifiers

The JW modifier is required to identify discarded billing units of a billing and payment code to calculate the refund amount. The JZ modifier is required when there is no payment under Medicare Part B for the discarded amount from the single-dose vial or package.

As stated, CMS requires providers and suppliers to report the JW modifier on all claims that bill for drugs and biologicals separately payable under Part B with unused and discarded amounts from single-dose containers or single-use packages. If there's no waste from single-dose containers or single-use packages, the claim must be reported with the JZ modifier.

The goal is to obtain rebates from manufacturers for money (to the tune of millions of dollars) spent on paying facilities for drug waste billed to Medicare with the JW modifier. The payer knows the actual dose that was billed, and CMS is asking for the remaining amount from that single-dose vial/package as a rebate if it was billed as waste. If no waste was billed, or if the product was used for another patient, thrown away, etc., then use of the JZ modifier would indicate there will be no rebate to CMS from the manufacturer.

CMS is not mandating that facilities bill for waste. It is asking facilities to identify when they do by using the JW modifier and when they don't by using the JZ modifier. So, if facilities don't bill for any waste, then the JZ modifier would be the only modifier used and only when used for a Medicare patient.

"Automatic" calculation of discarded amounts (e.g., a calculation performed by a software program) is acceptable as long as the facility is attesting the amount actually was waste and documented as such. There must be a match between what the EHR states and what is actually billed for the remainder of the drug in the single-use container. ❖

Reference

1. Centers for Medicare and Medicaid Services. ASP Billing Resources. Accessed at www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/asp-billing-resources.

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.

Overcoming Challenges of Delivering Quality Healthcare

Better health for all is on the horizon thanks to those who are implementing new strategies to improve care.

By Diane L.M. Cook

AS THE U.S. population increases and ages, the rate of illness and disease escalates too, so it is vitally important that providers are equipped to deliver quality healthcare. But both long-standing and new challenges make delivering quality healthcare difficult, and these challenges will undoubtedly continue into the future as well.

However, there is hope: Several healthcare associations have identified many of these challenges and are working toward implementing solutions that will make better healthcare available to populations that need it.

American Hospital Association

The American Hospital Association (AHA) represents nearly 5,000 hospitals, healthcare providers, networks and their patients and provides information on healthcare issues and trends. AHA is "committed to providing patients with high-quality, equitable, safe and person-centered care."

AHA has identified several challenges to providing quality healthcare, including historic workforce shortages, soaring costs, broken supply chains, severe payer underpayment and an overwhelming regulatory burden. They are implementing the following strategies to address these challenges:

• *AHA 2023 Advocacy Agenda.* This agenda is focused on quality, equity and transformation. AHA believes everyone deserves access to high-quality care, regardless of personal or community characteristics or geographic location, so strategic partnerships and solutions are being established to coordinate care across the continuum. AHA is also urging the government to support policies to support this effort, as well as improve maternal and child health outcomes with a particular focus on eliminating racial and ethnic inequities.[1]

• *Health Research and Education Trust Hospital Improvement Innovation Network 2.0.* Valuable best practices from this two-year contract awarded by the Centers of Medicare and Medicaid Services helped reduce all-cause inpatient harm by 20 percent and readmissions by 12 percent by 2019.

• *Age-Friendly Health Systems.* The number of Americans at or above 65 years of age (55 million) is projected to double by 2060. The goal of this program is to rapidly spread the 4Ms Framework to 20 percent of hospitals and medical practices by 2020.

• *Better Health for Mothers and Babies.* AHA collaborates with Alliance for Innovation on Maternal Health to safeguard mothers and babies by reducing maternal morbidity, especially in the hospital.

• *AHA Joint Initiative with Center to Advance Palliative Care.* Palliative care reduces symptom distress by 66 percent, with improvements often lasting months. This initiative reexamines palliative care, identifies patients needing additional support and builds a care plan centered on the whole patient.[2]

• *Quest for Quality Prize.* AHA recognizes hospitals and health systems that provide access to exceptional quality care that is Safe, Timely, Effective, Efficient, Equitable and Patient and family-centered (STEEP) with this yearly award.[3]

American Medical Association

The American Medical Association (AMA) represents physicians at the federal and state levels to help them remove obstacles that interfere with patient care and access to quality healthcare. AMA is currently leading the charge for Medicare payment reform to address long-standing and current patient care and access to quality healthcare issues that affect more than 50 million Americans:

On July 13, 2023, a proposed Medicare physician payment schedule

was released that will see a new rule bring another downward adjustment of 3.36 percent in 2024 (on top of the 2.0 percent payment reduction in 2023). The payment schedule estimates the Medicare Economic Index increase at 4.5 percent for 2024, the highest this century and in addition to last year's 3.8 percent in 2023.

According to AMA, "When adjusted for inflation, Medicare physician payment has effectively declined 26 percent from 2001 to 2023. These increasingly thin or negative operating margins disproportionately affect small, independent and rural physician practices, as well as those treating low-income or other historically minoritized or marginalized patient communities."[4]

In response, AMA and the Federation of Medicine developed a set of principles known as Characteristics of a Rational Medicare Payment System to guide efforts on Medicare physician payment reform. This is part of AMA's Recovery Plan for America's Physicians and represents its ongoing work.[5]

"Cuts, temporary measures and partial fixes to the Medicare physician payment system are not sustainable," explains AMA. "They hinder physicians' ability to adequately pay staff, purchase new equipment and invest in their practices. Without long-term reform, physicians could be forced to close their doors for good, leaving Medicare patients without access to high-quality care. Overall, a rational Medicare payment system would ensure financial stability and predictability, promote value-based care and safeguard access to high-quality care."[6]

According to AMA, providing and protecting high-quality care can be achieved by 1) advancing health equity and reducing disparities by risk-adjusting payment model innovations and recognizing physicians' contributions to reducing health disparities and 2) supporting clinical practices where they already are by recognizing that high-value care is provided by both small practices and large systems, and in both rural and urban settings.[7] Physicians need support as they care for historically marginalized, higher-risk, hard-to-reach or sicker populations.

American Nurses Association

The American Nurses Association (ANA) represents more than four million nurses and offers many opportunities for its members to foster excellence in patient care. ANA has developed three practice areas that help nurses address the challenges they have in providing quality healthcare:

1) Support nurses to manage the complexities of modern healthcare and deliver consistently excellent care. From ethical dilemmas to healthcare reform, ANA works to ensure that no matter what the challenge, nursing continues to improve healthcare for all.[8]

2) Emphasize advocacy as a pillar of nursing. Advocacy for patients in the workplace, community and government is important to advance the nursing profession and, ultimately, quality healthcare.[9]

3) Encourage use of digital health. Telehealth applications that include live (synchronous) video conferencing, remote patient monitoring and mobile health all help nurses overcome the challenges of delivering quality healthcare to patients who are not able to visit a doctor's office or a hospital in person; who need regular monitoring that does not require an office or hospital visit; or who live in remote locations where no doctor's offices or hospitals exist.[10]

In addition to these, ANA's American Nurses Credentialing Center's (ANCC) Pathway to Excellence Program is the premier designation for healthy work environments. It recognizes healthcare organizations that demonstrate a commitment to establishing the foundation of a healthy workplace for nurses. The professional development program fosters satisfied nurses by ensuring they are competent to provide care; it also provides mentoring, support and opportunities for lifelong learning. ANCC says that communities want satisfied nurses because they are better equipped to deliver higher-quality care, and with fulfilled staff, come higher standards of care and patient outcomes.[11]

From Adversity to Improvement

With adversity comes an opportunity for improvement. Though challenges remain, healthcare associations are actively attempting to address them. Thanks to their efforts, better access to and delivery of improved patient care is on the horizon. ❖

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Medicines

FDA Approves Wezlana, First Interchangable Biosimilar to Stelara

The U.S. Food and Drug Administration (FDA) has approved Wezlana (ustekinumab-auub) as a biosimilar to and interchangeable with Stelara (ustekinumab) for adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy; active psoriatic arthritis; moderately to severely active Crohn's disease; and moderately to severely active ulcerative colitis. It is also approved for pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy and active psoriatic arthritis.

FDA's approval of Wezlana is based on a comprehensive review of scientific evidence demonstrating it is highly similar to Stelara and that there are no clinically meaningful differences between the two products in terms of safety, purity and potency (i.e., safety and effectiveness). This evidence included comparisons of the products on an analytical level using an extensive battery of chemical and biological tests and biological assays that confirmed similarity in the structural and functional features of Wezlana and Stelara (including those known to impact safety and efficacy), and comparative human pharmacokinetic data, clinical immunogenicity data and other clinical safety and effectiveness data. The evidence also demonstrated that Wezlana met the other legal requirements to be interchangeable with Stelara at the pharmacy level.

Like Stelara, the most serious known side effect of Wezlana is infection. The most common adverse reactions with ustekinumab products are nasopharyngitis, upper respiratory tract infection, headache, fatigue, nausea, vomiting, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, sinusitis, abdominal pain, influenza, fever and diarrhea.

The labeling for Wezlana, like Stelara, contains a warning to alert healthcare professionals and patients about an increased risk of serious infections leading to hospitalization. There is also a warning that some malignancies, hypersensitivity reactions and cases of posterior reversible encephalopathy syndrome have been reported in patients who received Wezlana in clinical studies. ❖

FDA Approves Interchangeable Biosimilar for Multiple Inflammatory Diseases. U.S. Food and Drug Administration news release, Oct. 31, 2023. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-interchangeable-biosimilar-multiple-inflammatory-diseases.

Medicines

FDA Approves Celltrion's Zymfentra to Treat Ulcerative Colitis and Crohn's Disease

The U.S. Food and Drug Administration (FDA) has approved Celltrion's Zymfentra, a subcutaneous injection formulation of its infliximab Remsima, for maintenance therapy in adults with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD) following treatment with an infliximab administered intravenously. Zymfentra (infliximab-dyyb) is the world's first and only subcutaneous infliximab product. It is approved as a novel drug, and its development is based on Remicade (reference intravenous infliximab).

Approval was based on data from two Phase III pivotal trials that assessed the efficacy of Zymfentra as maintenance therapy in patients with moderate to severe UC (LIBERTY-UC) and CD (LIBERTY-CD). Study results show Zymfentra had a superior response in achieving clinical remission (UC and CD) and endoscopic response (CD) compared to placebo as maintenance therapy after induction therapy of intravenous infliximab over a 54-week period. The overall safety profile of Zymfentra was similar to that of placebo during the maintenance period in both studies, and no new safety signals were identified.

"There remains an unmet need for patients who suffer from the day-to-day burden of living with moderately to severely active Crohn's disease and ulcerative colitis," said Thomas Nusbickel, chief commercial officer at Celltrion USA. "The approval of Zymfentra provides an innovative and effective treatment option that offers patients with IBD [irritable bowel disease] an alternative administration option, providing control of how and where they receive their treatment, reinforcing our commitment to providing high-quality and affordable treatment options that deliver substantial value to patients and our healthcare system." ❖

Jeremias, S. FDA Approves First Subcutaneous Infliximab Product. AJMC, The Center for Biosimilars, Oct. 23, 2023. Accessed at www.centerforbiosimilars.com/view/fda-approves-first-subcutaneous-infliximab#.

Medicines

FDA Expands Approval to wilate for Prophylaxis in All Types of VWDr

Octapharma USA's wilate, von Willebrand factor (VWF)/coagulation factor VIII complex (human) lyophilized powder for solution for intravenous injection, has been given expanded approval by the U.S. Food and Drug Administration (FDA) for routine prophylaxis to reduce the frequency of bleeding episodes in adults and children aged 6 and older with any type of von Willebrand disease (VWD), the most prevalent bleeding disorder in the United States. Wilate is the first VWF concentrate indicated for prophylactic treatment across all forms of VWD.

Approval was based on Octapharma's WIL-31 study, a prospective, noncontrolled, international, multicenter Phase III trial that investigated the efficacy and safety of wilate prophylaxis over 12 months in people aged 6 and older with severe VWD of any type. All WIL-31 patients received on-demand treatment with wilate during a previous six-month, prospective, observational study (WIL-29). Patients who experienced at least six bleeding episodes (BEs), excluding menstrual bleeds, with at least two of these BEs treated with a VWF-containing product, were eligible to enter WIL-31. Patients in WIL-31 received wilate prophylaxis two to three times per week at a dose of 20-40 IU/kg for 12 months.

The clinical trial's primary purpose was to investigate whether prophylaxis with wilate lowered the mean total annualized bleeding rate (ABR) by more than 50 percent compared to the six months of on-demand treatment. Secondary goals were to measure spontaneous ABR and treatment-emergent adverse events. Researchers reported an 84 percent reduction in the mean total ABR compared with on-demand treatment during the prior study. The median spontaneous ABR decreased by 95 percent. Importantly, no serious drug-related adverse events or thrombotic events were observed during the study.

"Long-term prophylaxis with VWF concentrate, as compared to on-demand treatment for bleeding, is recommended for patients with severe VWD," said Shveta Gupta, MD, a specialist in pediatric hematology and oncology with The Haley Center for Children's Cancer and Blood Disorders at Orlando Health Arnold Palmer Hospital for Children. "The approval of wilate for VWD prophylaxis is a welcome new treatment option that can be lifesaving for many patients. Increased use of VWF prophylaxis in VWD patients may lead to improved patient care and a reduced burden of disease." ❖

Octapharma USA: FDA Grants Expanded Approval to wilate® as the First VWF Concentrate for Prophylaxis in All Types of VWD. Octapharma press release, Dec. 5, 2023. Accessed at www.prnewswire.com/news-releases/octapharma-usa-fda-grants-expanded-approval-to-wilate-as-the-first-vwf-concentrate-for-prophylaxis-in-all-types-of-vwd-302005285.html.

Medicines

FDA Approves Vaccine for Meningococcal Disease in Adolescents

Pfizer's PENBRAYA, a vaccine for meningococcal groups A, B, C, W and Y, has been approved by the U.S. Food and Drug Administration (FDA). PENBRAYA is the first and only vaccine to protect against the five most common serogroups that cause meningococcal disease in patients aged 10 through 25 years. The vaccine combines components from two meningococcal vaccines: Trumenba (meningococcal group B vaccine) and Nimenrix (meningococcal groups A, C, W-135 and Y conjugate vaccine). It is administered as a two-dose series given six months apart.

FDA approval was based on data from Phase II and Phase III trials, which included a randomized, actively controlled and observer-blinded Phase III trial. The trials assessed the safety and efficacy of PENBRAYA in comparison to current U.S.-licensed meningococcal vaccines, with the goal of determining immunologic noninferiority. The Phase III trial evaluated more than 2,400 patients from the United States and Europe. ❖

Husni, DG. FDA Approves Vaccine for Prevention of the Five Most Common Serogroups Causing Meningococcal Disease in Adolescents. BioPharm, Oct. 30, 2023. Accessed at www.biopharminternational.com/view/fda-approves-vaccine-for-prevention-of-the-five-most-common-serogroups-causing-meningococcal-disease-in-adolescents.

Research

Study Shows Positive Results for mRNA-Based Combination Influenza and COVID-19 Vaccine

A Phase I/II study evaluating the safety, tolerability and immunogenicity of Pfizer and BioNTech's mRNA-based combination vaccine candidates for influenza and COVID-19 among healthy adults 18 to 64 years of age show positive topline results.

In the clinical trial, the vaccine candidates were compared to a licensed influenza vaccine and the companies' Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine given at the same visit. The data from the trial showed the companies' lead formulations demonstrated robust immune responses to influenza A, influenza B and SARS-CoV-2 strains. According to the companies, immunogenicity results induced by lead formulations in the companies' trial showed point estimates for geometric mean titer (GMT) ratios that were consistent with the criteria applied to regulatory approved vaccines against the respective influenza and SARS-CoV-2 strains. Point estimates for GMT ratios for all matched influenza vaccine strains with lead formulations were >1 relative to a licensed quadrivalent influenza vaccine given concomitantly with the Pfizer-BioNTech COVID-19 vaccine.

"We are encouraged by these early results in our Phase I/II study of our combination vaccine candidates against influenza and COVID-19. This vaccine has the potential to lessen the impact of two respiratory diseases with a single injection and may simplify immunization practices for providers, patients and healthcare systems all over the world," said Annaliesa Anderson, PhD, FAAM, senior vice president and head of vaccine research and development at Pfizer. "mRNA-based vaccines have demonstrated their ability to induce robust antibody and T-cell responses, and we look forward to starting Phase III clinical development. Today's results are an important achievement towards our ambition of providing a broad portfolio of respiratory combination vaccines." ❖

Pfizer and BioNTech Announce Positive Topline Data for mRNA-based Combination Vaccine Program Against Influenza and COVID-19. Barron's, Oct. 26, 2023. Accessed at www.barrons.com/articles/pfizer-and-biontech-announce-positive-topline-data-for-mrna-based-combination-vaccine-program-against-influenza-and-covid-19-1c31c145.

Research

Cancer Drug Shows Promising Results in Clinical Trial

An international, early-phase clinical trial has found a "two-for-one" cancer immunotherapy, tebotelimab, is potentially more effective and at least as safe as standard immunotherapies. The findings, which involved hundreds of patients with different types of advanced solid tumors or blood cancers, could lead to a new path for bispecific therapies that more efficiently unleash the patient's own immune system to eliminate the cancer.

The study enrolled 269 patients with advanced disease, including types of ovarian, breast, head and neck, cervical and lymphoma cancers. Tumor size decreased in 34 percent of eligible participants. The researchers took the trial a step further and enrolled another 84 patients with advanced cancers positive for a protein called HER2 to test tebotelimab combined with an

approved drug for HER2-positive cancer, called margetuximab. The response rate in those participants was 19 percent, which Jason Luke, MD, director of the Immunotherapy and Drug Development Center at UPMC Hillman and associate professor of hematology and oncology at the University of Pittsburgh School of Medicine, said was impressive given the response rate is usually closer to 0 percent in these particular patients.

"No approved cancer drugs are like this. It is truly a novel development in the field," said Dr. Luke. "The patients in our trial had cancers that were not responding to other therapies, so to see double-digit response rates is encouraging."

Dr. Luke says the next step is to develop a biomarker test that will tell doctors which patients have cancers that are expressing the proteins that tebotelimab is designed to block and then conduct another trial to see if outcomes are improved further. Additionally, future trials could test the immunotherapy in combination with chemotherapy or radiation. ❖

Hydzik, A. Cancer Drug That Targets Two Immune-Evading Tumor Tactics Performs Well in Early Clinical Trial. University of Pittsburgh Medical Center, Oct. 19, 2023. Accessed at inside.upmc.com/cancer-drug-that-targets-two-immune-evading-tumor-tactics-performs-well-in-early-clinical-trial.

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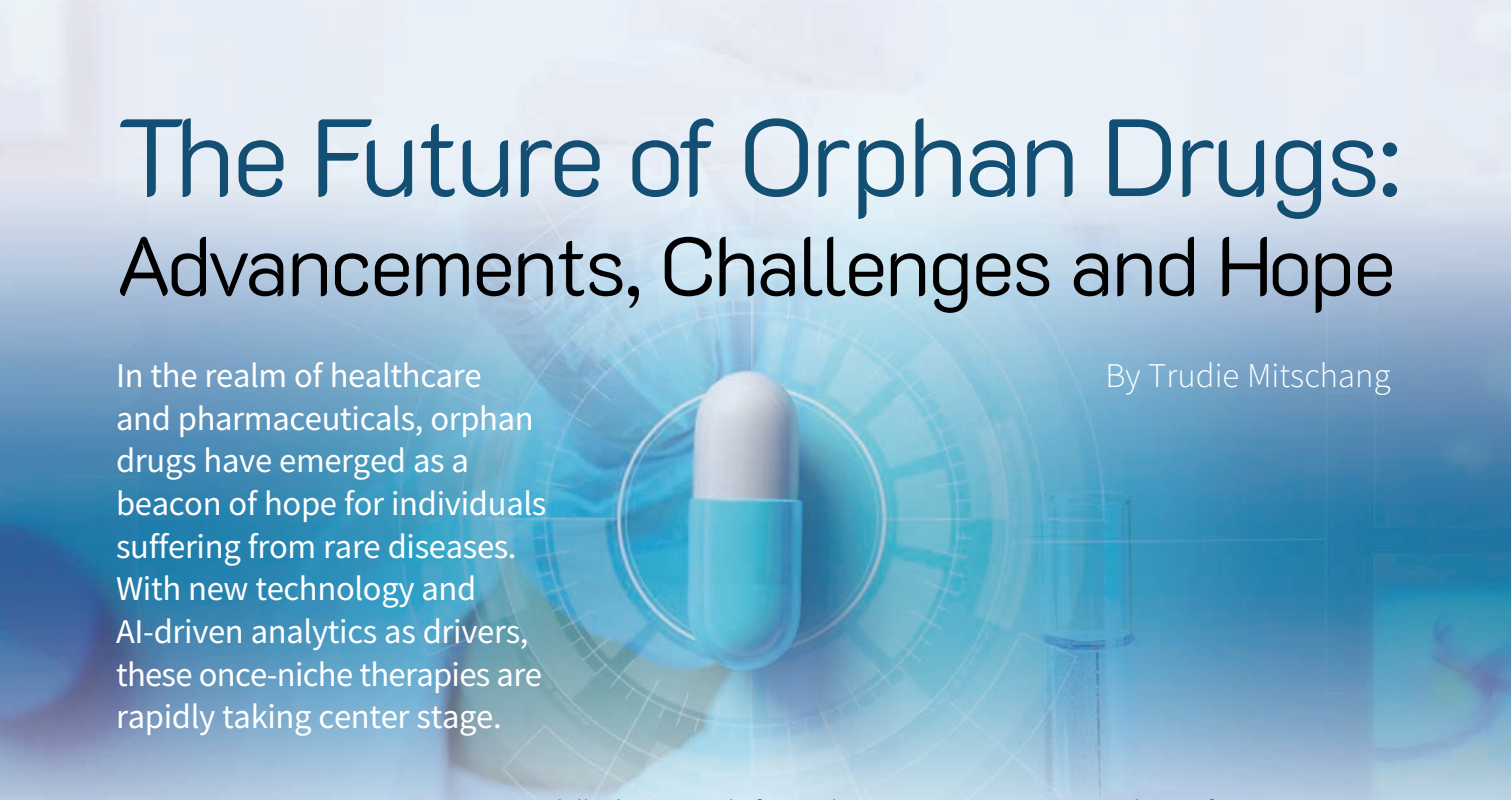
The Future of Orphan Drugs: Advancements, Challenges and Hope



In the realm of healthcare and pharmaceuticals, orphan drugs have emerged as a beacon of hope for individuals suffering from rare diseases. With new technology and AI-driven analytics as drivers, these once-niche therapies are rapidly taking center stage.

By Trudie Mitschang

AN ORPHAN DRUG is a pharmaceutical agent developed to treat medical conditions deemed rare diseases because they affect only a small percentage of the population. The term "orphan" signifies the limited patient population these drugs target. In terms of numbers, a rare disease in the United States is defined as one that affects fewer than 200,000 people. Historically, the development of drugs for these rare diseases was often neglected by pharmaceutical companies because of the low potential return on investment. All that changed when advocates rallied together and governments and regulatory bodies around the world introduced incentives and policies to spur the development of orphan drugs and improve the treatment outcomes and quality of life for impacted patient populations.

The origins of the orphan drug movement date back to the 1960s, when patients with rare diseases and their families began advocating for research into their conditions.[1] Fast forward to the early 1980s, when families, advocates and leaders of several rare disease patient organizations formed an ad hoc coalition that became instrumental in passage of the 1983 Orphan Drug Act, a landmark bill that created financial incentives for the development of treatments for rare diseases.[2] That coalition became the National Organization for Rare Disorders, or NORD, which celebrated its 40th anniversary in 2023.

The Orphan Drug Act's initial incentives included a seven-year market exclusivity, tax credits for clinical research, research grants and waived U.S. Food and Drug administration (FDA) fees.[3] The impact of these incentives was significant, leading to a boom in orphan drug approvals. Since the passage of the Orphan Drug Act, FDA has approved more than 500 orphan products and rare disease therapies, and orphan drugs currently make up more than 50 percent of new FDA drug approvals.[2]

Scientific Advancements Drive Development

The past decade has witnessed a surge in orphan drug development, driven by scientific advancements, increased understanding of rare diseases and regulatory incentives. Following are some key advancements in the field:

• Precision medicine: The era of precision medicine has ushered in a new approach to orphan drug development. Researchers are increasingly tailoring treatments to the specific genetic mutations or mechanisms underlying rare diseases, leading to more effective therapies with fewer side effects.[3]

• Gene therapy: Once considered a distant dream, gene therapy has become a reality in orphan drug development. One example is the groundbreaking treatment Luxturna, which targets a specific gene mutation that causes blindness. Its FDA approval hints at the potential of gene therapy for the treatment of rare diseases.[4]

• Advancements in rare disease diagnostics: Improved diagnostic tools such as Next-Generation Sequencing and biomarker identification have facilitated the identification of rare diseases and enabled more targeted drug development.[5]

Additionally, pharmaceutical companies are using recent advances in digital technologies to improve care strategies and provide hope for rare disease patients across thousands of different diagnoses. Thanks to growing sophistication in the use of data analytics and artificial intelligence, the industry is seeing improved diagnostics, accelerated research and development, and improved patient identification and tracking of disease progression. As a result, the rare disease industry is now on the brink of maturity and prepared for a

period of sustained growth.[6]

Access to enhanced analytics also has the potential to decrease diagnosis time for patients who sometimes spend years waiting for a diagnosis and targeted treatment plan. Recent advances in analytics, coupled with greater accessibility of large data sets, give pharmaceutical companies an opportunity to identify and spotlight patient groups more quickly. Case in point: One global pharmaceutical company with a sizable rare disease operation deployed digital and analytic tools to improve its patient identification approach for one of its rare disease treatments. Using multiple core data sets of potential patients, the company built a predictive model to estimate the likelihood of any given individual having the targeted rare disease. They then used this model to identify a large population of undiagnosed patients and the physicians who were disproportionately likely to oversee patients with the disease. This more precise engagement of physicians enabled an increase of more than 40 percent in the number of patients who could benefit from earlier and better access to diagnosis and care in the five years following treatment launch.[6]

Assessing the Challenges with Clinical Trials

One of the key challenges in the development of orphan drugs is limited ability to enroll, engage and retain patients for clinical trials. Because patients are few and often geographically scattered, it can be hard to recruit enough candidates for trials and expensive to arrange the logistics. By necessity, many rare disease clinical trials are often multinational for sufficient patient recruitment, even in Phase I and II trials. This can challenge the defining of protocols, ethical reviews, organization of clinical services and standards of care. Language differences and working across varied time zones add further complications. Potential participants may also be discouraged by trial requirements such as taking additional medication, completing diaries and recording symptoms or side-effects — tasks that add to the daily disease burden that patients already face.[7]

"Assembling enough patients to conduct longitudinal studies and clinical trials is challenging when so few people live with a specific disease," said James Wilson, MD, PhD, who directs the Orphan Disease Center at the University of Pennsylvania. "For genetic diseases caused by a single gene defect, between two-thirds and three-quarters of affected individuals reside beyond the United States. We have to broaden our horizon outside of the U.S., not only to make sure we gain access to enough patients, but we also want to make sure that any advances that happen are distributed globally so that there's global access and global impact."[8]

Another challenge impacting clinical trial development is the overall lack of information about any given rare disease and its likely path of progression. "For rare diseases, oftentimes, there's not enough known about the natural history to design a proper clinical trial because you have to select, in most study designs, a single primary endpoint on which the trial hinges. How do you pick the right one if you don't know very much about the disease or its rate of progression or its main features?" asked Edward Neilan, MD, PhD, chief medical and scientific officer of NORD.[8]

To address these and other challenges, researchers at the Orphan Disease Center initiated a global study of individuals with Lesch-Nyhan disease, an extremely rare and severe neurological disorder caused by a single gene defect that affects approximately one in 300,000 people. Using a specialized rare disease data platform, the team is compiling medical records and analyzing motor function and behavioral symptoms in people of different ages to construct a picture of the evolution of the disease over time.[8]

To enable similar studies for the entire spectrum of rare diseases, NORD has launched the IAMRARE registry program through which patients complete surveys about their experiences living with rare diseases. Since its launch, more than 13,000 people representing approximately

Rare Disease Facts and Statistics

- Any disease affecting fewer than 200,000 people in the United States is considered rare.
- Currently, more than 7,000 rare diseases have been identified.
- Twenty-five to 30 million Americans are living with a rare disease.
- Many rare diseases may result in the premature death of infants or can be fatal in early childhood.
- All pediatric cancers are rare.
- There are more than 500 types of rare cancers.
- More than 90 percent of rare diseases are still without an FDA-approved treatment.
- Rare diseases affect an estimated 35 million people worldwide.
- Men, women, children and the elderly are all impacted. In actuality, rare diseases are not so rare!
- Rare Disease Day is celebrated globally on the last day of February each year (the most rare day on the calendar) to raise awareness about rare diseases and the issues patients face.

Source: National Organization for Rare Diseases. Rare Disease Facts & Statistics. Accessed at rarediseases.org/understanding-rare-disease/rare-disease-facts-and-statistics.

Five Rare Diseases People Never Knew Existed

1) **Stoneman syndrome:** Fibrodysplasia ossificans progressiva (FOP), colloquially known as Stoneman syndrome, slowly turns connective tissue such as tendons, muscles and ligaments into bone. Frequency: one in two million people
2) **Alice in Wonderland syndrome:** The most prominent and often most disturbing symptom is that of altered body image (confusion as to the size and shape of their body parts, usually the head and hands); the second major symptom is the distortion of visual perception (the eyes themselves are normal, but the sufferer 'sees' objects with the wrong size or shape and/or finds that perspective is incorrect). Frequency: currently known
3) **Hutchinson-Gilford progeria syndrome:** A genetic condition in which there is a rapid dramatic appearance of aging beginning in childhood. The characteristic facial appearance includes prominent eyes, a thin beaky nose, thin lips, small chin and protruding ears. Frequency: one in four million
4) **Alkaptonuria (or black urine disease):** This is a very rare inherited disorder that prevents the body from fully breaking down two protein building blocks (amino acids) called tyrosine and phenylalanine, resulting in a buildup of a chemical called homogentisic acid in the body. Frequency: one in one million people globally
5) **Chronic focal encephalitis (Rasmussen's encephalitis):** Usually occurring in children under the age of 10 (more rarely in adolescents and adults), it is characterized by frequent and severe seizures, loss of motor skills and speech, paralysis on one side of the body (hemiparesis), inflammation of the brain (encephalitis) and mental deterioration. It can lead to the destruction or removal of a part of the affected child's brain. Frequency: in Germany, 2.4 cases per 10 million people; in the United Kingdom, 1.7 per 10 million people

Source: Five Rare Diseases You Never Knew Existed. Open Access Government, Feb. 28, 2023. Accessed at www.openaccessgovernment.org/five-rare-diseases/60001.

40 rare diseases have participated in the registry. At its most basic level, the registry helps identify patients with a rare disease that may enroll in a clinical trial. "The real desire of the IAMRARE platform is to do patient-led natural history studies," Dr. Neilan said, noting that while there are about 7,000 rare diseases, the pharmaceutical industry has focused on only 100 or 200 of them. "That uneven attention is another problem that we're trying to solve."[8]

The Rare Diseases Clinical Research Network through the National Institutes of Health also shares the goal of laying the groundwork necessary to prepare rare disease indications for clinical trials. Currently, researchers and patient advocates come together to form consortia for related rare diseases and work together to determine the "who, what, where, when and how" of clinical trial design.[8]

Orphan Drug Success Stories

The success stories of orphan drugs are a testament to the incredible impact they can have on patient populations and their families. Among some of the standouts:[9]

• Coagulation factor IX (FIX) (BeneFIX/Rixubis/Alprolix) is approved to help control and prevent bleeding in people with hemophilia B. Coagulation FIX reached the U.S. market in 1997 and represented a shift in standard of care. Prior to recombinant coagulation FIX, patients received FIX from human plasma, which had the risk of passing on infectious disease. Coagulation FIX is on the World Health Organization list of essential medicines and has one of the highest volumes of orphan drugs in the United States.

• Imatinib (Gleevec) is a groundbreaking drug that revolutionized the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors. It is considered one of the most successful orphan drugs to date. Prior to imatinib, allogeneic stem cell transplantation was the only treatment for long-term control of CML. In one eight-year follow-up study, the estimated overall survival of all patients randomized to receive imatinib was 85 percent.

• Cystic fibrosis modulator drugs such as ivacaftor (Kalydeco) and its combinations have transformed the treatment of cystic fibrosis, significantly improving the quality of life for patients. Prior to the approval of ivacaftor in 2012, only one other therapy was available to cystic fibrosis patients. The availability of ivacaftor, along with ivacaftor/lumacaftor (Kalydeco) and dornase alfa (Pulmozyme) has increased the life expectancy of cystic fibrosis patients.

• Rucaparib (Rubraca) was approved to treat women with advanced ovarian cancer who had been treated with two or more chemotherapies and whose tumors had a specific gene mutation (deleterious BRCA) as identified by an FDA-approved companion diagnostic test. Approximately 15 to 20 percent of patients with ovarian cancer have a BRCA gene mutation. FDA approved rucaparib under its 2017 accelerated approval program.

As far as breakthroughs and success stories on the horizon, there are a number of biotech companies actively making strides in developing rare disease therapies and treatments. Worth noting: London-based Alchemab Therapeutics is a biotechnology company working on harnessing the power of the immune system to create the next generation of antibody therapeutics for hard-to-treat diseases that do not yet have disease-modifying therapies. By studying the naturally-occurring antibody response in individuals who are resistant to or have overcome a certain disease, the company aims to develop antibodies into therapies for people who don't have the same protective response. Also notable is Horizon Therapeutics, led by CEO Tim Walbert, who has a rare disease that causes inflammation throughout his body along with chronic pain. The company's vision is to achieve medical breakthroughs for people with rare, autoimmune and severe inflammatory diseases, and they already have several in the pipeline.[10]

What the Future Holds

According to data in Evaluate's 2022 Orphan Drug report detailed on PharmExec.com, the orphan drug market is growing more than twice as fast as the non-orphan market, with a 2021-2026 compound annual growth rate of 12 percent. That means orphans will account for 20 percent of all prescription drug sales and almost one-third of the global drug pipeline's value by 2026.[9] The report goes on to state that orphans are forecast to match or outsize several mass-market drugs for chronic, widespread diseases, despite dramatically smaller patient numbers. Citing just one example, AbbVie/Johnson & Johnson's chronic lymphocytic leukemia drug Imbruvica (ibrutinib) is expected to be the biggest orphan drug in 2026 with $13 billion in worldwide sales.[11]

Orphans also have strength in numbers: More than half of the FDA's Center for Drug Evaluation and Research approvals in 2021 had orphan designations. In the first three months of 2022 alone, FDA approved seven rare disease drugs compared to just four for non-rare conditions. In fact, new medicines for chronic, widespread and highly complex conditions such as diabetes, heart disease or kidney disease are now in the minority.[11]

If these statistics are any indication, the future of orphan drugs is a promising one, driven by scientific advancements, regulatory incentives and collaborative efforts. These drugs have the potential to transform the lives of individuals affected by rare diseases, offering hope where there was once despair. As research continues to advance and access to treatments improves, the future looks bright. ❖

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Platelet-Rich Plasma Therapy: The Future of Healing?

The effectiveness of this controversial therapy in treating musculoskeletal disorders and other arthritic conditions is uncertain due to mixed results. Nevertheless, the PRP industry is booming.

By Amy Scanlin, MS

PLATELET-RICH PLASMA (PRP), a purported solution for ameliorating pain and promoting healing, is as controversial as it is enticing. After all, could an injection of one's own plasma be the antidote to many common ailments? With noticeable results reported in as little as two weeks, patients are asking and physicians are prescribing. But what is PRP and how effective is it really?

PRP has been in use for more than 30 years. Even in its early days, there was great excitement for its role in promoting tissue adhesion in wound care, facilitating healing of musculoskeletal disorders and easing the pain of osteoarthritis and other conditions. PRP works, it is thought, by promoting synthesis of connective tissues and revascularization, which leads to reduced inflammation at the site of injection, cellular proliferation and, ultimately, remodeling thanks in part to PRP's assumed role in adaptive immunity.[1]

The PRP industry is booming, estimated to be worth nearly $500 million and projected to grow more than 12 percent annually through 2026.[2] However, results of studies examining the effectiveness of PRP have been mixed, and with good reason. With no uniform standards in preparation or dosing, huge variability in the health of patients receiving PRP and a lack of standardization in study protocols, understanding its effectiveness is still in its infancy. Even so, PRP shows great potential.

What Is PRP?

PRP is a living biomaterial, derived from a patient's own blood and injected back into the body. Initially dormant, once PRP is injected, activation and aggregation of platelets begins.

U.S. Food and Drug Administration (FDA) Code of Federal Regulations 21 CFR, Part 640, subchapter F, Biologics, regulates some parts of protocols used in PRP such as how blood is to be drawn from the patient: "by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue," as well as the time frame in which platelets must be separated from red blood cells by centrifugation: "within four hours after completion of the phlebotomy or within the time frame specified in the directions for use for the blood collecting, processing and storage system." Once prepared, PRP is to be injected into the patient without the addition of preservatives.[3] Otherwise, there are no U.S. regulations on its preparation or concentration.

FDA has approved certain class 1 and class 2 medical device centrifuges for PRP preparations. As a biologic, PRP is not an FDA-approved drug. Physicians choosing to administer PRP must use discretion if they believe there will be a healing benefit for their patient.

PRP may be administered along with a local anesthetic by injection into the injured area, or it may be used as a healing agent during surgeries through a special preparation that allows the PRP to be stitched into torn tissues.[4]

From a patient perspective, PRP injections are thought to be low-risk, with no major side effects because it uses their own blood cells. Soreness at the injection site is possible, as is feeling light-headed during the blood draw (just as a patient might feel when donating blood). But other risks appear to be similar to those of cortisone injections.[4]

However, the risk of adverse events is certainly heightened in the event preparation of PRP is outsourced to facilities that operate in unsanitary conditions. Some FDA inspection findings for facilities, including compounding

facilities preparing PRP, include poor aseptic practices, dirty equipment and a lack of properly designed equipment to allow maintenance of appropriate levels of cleanliness.

Effectiveness of PRP

Thoughts on the effectiveness of PRP vary as do results of studies investigating its potential benefits. In part, that variability depends on the overall health of patients, any drugs they may be taking such as nonsteroidal anti-inflammatory drugs, aspirins or other medications that decrease growth factor response, the timing of the PRP administration, the type and severity of the injury and how the PRP was prepared. Downstream, because of so many variables, it is difficult to produce consistent clinically beneficial effects.[1]

One big challenge for studying the effectiveness of PRP is the number of medical devices commercially available from which PRP can be prepared. Each piece of equipment has its own validations, specifications and unique instructions, and these preparation inconsistencies negatively affect the ability to conduct reproducible studies. With no best practices for collection volumes or blood preparation, the resulting platelet density and PRP composition vary. White blood cell and red blood cell counts, platelet growth factors and the risk of contamination may all be impacted. Likewise, how the patient's body interacts with the PRP also contributes to the challenge of defining effectiveness.

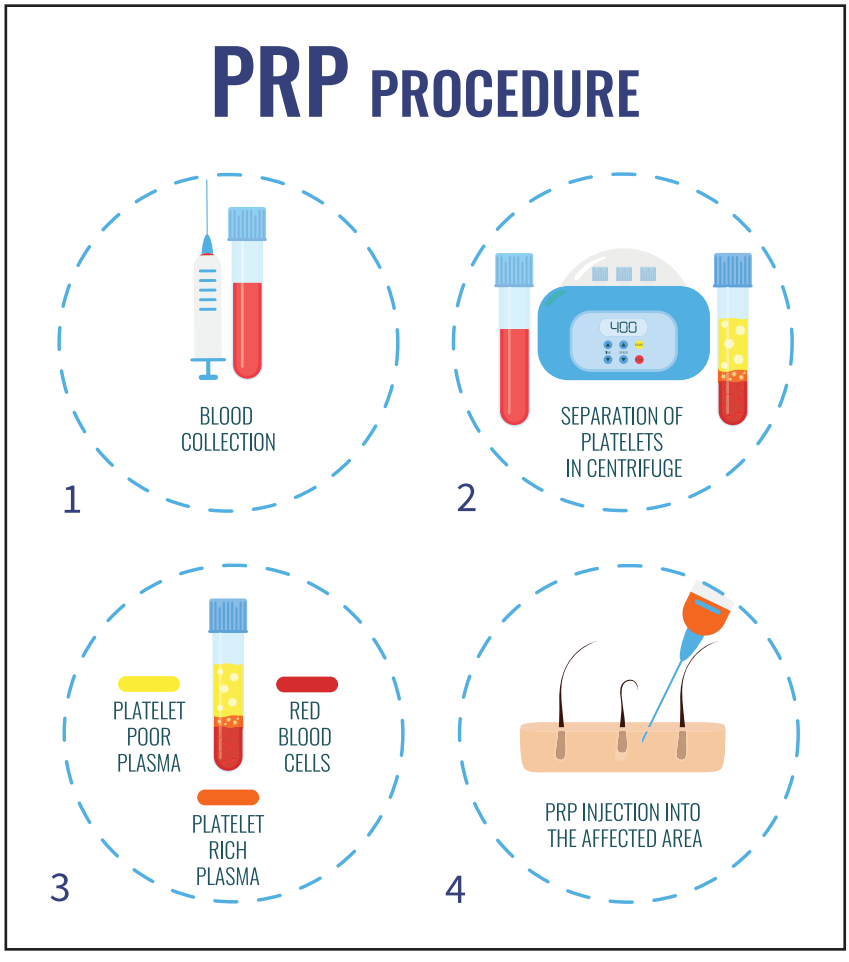
For example, common PRP uses include chronic tendon injuries at the knee, elbow and Achilles tendon. However, currently no study data confirms PRP is actually more effective than traditional treatments. Likewise, PRP appears to show little to no benefit in healing after an anterior cruciate ligament or rotator cuff surgery. And, studies looking at its effectiveness in meniscus repairs are ongoing.

One common use of PRP is in treating knee osteoarthritis, and some report the benefits can last as long as two years. Even so, clinical guidelines generally do not recommend PRP for osteoarthritis due to a lack of definitive clinical efficacy,[5] which could be demonstrated in double blind, peer-reviewed study data where no bias enters into the results.[2]

Finally, long-term studies on the effectiveness of PRP are not only limited but challenging since they must take into account consistent rehabilitation programs and patient compliance with them, particularly with home-based programs. However, Phase I and II studies on post-injection PRP for Achilles tendinopathy have found supervised rehabilitation programs increased exercise compliance and improved outcomes.[1]

PRP Preparation

PRP originates from a peripheral blood draw that is then placed into a centrifuge that separates whole blood components into plasma and red blood cells, leukocytes and other proteins, the concentrations of which are dependent on preparation, both device- and protocol-specific. There are various schools of thought on the platelet concentration needed for beneficial effect. In some literature reviews, it is suggested that PRP should have anywhere from a five



to 10 times greater concentration of platelet growth factors than whole blood, with leukocytes and monocytes (part of the innate immune system), T and B lymphocytes (adaptive immune system) and other components present in varying amounts, depending on the preparation method used. Others suggest lower concentrations such as 1.6 to five times that of whole blood[4] with 80 percent platelet recovery.[5] While preparation methods and formulations are unique, many think that leukocyte-rich PRP may have a greater therapeutic impact thanks to its potential for tissue healing and remodeling.[1]

There are two main types of PRP preparation devices. In medical office settings, a gravitational centrifuge is often used to isolate the buffy coat layer from the blood. This process can take about five minutes, and fresh PRP preparations are given to the patient at each visit. Another preparation uses a continuous flow disk separation technique. Not only are the yields between the two techniques different, but so are the concentration, purity and viability. Platelet surface receptors, called integrins, and adhesion molecules will also affect PRP.[1]

Unfortunately, PRP clinical studies are often inconsistent in referencing how formulations are prepared, making their outcomes difficult to extrapolate in a larger discussion of PRP effectiveness.

Platelet Dosing

Theoretically, one would assume that higher platelet counts would equate to better healing outcomes, but this has not necessarily been demonstrated. Neither a definitive optimal PRP concentration nor PRP dosing as of yet has been determined. Differences between base platelet counts, a patient's age, PRP preparation methods, delivery modes, etc., can all impact healing.

In fact, at least one study showed that very high concentrations of platelet growth factors may be counterproductive, with detrimental effects possibly due to too few available receptors.[1] That being said, high concentrations of PRP are commonly delivered to the target site, particularly for regenerative therapies.

The age of a patient plays into the quantity of PRP needed to be effective since aging has a negative effect on the quality of stem cells, growth factor receptors, etc. However, some preliminary studies demonstrate it may be possible that PRP could have a positive impact on cellular senescence, particularly in aging cartilage. Decreases in inflammation in osteoarthritic patients have also been demonstrated when PRP is injected into the subchondral bone, particularly when combining high concentrations of PRP with bone marrow aspirate concentrates.[1]

PRP Applications

PRP is frequently used to help ease chronic pain, and clinical evidence of PRP in these modalities appears to be favorable treatment for inflammatory responses associated with osteoarthritis of the knee. However, a recent double blind study of PRP found no significant difference in patient outcomes over a saline placebo, echoing an earlier double blind study of PRP in ankle arthritis. In fact, in the osteoarthritis trial, patients receiving PRP had a statistically greater significant incidence of cartilage thinning. However, participants who received PRP also generally reported better functional movement in a year follow-up, although the investigators did not believe that PRP had slowed disease progression.[2]

Costs and Insurance

PRP can cost a patient hundreds of dollars per treatment and is generally not covered by insurance. A review of the Centers for Medicare and Medicaid Services (CMS) website shows CMS covers PRP only for certain chronic, non-healing wounds when all the following conditions are met: 1) The patient is enrolled in a clinical research study that addresses a particular set of questions regarding chronic non-healing diabetic, pressure and/or venous wounds using validated and reliable methods of evaluation; and 2) Clinical study applications for coverage pursuant to this National Coverage Determination were approved by Aug. 2, 2014.[6]

Final Thoughts

Despite the questions and inconsistencies surrounding PRP, demand continues to grow, and physicians are challenged with meeting that demand while counseling patients on a lack of definitive information that confirms its effectiveness. While some believe PRP can speed healing and reduce painful inflammation, until confirmation of these results are demonstrated in repeatable double blind clinical studies, the question concerning its effectiveness remains inconclusive. ❖

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The Proven Success of Immune Globulin Therapy to Treat Chronic Inflammatory Demyelinating Polyneuropathy

Numerous studies show the efficacy of both IVIG and SCIG for treating CIDP, making these the best treatment options for this rare neurological disease.

By Lee Warren

CERTAIN DEBILITATING CONDITIONS can leave doctors and patients frustrated as they grasp for understanding and answers. Chronic inflammatory demyelinating polyneuropathy (CIDP) is certainly one of those conditions. It affects relatively few people and hides behind symptoms that masquerade as any number of neurological ailments. But once a diagnosis has been made, patients are finding hope with clinical breakthroughs and successful treatment study results. The path to managing CIDP isn't an easy one, but in many cases, patients are seeing their quality of life increase.

What Is CIDP?

CIDP, a rare autoimmune disorder, is reported in one to two new cases per year per 100,000 people.[1] Symptoms of CIDP generally develop over eight weeks and include tingling or loss of all feeling in fingers and toes, weakness in arms and legs, loss of tendon reflexes, fatigue and unusual feelings in the body.[2] The disease can be present for years prior to a diagnosis, so the prevalence reflecting the accumulation of cases over time may be as high as nine per 100,000.[1]

Given its rarity, the disease is difficult to diagnose because the symptoms are similar to Guillain-Barré syndrome (GBS), which has been referred to as CIDP's cousin. Distinctions include the following: GBS is considered acute and begins with an infection, while CIDP is chronic with no infection present. Making CIDP even more difficult to

diagnose is the fact that more than 15 sets of diagnostic criteria have been used over the last 50 years.[3]

CIDP is not genetic, and its cause is unknown. The disease can be traced to inflammation of nerves and nerve roots. As swelling occurs, it can destroy the protective covering around nerves, known as myelin, which can hurt nerve fibers and slow the nerves' ability to send signals. This is the cause of patients' numbness, weakness, pain and fatigue.[4]

In general, CIDP affects more men than women and is more common in those over 50 years of age.[5] Ten percent of the cases are in children, rarely occurring in children under the age of 1 year.[6]

History and Diagnosis

Hermann Eichhorst, MD, a German neurologist, first described patients with CIDP in 1890.[6] In the 1950s, inflammatory polyneuropathies responded to treatment with corticosteroids. By the 1970s, chronic recurrent inflammatory polyneuropathy was described as a separate disease. Finally, in the 1980s, Peter J. Dyck, MD, and colleagues introduced the English name of CIDP.[7] Since then, many varieties and diagnostic criteria have appeared.

In addition to GBS, CIDP can be misdiagnosed as other diseases that impact the nervous system, including multiple sclerosis and amyotrophic lateral sclerosis, making the diagnosis of CIDP a process of elimination. It can include a physical exam to evaluate symptoms, which also may include blood sample collection, a neurologic evaluation, an electromyography test, a lumbar puncture or spinal tap, an MRI or a nerve biopsy.

Treatment Options

Several treatment options are available including:

- *Plasma exchange.* This process removes proteins from a patient's blood, including proteins that may cause the disease, and then returns his or her white and red blood cells, as well as platelets, back into the patient's circulation.
- *Corticosteroids.* These drugs imitate the effects of hormones produced by the body to suppress the immune system and reduce inflammation.
- *Physical therapy.* This helps recondition a patient's muscle strength, function and mobility.
- *Immune globulin (IG) therapy*. While many patients respond to plasma exchange, corticosteroids and/or physical therapy, others become resistant to them or develop side effects that cause them to discontinue treatment. This issue led to studies to find a safer and more effective method of treatment, namely intravenous immune globulin (IVIG) therapy, followed by subcutaneous immune globulin (SCIG) therapy.

IVIG Success

IVIG provides antibodies to block the immune and inflammatory processes that attack and destroy myelin. IVIG therapy was established based on five randomized, placebo-controlled trials between 1993 and 2008[8] in which the percentage of patients with improved disability at 24 weeks was much greater (54 percent) when compared with a placebo (21 percent). IVIG responders also achieved maximal response by week six. In addition, Medical Research Council muscle and grip strength saw significant improvement. In the extension phase of these studies, 87 percent of IVIG-treated patients remained relapse-free over an additional 24 weeks compared to 55 percent of placebo-treated patients.

One systematic review[9] of randomized controlled trials conducted between January 1985 and May 2008 analyzed 332 participants, with five of the studies (235 participants) comparing IVIG against a placebo. In these studies, a significantly higher proportion of participants improved in disability within one month after IVIG treatment compared with a placebo (risk ratio [RR] 2.40, 95% confidence interval [CI] 1.72 to 3.36; number needed to treat for an additional beneficial outcome 3.03 [95% CI 2.33 to 4.55], high-quality evidence). However, the review noted that the improvements may not be equally clinically relevant since each trial used different disability

Features of SCIG versus IVIG in CIDP Treatment[19]

Infusion	SCIG	IVIG
Concentration	20% solution infused subcutaneously	10% solution infused intravenously
Volume infused	Generally smaller amounts* (recommended maintenance dose: 0.2 g/kg bw up to 140 mL/session; maximum 50 mL/site)	Larger amounts (typical maintenance dose: 1 g/kg bw)
Frequency of dosing	Administered weekly in 1 or 2 sessions over 1-2 consecutive days	Every 3 weeks
Administration	Can be self-administered after training from an HCP	Requires administration by a trained HCP — usually at a clinic or at home
Duration of infusion	Approximately 1 hour (20-50 mL/hour)	Approximately 4-6 hours

** Based on an equivalent dose in grams* *bw = body weight; HCP = healthcare professional*

Characteristics of Patients Who May Be Suitable for Switching to SCIG Treatment for CIDP[19]

- Poor venous access
- High risk for intravenous-related adverse events (e.g., patient with a port)
- Requiring more frequent infusions to manage their disease
- Having systemic adverse reactions on IVIG (e.g., headache and nausea)
- Preference for independence and flexibility (often due to work, travel, responsibilities, lifestyle)
- Lack of reliable access to infusion clinic or home nurse visits (patient living a long distance from clinic, without own transportation, without insurance to cover home visits)
- Inconvenience of infusion clinic or home nurse (due to unpredictable work or personal schedule, difficulty taking time off from work)

scales and definitions of significant improvement.

A study[10] of 30 CIDP patients (16 men, 14 women) who received IVIG treatment were compared with 23 people (12 women, 11 men) who were given a placebo; there were two dropouts in the placebo group and one in the IVIG group. The mean average muscle score improved at day 42 when comparing IVIG with placebo (0.63 versus –0.1, p = 0.006), and improved strength was seen by day 10. The placebo group lost strength over this same interval. In the IVIG group, 11 subjects improved by the functional disability scale and none worsened. This differed (p = 0.019) from those in the placebo-treated group (two improved, two got worse and the rest remained unchanged).

In another study[11] of 119 CIDP patients who received treatment three times a week for up to 24 weeks (59 received IVIG-chromatography [IVIG-C] purified treatment, and 58 received a placebo), the IVIG therapy was more successful. Fifty-four percent of patients on IVIG-C (10% caprylate/chromatography purified) treatments showed improved functional disability at 24 weeks in comparison to 21 percent of those who received the placebo; 60 percent of patients showed a maximal IVIG response by six weeks.

Even with such results, reports suggest the effects of IVIG can wear off for some patients between doses, and some patients experience adverse effects to IVIG. This makes them good candidates to transition to IG therapy that is administered via the subcutaneous route (SCIG), which was approved by the U.S. Food and Drug Administration (FDA) in 2018.

SCIG Success

SCIG is a process in which IG infusions are given by slowly injecting purified IG into fatty tissue underneath the skin. This requires patients or caregivers to administer one to three injections per week to multiple injection sites based on personal preference, often in the lower abdomen. SCIG doesn't require venous access or premedication, and it has a reduced frequency of systemic adverse events than IVIG, making it a good option for some patients, especially given the clinical results of SCIG therapy.

A short-term observational study[12] reported successful results after reviewing four-month follow-up data of 66 CIDP (and 21 multifocal motor neuropathy) patients who transitioned from IVIG to SCIG treatment. The Overall Neuropathy Limitation Scale score improved in the group of 66 CIDP patients (P = 0.018), with one subject reporting a worsening of one point. This study confirmed the short-term clinical equivalence of SCIG versus IVIG and a possible improvement in the patients' perception of a therapeutic setting with SCIG.

A long-term study[13] followed 17 CIDP patients (10 men, seven women) over seven years to consider the safety, tolerability and patients' perception of SCIG treatment. All patients had been treated with IVIG every four to six weeks before being switched to SCIG treatment. Fifteen of the 17 patients exhibited a good SCIG compliance. The other two patients decided to stop treatment after two years and six years, respectively. Another patient returned to IVIG for personal reasons, despite a clear clinical stabilization. And one patient was not satisfied with SCIG, so she continued with steroids and IVIG boluses, still with mild benefit. When submitted to the Life Quality Index questionnaire score, all 17 patients evidenced an improvement. During the follow up, two patients relapsed four and 36 months, respectively, after starting SCIG treatment.

The Polyneuropathy and Treatment with Hizentra (PATH) study[14] published in 2019 showed SCIG was efficacious in CIDP maintenance. One hundred and seventy-two subjects were randomized to placebo (n = 57), 0.2 g/kg IgPro20 (n = 57) and 0.4 g/kg IgPro20 (n = 58). Much higher proportions of IgPro20-treated subjects improved and maintained their health status on the EQ-5D usual activities dimension, as well as in additional dimensions (mobility and pain/discomfort) in sensitivity analyses. TSQM and WPAI-GH scores were more stable with IgPro20 treatment compared with placebo.

Another study[15] included 15 CIDP subjects who transitioned from IVIG to SCIG, with four of the participants meeting one of two endpoints. According

to the study, the Short-Form 36-item Health Survey showed a statistically significant improvement for the domain of role limitations-physical after 24 weeks (P = .03), with no significant differences observed in other domains. The Treatment Satisfaction Questionnaire for Medication and Chronic Acquired Polyneuropathy Patient-Reported Index also showed significant differences in favor of SCIG (P = .003 and .02, respectively). No significant differences were observed in efficacy after 24 weeks, except for limb motor strength testing, which favored SCIG (P = .003). Eight of the 12 study completers (67 percent) continued treatment with SCIG.

Most recently, a study[16] was conducted to assess whether facilitated SCIG (fSCIG) 10% could prevent relapse in patients with definite or probable CIDP who had received stable IVIG for equal to or more than 12 weeks before screening. The Phase III, double-blind, placebo-controlled ADVANCE-CIDP 1 trial conducted at 54 sites in 21 countries found that CIDP relapse was reduced with fSCIG 10% versus placebo. And while adverse events were more frequent with fSCIG 10% than placebo, severe and serious adverse events were less common.

Further Study: FcRN Inhibitors

The use of FcRN inhibitors, or blockers, to treat CIDP is currently under investigation.

One such FcRN inhibitor, efgartigimod (VYVGART), has been approved by FDA to treat myasthenia gravis (MG), another autoimmune neuromuscular disease. One study[17] included treatment with efgartigimod alfa plus hyaluronidase-QVFC and led to a significantly lower risk of relapse. The study evaluated 322 adults with CIDP for up to 12 weeks. Responders from Stage A were randomly assigned efgartigimod alfa plus hyaluronidase-QVFC or a placebo for 48 weeks (Stage B). Patients in Stage A showed that 67 percent (n = 214/322) of patients met the primary endpoint. Among the 221 responders who entered Stage B, treatment with efgartigimod alfa plus hyaluronidase-QVFC reduced the risk for CIDP relapse by 61 percent at week 48 compared with a placebo.

Rozanolixizumab (Rystiggo), another FcRN inhibitor, is also being assessed for CIDP treatment. It is being developed to treat autoimmune diseases and has been approved in the United States for treatment of generalized MG in adults who are anti-acetylcholine receptor or anti-muscle-specific kinase antibody positive. In a study[18] conducted between 2019 and 2021, in which 17 subjects were given a subcutaneous injection once weekly for 12 weeks, five did not complete it due to lack of efficacy; one withdrew. Seventeen subjects were given a placebo; four did not complete it due to lack of efficacy, one relapsed and none withdrew.

It should be noted there are no direct parallels that can yet be drawn between these products and IG treatments.

IG Offers the Greatest Efficacy

Presently, IVIG and SCIG offer patients the most promising treatment. The remarkable clinical results, enhanced muscle and grip strength and a higher rate of relapse-free periods offer a compelling picture of its efficacy. And, while IVIG has been a lifeline for many and may continue to be for some patients, SCIG offers a more convenient, well-tolerated and potentially longer-lasting solution for many patients. ❖

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Why Bedside Manner Matters — and How to Make Yours Better

Patient-centered care is more than a buzzword: It's a behavior that makes good doctors *great*.

By Rachel Maier, MS

IMAGINE THIS: An overworked, burned-out physician with a long list of patients still to be seen bustles through an exam room door to see a patient who has been waiting for over an hour. The physician barely looks at the patient before bombarding him with questions, then sends the patient away with a prescription and a promise that taking it for a week will cure his ailment. The physician leaves the room as quickly as she came into it, moving on to the next exam room while the patient walks away unsure the doctor really heard him and not at all confident the prescription will help. The patient leaves feeling like a problem to fix, not a person to treat.

As a medical provider, you might be good at diagnosing and treating ailments, and the medication you prescribe may indeed alleviate patients' symptoms, but knowledge, know-how and a bottle of pills aren't nearly enough for treating patients well.

The best doctors aren't just educated: They're also empathetic. Good care is competent, but great care is also compassionate. It values and prioritizes the provider-patient relationship. Great care remembers patients are people, not just problems, and it treats them accordingly, working hard to establish and maintain trust. The best providers understand that patients who feel comfortable with their doctors are more likely to follow the recommended care plan, which can lead to improved outcomes.

And it goes further than that, too: For everyone who works in the healthcare industry — doctors, physician assistants, nurses, medical assistants, the list could go on — the difference between good patient care and great patient care comes down to bedside manner.

What Is Bedside Manner?

An integral part of patient-centered care, bedside manner involves the attitude and actions with which a medical professional interacts with patients. It's a broad term that encompasses many things: dress, deportment and demeanor, as well as bearing and behavior. Bedside manner can be either good or bad, but either way, one knows it when one sees it.

Poor bedside manner can also be many things, but it is often dismissive, rude, condescending or even detached, disinterested or distracted. It is often associated with lack of patient trust. Patients who do not perceive their providers as caring are less likely to put their confidence in them.[1]

On the other hand, good bedside manner is influenced by providers' unique personalities and temperament. Providers who are friendly and attentive, make eye contact and offer a kind touch are consistently described as having good bedside manner, and patients who report good communication with their doctors are more likely to be satisfied with their care.[2]

Poor bedside manner diminishes patients' humanity, while good bedside manner preserves patients' dignity.

Reasons to Improve Bedside Manner

Treating a patient with respect is of the utmost importance, but there are other reasons to prioritize good bedside manner:

1) *Patients care about it.* In 2020, Healthgrades and Medical Group Management Association conducted an analysis of 8.4 million healthcare provider reviews and published its findings in the Patient Sentiment Report. The report provides insights into how patients experience healthcare and the factors that most strongly influence their perceptions of care quality.[3] It showed patients consistently cite bedside manner as a major influence upon their perception of a given provider. In fact, 59 percent of all comments mentioned bedside manner, including the doctors' personalities, the patients' comfort with their doctor and how doctors made patients feel.[3]

2) *It reduces patient stress.* "Patients bring fear, anxiety and self-pity into the exam room," says Barry D. Silverman, MD, a cardiologist in Atlanta, Ga.[4] Worrisome symptoms make them feel uncertain and even hopeless, and they seek the opinion and expertise of trained medical professionals for help. According to Dr. Silverman, "it has always been the doctor's responsibility to calm their fears and provide hope. The accomplished doctor has a bedside manner that is humane and compassionate, empathetic and supportive."[4] Clinicians' positive, upbeat and kind manner can put patients at ease, help them feel more comfortable and ultimately reduce stress during a difficult situation.

3) *It improves patient outcomes.* Patients who feel rushed during appointments tend to underreport their symptoms and/or concerns, and they also tend to shy away from asking questions. But when patients leave out important, relevant information, their outcomes can be negatively affected. However, a positive attitude and a kind word from a provider who demonstrates genuine concern about and care for patients can encourage them to share more openly, which can ultimately have a positive influence on patients' recovery.[5] But it's not just about what providers say, it's also about how they express it. "With good bedside manner, providers are ultimately able to improve communication and reduce errors," according to UCLA's David Geffen School of Medicine.[6] "[Good bedside manner] is a crucial part of their patients' recovery. Not only does it affect how patients feel in the hospital, but also how much they learn about caring for themselves at home."

Good bedside manner understandably puts patients at ease. It can even influence patients' perceptions of how well a care plan or given treatment is working. "Patients who perceive that their doctor has good bedside manner are more likely to view their treatment as effective, more likely to be treatment-compliant and more likely to experience a reduction in symptoms and improved recovery," says Sophia Parnas, MS, clinical psychologist and lead author of "Navigating the Social Synapse: the Neurobiology of Bedside Manner."[7]

While good bedside manner is related to better outcomes, bad bedside manner is also related to poor outcomes, and in some situations, can even be considered malpractice. "While bad bedside manner is not a direct medical error, it can impact the quality of care a patient receives," explains Donovan, O'Connor and Dodge, a law firm that represents patients suffering repercussions of medical malpractice.[1] "Patients who feel disrespected or ignored may be less likely to trust their doctor's advice or comply with their potentially lifesaving treatment plans [...] For example, if a doctor's dismissive attitude causes a patient's condition to worsen, resulting in additional medical expenses or lost wages, the patient may be able to pursue a malpractice claim."

4) *It fosters a positive patient experience.* Doctors may be knowledgeable and accomplished, but if they have poor people skills or even just a bad attitude,

Take Time to C.A.R.E.

C — Connection
Establish a bond with patients right away. Greet them by name and shake their hand. *Smile.*

A — Attention
Make eye contact. Ask questions and listen to the answers. Focus on the person, not just the condition.

R — Respect
Remember your patients are people. Consider the situation from their point of view. Listen to their concerns without dismissing them. Avoid using medical jargon, and use language they can understand.

E — Empathy
Let patients know you understand, and show them you care.

they can negatively affect the patients' perceptions of their overall experience, even if the providers are competent. "Patient experience has less to do with the final result of care provided and focuses instead on the delivery of the healthcare a patient receives from a provider in entirety — clinical and nonclinical — from the perspective of the patient."[8] In other words, the principles of good bedside manner ought to extend beyond the exam room. Every interaction between patients and the practice or hospital, from specialists and support staff to online portals and parking spaces, ought to be professional, courteous and conducted with patients in mind. Things such as plenty of accessible parking; friendly and courteous support staff; after-hours contact information; limited wait time; updated and easy-to-navigate websites; clean, stocked restrooms; even a clean, comfortable waiting room — demonstrate providers care about the patients' overall experience.

5) *It increases healthcare professionals' job satisfaction.* According to HospitalCareers.com, "healthcare professionals who find that they get along more easily with their patients also tend to enjoy their careers more than those who don't value their patients."[5] Further, they tend to "receive more favorable reviews, work harder than their peers and find success throughout their career as they're granted additional opportunities to advance in their career."[5]

8 Ways to Improve Bedside Manner

1) *Connect with your patients.* Enter the room with a smile, and greet patients by name. Pronounce patients' names correctly; if you're unsure, politely ask for clarification. Introduce yourself to patients and anyone accompanying them. Shake hands and smile. Break the ice by asking open-ended questions when you first meet them. Ask them about their weekend plans, whether they are enjoying the sunshine (or tired of the rain) or what grade they are in at school. Showing an interest in them will help put them at ease.

2) *Be aware of body language.* Sit down, unfold your arms and make eye contact. *Smile*.

3) *Really listen.* Ask what brings them in today. Let your patients tell their stories. Actively listen to what they have to say. To the best of your ability, enter clinical notes into patients' charts after patients are done talking.

4) *Show empathy*. Consider the situation from their point of view. Be honest and direct without being rude or condescending.

5) *Value their time.* Don't rush through the appointment. Make sure to focus your attention completely on them with what little time you do have, and don't abruptly leave the room.

6) *Use language patients understand.* Avoid medical jargon. Choose simple lay terms instead. Be candid but diplomatic.[9]

7) *Develop a care plan together*. Treat patients as equal partners in their care.[9] Ask for their input and, if possible, give them choices.

8) *Validate patients' feelings.* Show your patients you "get it." Acknowledge their concerns and reassure them they are in good hands. Ask if they have any questions or if there is anything else you can do for them.

Practice Makes Progress

Bedside manner is a nebulous and yet necessary part of practicing medicine that is — in theory — easy to learn, but in reality takes discipline to develop. Learning from colleagues who have excellent reputations is a helpful practice: Watch how they interact with patients and incorporate what you observe into your own interpersonal style.

And remember: Bedside manner is all about building trust. Providers see patients when they are at their most vulnerable. They're often in the middle of a stressful situation; worried about what their symptoms might mean; uncomfortable with divulging personal information to strangers; uncertain about what their future holds. They come to medical providers for expertise, experience and empathy, but before providers can address the medical problem, they must put their patients at ease so that they can better focus on listening and responding to what the providers are saying.

Patients want to be seen as people, not just problems. Taking the time to develop good bedside manner is a worthy pursuit, one that will elevate good doctors to great ones. As the father of modern medicine Sir William Osler once said, "The good physician treats the disease; the great physician treats the patient who has the disease." ❖

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Update on Molluscum Contagiosum

Though mostly benign, this bothersome skin disease could be dangerous for those with a compromised immune system. But while an effective, FDA-approved treatment specially formulated for the highly contagious poxvirus has eluded the disease — that's no longer the case.

By Jim Trageser

MOLLUSCUM CONTAGIOSUM is one of the most easily spread skin diseases, making it so common that public health agencies don't even know how many people contract it each year. In fact, the infection is very mild for the vast majority of patients; the lesions typically do not cause pain or itching and tend to heal without treatment, so finding a cure has not historically been a high priority.

But for those with a compromised immune system, molluscum contagiosum can lead to dangerous secondary infections — as well as making these individuals more susceptible to contracting secondary infections in the first place. And for HIV-positive patients, a case of molluscum contagiosum can be an indication their disease is advancing to full-blown AIDS.

Fortunately, a new, FDA-approved treatment offers physicians an effective tool to tackle molluscum contagiosum.

What Is Molluscum Contagiosum?

Although it had been described even earlier, molluscum contagiosum was named in 1817 by British doctor Thomas Bateman, MD, FLS. However, the infection was also referred to by other names until 1899, when an editorial in the *Journal of the American Medical Association* endorsed Dr. Bateman's suggestion.[1]

Soon after, German physician Fritz Juliusberg published a paper in 1905 explaining how he had extracted the virus he thought responsible for molluscum contagiosum from a patient's lesions.[2] Later, it was discovered that a type of poxvirus — the molluscum contagiosum virus (MCV) — is responsible for the disease.

There are four subtypes of the virus, designated MCV-1 through MCV-4. MCV-1 is responsible for 98 percent of all cases and is almost always the cause of pediatric molluscum contagiosum.[3] The other variant present in North America and Europe is MCV-2, which is generally responsible for sexually transmitted cases (that primarily affect the immunocompromised).[3] The other two variants are confined to Asia and Australia.

Notably, MCV is confined to the epidermis: It cannot be spread through coughing or sneezing or the exchange of bodily fluids.[4]

Pediatric MCV is most prevalent among younger children, ages 2 to 5.[3] The virus can be spread through physical contact or by touching infected items such as toys, towels or playground equipment. It can also spread further on a patient's skin through scratching or picking at the lesions.

While MCV is less common in adults, it does occur, and by the same infectious pathways. There have been recent reports that it has also spread through tattoos[5] and eyebrow stitching.[6]

Among patients with a compromised immune system, particularly older teens and adults with HIV, transmission is the same as with healthy children but also is spread through sexual contact. It is estimated that as many as one-third of all HIV-positive patients will develop MCV at some point.[7]

For reasons that are not entirely understood, the virus seems to be more common in tropical climates.[8]

Infection with MCV does not provide immunity or protection against future infection.[9]

Symptoms and Progression

The primary symptom of molluscum contagiosum is the appearance of small, round bumps referred to as "mollusca."[10] They may be either pink in color or the same color as the surrounding skin.[11] The lesions are small, generally with a diameter of a quarter of an inch or less. After a few weeks, the center of the lesion will collapse, leaving a white, waxy core that gives them a distinctive appearance often described as

similar to a doughnut or bagel. The lesions are generally painless. In some patients, the lesions may cause minor itchiness.[10]

In children, the lesions will most often appear on the arms and legs, the trunk or the face. The number of mollusca can vary widely, from one or two to large clusters containing dozens.

In most patients, there are usually no other accompanying symptoms, not even those often associated with a viral infection such as aches, fever or fatigue. (Those symptoms, if they appear in conjunction with the lesions, may be a sign of a more serious, secondary infection.[12])

In most healthy patients, the mollusca will disappear sometime after six months to two years with no treatment.[13]

In sexually transmitted cases, MCV will manifest as lesions on the genitals, thighs or lower abdomen.[13]

Immunocompromised patients typically have far more lesions than a healthy patient, with more than 100 lesions not uncommon. The lesions can also be far larger than the typical quarter inch or smaller diameter in healthy patients — up to three-quarters of an inch or more.[14] In patients with weakened immune systems, the lesions will not show any sign of healing even after several months.

In addition, the mollusca can host secondary bacterial infections, particularly in immunocompromised patients.

There have also been reports of patients reacting to the medicines used to treat molluscum contagiosum, with one child developing an autoimmune disease in response to an off-label application of imiquimod (Zyclara and Aldara).[15]

Another complication occurs when the lesions appear on the eyelids or other tissue near the eyes, which can lead to a form of conjunctivitis.[16]

Patients are contagious so long as the mollusca are visible; once the skin clears, patients are no longer shedding the virus.[4]

Diagnosis and Treatment

Due to the distinctive appearance of the lesions, diagnosis is usually made by an examination of the mollusca. If there is any doubt, a tissue sample can be sent to a laboratory for confirmation.[17]

For most patients, simply waiting for the body's immune system to get rid of the MCV is the proper course of action. Young children who may spread their lesions or create scarring by scratching or scraping them may be encouraged to cover their lesions. In those cases where there is itchiness, analgesic medications may be used to relieve the symptoms. Patients with another skin condition such as eczema may require treatment to remove the lesions.

Patients with HIV or another immune disease are likely to require treatment as well. When HIV-positive patients contract MCV, it can be a sign that the disease is progressing, and further tests may be called for to determine the state of the immune system and whether the patient is developing AIDS.[18] If an HIV patient presents with MCV, the physician should order tests to check the patient's immune system.

Patients may desire immediate physical removal of the lesions, and this can be accomplished via cryotherapy (applying liquid nitrogen to freeze the cells and kill them), scraping them off or burning them off with a laser. However, the Centers for Disease Control and Prevention cautions that each of these methods will not only result in post-procedural pain and itching, but also carry the risk of permanent scarring.

Other off-label treatments that take longer to remove the lesions but don't carry the risk of scarring include:[19]

- Imiquimod: a prescription topical medication that stimulates the body's immune system (It is approved by the U.S. Food and Drug Administration [FDA] to treat genital warts and skin cancer, but has also shown promise in promoting the healing of MCV lesions.)
- Sinecatechin: a prescription topical medication developed to treat genital warts
- Salicylic acid: an over-the-counter topical treatment for warts that shows promise against MCV
- Tretinoin: an anti-acne medication applied to the lesions that provokes the body's immune system

In severe cases in which patients with eczema also have extremely large patches of MCV lesions, and the above medications have not proven effective, the oral ulcer medication cimetidine has shown some success.[18]

The primary symptom of molluscum contagiosum is the appearance of small, round bumps referred to as "mollusca."

Until just this year, treatment options were limited to these off-label drug uses,[20] but FDA recently approved a new treatment specifically for MCV: YCANTH (catharidin) topical solution 0.7%.[21]

What Is YCANTH?

YCANTH is the first and only clinically proven treatment option formulated specifically to treat molluscum contagiosum. In summer 2023, Verrica Pharmaceuticals received FDA approval

for this new treatment for adult and pediatric patients 2 years of age and older. YCANTH is administered to patients only by healthcare providers who apply a single application of the medicine on the areas of patients' skin with molluscum bumps every three weeks as needed.

The efficacy of YCANTH was established in two double-blind, randomized, placebo-controlled trials (Trial 1 [NCT03377790] and Trial 2 [NCT03377803]). In the trials, 528 subjects ranging from ages 2 to 60 years with molluscum contagiosum were randomized by household to receive either YCANTH or a placebo treatment. Subjects received treatment or placebo at 21-day intervals until bumps were completely cleared or for a maximum of four applications. A healthcare professional who was blinded to the treatment group counted the number of lesions at each visit. The primary efficacy endpoint was the proportion of subjects achieving complete clearance of all treated molluscum bumps by day 84. Results showed 54 percent of subjects treated with YCANTH achieved complete clearance of all treated molluscum bumps by day 84 compared to 13 percent of subjects treated with placebo.

The most common adverse reactions to YCANTH occurred at the application site and included blistering, pain, itching, scabbing, reddening, discoloration, dryness, edema (swelling) and erosion of the skin. According to the researchers, life-threatening or fatal toxicities can occur if administered orally. As such, contact with the treatment area should be avoided, including oral contact, after treatment.

Prevention

There is no vaccine for molluscum contagiosum. The best prevention is to avoid physical contact or sharing clothes, bedding or toys with someone who is infected. Since most cases occur in young children, it is important that when patients are contagious their parents work to reduce the risk of transmission by covering lesions if in a group environment and by limiting the sharing of towels or bedding in the home.

In adults, chances of contracting sexually transmitted MCV can be reduced by using a condom, but it will not eliminate the risk completely, as MCV is spread through skin contact and not bodily fluids.[21]

Continuing Research

Due to the mild nature of most cases of molluscum contagiosum, there is relatively little research into treating or curing it. In the fall of 2023, there were fewer than two dozen clinical studies listed in clinicaltrials.gov. Several of them were looking at the effectiveness of using potassium hydroxide on MCV lesions. Another, completed early in 2023, looked at the antiviral topical berdazimer,[22] which shows promise against MCV. If granted final FDA approval, it could be on the market in 2024. And, while there are a handful of studies looking at further potential uses of cantharidin in treating MCV, YCANTH is a proven FDA-approved treatment for molluscum contagiosum available now.

Looking Ahead

Because of its highly contagious nature and the difficulty of devising a vaccine for a virus that resides in the outer layer of skin, physicians are likely to continue helping patients mitigate against MCV for the foreseeable future. Thankfully, the newly FDA-approved YCANTH is now a viable, available option for effectively treating it.

While most otherwise healthy patients will heal on their own, those with weakened immune systems need quick diagnosis and treatment, and YCANTH is an effective solution that meets this critical need. ❖

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- Itchiness *, soreness, or swelling of affected skin

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The FDA urges caregivers not to use OTC products that claim to treat molluscum: no OTC products for molluscum have been approved by the FDA[2]

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[1]https://www.cdc.gov/poxvirus/molluscum-contagiosum/index.html
[2]https://www.fda.gov/consumers/consumer-updates/safely-treating-molluscum-common-skin-condition#:~:text=The%20FDA%20has%20approved%20Ycanth,only%20by%20health%20care%20professionals.

Myths & Facts: Plasma Donation

Dispelling the misconceptions about donating plasma could help to shore up the worldwide shortage of this lifesaving blood component used to treat rare and chronic diseases.

By Ronale Tucker Rhodes, MS

PLASMA DONATIONS save countless lives each year. Donated plasma is used to produce a variety of plasma-derived medicines that are often the only therapies for many rare and chronic diseases.[1] Some of the uses of plasma include treatment for trauma, burn victims, cancer patients and those with immune system disorders.[2]

Plasma is the single largest component (55 percent) of human blood that acts as a transporting medium for cells and a variety of substances vital to the human body.[1] It is composed of approximately 92 percent water, with the remaining eight percent a mix of vital substances such as glucose, hormones, proteins, mineral salts, fats and vitamins. The proteins in plasma include antibodies that alert the immune system to the presence of potentially harmful foreign substances.[2]

According to Olgam Life, a plasma donation service, there were 737 plasma donation centers in the U.S. in 2018.[3] In 2010, approximately 19.8 million plasma donations were made. Nine years later, the annual number of donations was 53.5 million. Unfortunately, however, the number of donations significantly declined in the following two years.[4] While the blame for this is mostly due to the pandemic, a myriad of misconceptions about donating plasma also contribute to the decline. Therefore, it is crucial that individuals understand the facts about plasma donation to help save the lives of those treated with these critical therapies.

Separating Myth from Fact

Myth: Plasma donation isn't necessary because people can just donate blood.

Fact: Individuals are allowed to donate blood only every 56 days (or approximately every two months) for a total of six donations per year.[5] However, because plasma is 92 percent water and regenerates much faster than blood, individuals can donate plasma up to two times per week. In fact, countries that collect source plasma rather than extracting it from blood (known as recovered plasma) are about 800 percent more efficient.[6]

The critical starting material for medicine used to treat patients with immune disorders, critical care in hospitals, hemophiliacs, etc., is plasma. It cannot be synthetically produced and is dependent on the generosity of donors who take the time to donate.

Myth: Only certain individuals can donate plasma.

Fact: It's true that not everyone is eligible to donate plasma, but most are.

According to Olgam Life, eligibility criteria ensure both the safety of the donor and the quality of the collected plasma. Generally, donors must be at least 18 years old and weigh at least 110 pounds (50 kilograms). They must be in good health and pass a medical examination. Additionally, potential donors must complete a health history questionnaire to rule out risky behaviors and exposure to certain diseases. However, it's important to note that these criteria may vary slightly among different plasma donation centers.[2]

In addition, individuals can donate plasma regardless of their blood type. The plasma used in therapeutic treatments is known as AB plasma, which is universal, meaning it can be given to anyone. As such, the plasma of people with an AB blood type is especially helpful. But, again, it doesn't matter what the blood type is; plasma from any blood type can be used in therapeutic treatments.[2]

Myth: Donating plasma is painful.

Fact: Many people believe donating plasma is painful, but that's not necessarily true. Donating plasma is similar to donating blood. During the donation process, a small needle is inserted into a vein in the arm, which can result in a little discomfort.[7] After the needle is inserted, staff at the donation center do all they can to make donors comfortable throughout the process. The one difference between plasma and blood donation is that individuals are also required prior to plasma donation to submit to a finger stick test each time so the collection center medical staff can evaluate their protein and hemoglobin levels.[8]

Myth: Plasma donation is time-consuming.

Fact: Yes, the plasma donation process is more time-consuming due to the health screening process and the process of separating the plasma from the blood, but it still only takes a little longer than donating blood. The first plasma donation appointment typically takes approximately two hours, while subsequent appointments take about 90 minutes.[8]

Myth: Donating plasma increases one's risk of getting sick.

Fact: While some people think donating plasma can make them sick, it is completely safe and is monitored by trained professionals throughout the donation process. In fact, strict safety protocols regulated by the U.S. Food and Drug Administration ensure both the safety of donors and the quality of plasma products.

Plasma is a type of apheresis donation, which means the donor gives blood with the help of a machine that draws out whole blood, centrifuges (i.e., spins to separate) it, retains the plasma and then returns the other blood products back to the donor, all through the same needle. This allows the collection of a greater quantity of plasma without risking the health of the donor. A single donor can safely donate up to four units (pints) of plasma every four weeks due to its abundance in the body and ability to quickly replenish.[9]

Plasma donation in collection centers

Parsing Out Plasma Therapies

Plasma Protein	Used to Treat	Outcomes
Immune globulins	• Immunology immunodeficiencies • Neurology immune-mediated diseases • Hematology • Dermatology	• Infection prevention • Regulation of overreacting immune system • Improved quality of life • Increased life expectancy
Clotting factors	• Bleeding from trauma • Overdosage of anticoagulants • Liver disease • Bleeding disorders • Other rare coagulation disorders	• Improved quality of life • Increased life expectancy
C1 esterase inhibitor	• Hereditary angioedema	• Improved quality of life • Increased life expectancy
Alpha-1 protinase inhibitor	• Alpha-1 antitrypsin deficiency	• Improved quality of life • Halts disease progression
Hyperimmune globulins	• Rabies, tetanus and hepatitis • Rh negative pregnancy • Transplant therapy	• Prevention • Treatment • Protection of babies in utero
Albumin	• Cardiac surgery • Liver disease • Severe infections • Emergency and surgical medicine	• Lifesaving in severe situations • Decreased morbidity and mortality

Source: Plasma Protein Therapeutics Association. Plasma. Accessed at www.pptaglobal.org/plasma#plasma-therapies.

Plasma Donation FAQs

- Individuals between the age of 18 and 69 years are eligible to donate plasma.
- A plasma donation can range from 690 mL to 880 mL depending on the donor's weight.
- Approximately 70 percent of the globally collected plasma is used to treat primary immune deficiencies.
- The U.S. is the largest exporter of plasma, contributing around 70 percent of the global supply.
- Approximately 55 percent of blood is plasma.
- Plasma is used in the treatment of a variety of autoimmune diseases such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy.
- The process of collecting plasma is called plasmapheresis. It separates the plasma from the blood cells, which are then returned to the donor.
- Plasma donors are often compensated for their time and can typically receive, on average, $500 per month, depending on what state they live in.

Source: Olgam Life. Plasma Facts and Info. Accessed at olgam.com/usa-plasma-donation-statistics.

is performed in a highly controlled, sterile environment by professionally trained medical staff. All plasma collection equipment is sterilized, and any equipment that comes into contact with the donor is used only once to eliminate the possibility of transmitting viral infections.[8] In addition, all supplies used in the donation process are single use.[6]

All new plasma donors go through medical screening during which their vital signs, hematocrit and total protein levels are checked, a physical exam is performed, and medications and health conditions are reviewed. Only when they are determined to be healthy to donate are they allowed to. Indeed, many potential donors do not pass this rigorous health screening. If they are allowed to donate, each time they return, they go through another medical screening and are allowed to donate only if their vital signs, hematocrit or total protein levels are in range. Protein levels are also checked periodically, and if they are not within range, the donors are temporarily deferred until the protein levels return to normal.[6]

There is of course, as with any other procedures, a small risk of side effects. Bruising and nerve irritation are among the most common side effects, typically around the injection site, which can be treated with cold packs. Nerve irritation causes immediate, intense pain at the injection site and can cause shooting pain down the arm and into the hand. If this happens, a technician will immediately remove the needle.

More serious risks of donating plasma may be a drop in blood pressure, which can result in lightheadedness or fainting. Other possible side effects include sweating and paleness, weakness, sudden warmness and nausea or vomiting. Dizziness and blurred or tunnel vision may also occur. A citrate reaction could occur if individuals are sensitive to the chemical citrate, which is added to the separated blood to prevent clotting. If a severe citrate reaction occurs, the donation process is halted. When the remnants of the donation are returned, individuals may experience tingling around their mouth, face, hands or feet. More severe reactions include cramping of the hands or feet, sudden weakness, muscle spasms, chills and shaking, nausea or vomiting, and numbness around the mouth.[10]

Myth: Plasma donations are used only for research.

Fact: While research is critical for the advancement of science and medicine, only a very small number of plasma donations are used for research. Rather, the majority of plasma donations are used to produce important medicines that treat patients with rare and chronic conditions but also to treat victims of severe shock, trauma and burns. They are also used to provide temporary immunity in life-threatening situations such as potential exposure to rabies, tetanus and hepatitis A or B.[11]

When plasma donations are used in research, frequently it is to characterize plasma-treated cells in specific applications, for example in cytokine release and cell count viability. Currently, researchers in search of treatments and cures for serious diseases such as autoimmune disorders and hemophilia use antibodies and proteins found in human plasma to support their work. In addition, different types of proteins (including antibodies) and small molecules are found in human plasma that have the potential to be made into new and existing therapeutics.[9]

Myth: The history of plasma donation is controversial so people should question it.

Fact: Donating plasma *has* raised some ethical questions for some time. The reason? Plasma donors are paid. The global demand for plasma continues to rise by six to eight percent each year, and the United States supplies two-thirds of the world's blood plasma, the majority of which is used to develop lifesaving drugs and to treat life-threatening conditions. There is no synthetic substitute for plasma, so drug manufacturers rely on a steady stream of human donors to make up their supply. Treating just one patient with plasma therapies for a year takes between 130 and 1,300 donations. Unfortunately, global demand for plasma

far outpaces supply. "The bottom line is if the U.S. didn't compensate donors, there would not be enough plasma and lives would be lost globally," the president of the Immune Deficiency Foundation wrote in a February 2019 statement.[12]

Myth: Plasma donor centers target the disadvantaged.

Fact: The fact that plasma donors are paid has led many to believe that donor centers target low-income individuals. It's true that many individuals donate plasma to supplement their income. A study from the Center for Health Care Research and Policy found that 57 percent of donors at one Cleveland center reported at least a third of their income that month would come from donating plasma. But, others donate to help save lives.[12]

Still, the donor suitability and screening process is the same for all donors whether they are low-income or high-income.[6] In addition, payment for donations does not change depending on a person's income. In fact, donation centers don't inquire about individuals' income.[2] The only factor donation centers consider is the donors' health.

Myth: Many plasma donors donate to support unhealthy lifestyles, so the quality of plasma could be tainted.

Fact: While it's true that compensation is beneficial, especially for those who need it, individuals are intensely screened to ensure that any effects of unhealthy lifestyles don't affect the quality of the plasma. Again, strict health screenings are conducted at the beginning of each donation to help ensure the donor is healthy. Every single donation is also tested for transmissible diseases such as HIV, hepatitis A, B, C and syphilis.[6] Throughout the entire process, a donor interacts with a minimum of four staff members who are trained to identify signs and symptoms that suggest an unhealthy lifestyle. If a donor does not pass the strict health screening criteria, he or she cannot donate plasma.[11] Those donors are then entered into a national database that plasma centers must check prior to registering a new donor.[6] And, if an approved donor's medical tests come back positive for certain viruses/diseases, his or her plasma is immediately destroyed.[13]

In addition to screening, plasmapheresis and fractionation are intensive processes that create clean, safe plasma for those in need. As mentioned earlier, plasmapheresis is a sanitary, self-contained, automated process during which plasma is separated from red blood cells and other cellular components of blood that are then returned to the donor. According to the Plasma Protein Therapeutics Association, the manufacturing process is known as fractionation. During fractionation, "proteins are separated to create a number of plasma protein therapies using well-established purification methods such as precipitation, centrifugation, separation and filtration. Fractionation employs time, temperature, pH and alcohol concentrations to extract specific therapeutic proteins. These are then subjected to various purification methods and viral inactivation and removal processes to further ensure their safety and efficacy. Preparing a therapy often takes between seven and 12 months between donation and final product release. This sets the production of plasma protein therapies apart from chemical pharmaceuticals and other biologics whose manufacturing processes are much more condensed and whose direct manufacturing costs are a significantly smaller portion of the overall cost. In addition, fractionators invest substantially in research and technologies to increase the quality of proteins extracted from plasma, known as the "yield," and create new and more effective therapies."[14]

Dispelling the Myths Now

Donating plasma is a selfless act. It saves lives, and it is the only way to provide those who require plasma protein therapies with the treatments they need to survive. What's more, donating plasma is safe, and adverse events are infrequent.

The future of treatments with plasma-derived therapies depends on the supply of plasma. Unfortunately, misconceptions about plasma donations can prevent people from donating, ultimately contributing to plasma shortages. Healthcare providers can help to prevent shortages by encouraging their patients to donate plasma, as well as by setting the example by donating plasma themselves. ❖

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Chronic Inflammatory Demyelinating Polyneuropathy: *A Patient's Perspective*

By Trudie Mitschang

IN JULY 2020, Angye Hawkins was a fit and active 67-year-old who kept in shape by walking up to five miles a day. It was during one of those walks that she noticed her posture had become slumped and she had a hard time standing up straight. The following week while enjoying another walk, she recalls feeling unusually fatigued, with a pronounced weakness in her legs. "I called my daughter and said I didn't think I could make it home on my own," explains Angye. "She had to get the car and come pick me up, which was very concerning. I immediately scheduled an appointment with my primary care doctor for the following week to find out what might be wrong."

Angye underwent a battery of tests, including X-rays and a CAT scan, but results were inconclusive. Meanwhile, her condition continued to deteriorate and within weeks, she was unable to lift her arms, lost more feeling and function in her legs and began using a walker to get around. Soon, she says, her feet and ankles became completely numb. "It was devastating, and I was scared — I didn't know what was going on with me and I thought I was going to keep declining," she recalls. "I went from being very independent to being unable to drive, feed or even toilet myself. It felt like my body was caving in on itself."

Alarmed by Angye's sudden lack of mobility, her doctor referred her to a neurologist where she underwent a thorough exam, including an electromyogram to test her nerve function and response. Ten days later, she was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP), three months after the onset of her initial symptoms.

Immediately following Angye's diagnosis, she was admitted to the hospital for a five-day course of intravenous immune globulin (IVIG) and both physical and occupational therapy. Although thankful for the attentive care, Angye recalls one big challenge was the COVID-19 protocols in place at the time that kept her from having visitors. "The nurse encouraged my daughter to come around the side of the hospital near my window. She would call me on the phone, and we could at least see each other while we talked. It was a very strange time."

Thankfully, the IVIG treatment plan quickly began restoring some of Angye's mobility and function, but she says it was the additional two weeks of rigorous therapy that really made a difference. She spent as much as four hours each day relearning how to climb stairs, roll over in bed, safely get into and out of the shower and even fold laundry. Her treatment plan continued at home for an additional six weeks as she navigated the long road toward recovery.

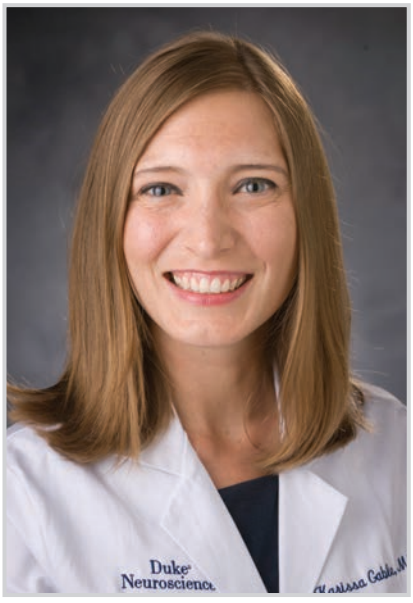
As part of her ongoing treatment plan, Angye receives IVIG every three weeks at home, and once her insurance approved it, she was prescribed the immunosuppressant mycophenolate (CellCept), which she credits with greatly restoring her quality of life.

In terms of her formerly active lifestyle, Angye is back to walking most days (she's proud to be clocking a quarter of a mile without her walker and a mile and a half when using it). Angye also joined a CIDP Facebook support group to meet others who share her diagnosis. "I credit the early diagnosis and intervention and the emphasis on physical and occupational therapy that helped me regain a measure of my independence," says Angye. "I recently turned 70, and my condition is manageable. My goal is to encourage others not to give up and to keep seeking support and answers." ❖

Understanding CIDP

- CIDP is a neurological disorder that involves progressive weakness and reduced senses in the arms and legs.
- CIDP is caused by damage to the fat-based protective covering on nerves called the myelin sheath.
- One of the challenges with diagnosing CIDP is that medical experts do not know exactly what triggers it, and unlike Guillain-Barré syndrome, there is usually no infection preceding the condition, nor is there a genetic link.
- Although CIDP can occur in anyone, people in their 50s and 60s seem more likely to develop it than other age groups, and men are twice as likely as women to get the disease.

Source: Johns Hopkins Medicine. Chronic Inflammatory Demyelinating Polyradiculoneuropathy. Accessed at www.hopkinsmedicine.org/health/conditions-and-diseases/chronic-inflammatory-demyelinating-polyradiculoneuropathy.



CIDP: *A Physician's Perspective*

KARISSA L. GABLE, MD, is a neurologist in Durham, N.C., and is affiliated with Duke University Hospital. In 2019, she was awarded a research grant to investigate the pathophysiologic mechanisms of chronic inflammatory demyelinating polyneuropathy (CIDP) by the GBS|CIDP Foundation International.

BSTQ: What are early warning signs of CIDP?

Dr. Gable: The symptoms of typical CIDP include progressive symptoms of symmetric muscle weakness and sensory changes in the arms and legs. These symptoms progress over the course of eight weeks or more. Typically, this is painless weakness of the upper arms, upper legs and hands and feet, along with numbness, tingling or sensory loss. Although there are variants with asymmetric weakness, focal limb, pure motor or pure sensory, or types that just affect the hands and feet, the typical variety is the most common.

BSTQ: How is CIDP typically diagnosed?

Dr. Gable: Typical CIDP is diagnosed by meeting the criteria of symptoms (muscle weakness and sensory loss) in a certain pattern of the type of muscles affected (upper arms and legs, feet and hands) and also includes certain features on the exam findings that a neurologist can test for such as loss of reflexes. The other component of the diagnosis involves blood testing, as well as electrodiagnostic testing. Electrodiagnostic testing will show what part of the nerve is affected. Also, certain criteria should be met to help support the diagnosis. Sometimes, that is all that is needed if the diagnostic criteria are met. However, sometimes further supplemental testing is required such as imaging studies or spinal fluid testing.

BSTQ: How does CIDP differ from Guillain-Barré syndrome (GBS)?

Dr. Gable: GBS is a monophasic disease, meaning it occurs rapidly, creates symptoms of muscle weakness and sensory loss that progress over a few days to weeks, but typically symptoms are at the worst at around a month after symptom onset and do not progress beyond eight weeks. CIDP has similar symptoms but those symptoms progress beyond eight weeks. Although symptoms are similar, the underlying disease processes are different and, thus, are treated differently with some treatment overlap. Not all treatments that work for CIDP work to treat GBS. And, GBS does not need to be treated long term, while CIDP is a chronic autoimmune disease and treatment is required long term in at least two-thirds of patients.

BSTQ: What can you tell us about your grant to study the origins of CIDP?

Dr. Gable: My area of interest in this grant was to look at the underlying immunologic signature of patients with CIDP who were on treatment with stable disease and compare that to patients without autoimmune neuropathy, as well as healthy controls. Understanding the underlying immunologic details of CIDP can help provide more understanding of how the disease works, which should in turn help determine if there are other targets or subgroups of patients who may respond to one treatment better than another, as well as ideally identify active disease or CIDP that is in remission.

BSTQ: What role does physical therapy play in an effective treatment plan?

Dr. Gable: Supportive care such as physical and occupational therapy, in addition to the right medication treatment, is so important as part of the treatment of CIDP to help get patients back to the best quality of life.

BSTQ: Are there any promising or innovative new treatment advances?

Dr. Gable: There are a number of new targets for medications in development that are very exciting for providing more options for patients going forward. One novel target is in the area of complement inhibition. Other neuromuscular autoimmune diseases seem to respond to complement inhibition well, so it is of interest to see how this could apply to CIDP. Another novel target is the anti-FcRn inhibitor class of medications and their potential use in CIDP. Initial data publicly released regarding preliminary results in the ADHERE study are promising. Having additional options that are effective beyond the first-line therapies of corticosteroids, immune globulin and, in some cases, plasma exchange just broaden the opportunities to tailor medication treatment to the individual and provide better long-term treatment options. ❖

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Coming Soon: Dried Plasma for Hemorrhagic Trauma in the Prehospital Setting

By Keith Berman, MPH, MBA

UNCONTROLLED BLEEDING continues to be the leading cause of preventable death in victims of trauma. Whether it's a civilian or a wartime combatant, the primary field management goal for an individual experiencing severe acute hemorrhage is to restore blood pressure and maintain perfusion of vital organs. Most hemorrhagic trauma victims with survivable injuries can be stabilized with infusions of crystalloids alone until they reach surgery. It is only in a minority of cases — mainly rapidly bleeding individuals facing a hospital transport time well exceeding 20 minutes — in which there is meaningful survival benefit from prehospital transfusion of red blood cells (RBCs).*

Yet too often in cases of severe acute trauma-related blood loss when blood pressure has been quickly restored in the field and surgeons successfully control bleeding at the site or sites of vascular injury, death ensues anyway over the next several hours. A seminal 1982 study of major abdominal vascular injuries in 123 patients found that 89 percent of mortality was attributable to bleeding, yet half of these hemorrhage-related deaths occurred after mechanical control of bleeding sites.[1] The cause of this early mortality is seriously deranged coagulation function, or what leading specialists now call trauma-induced coagulopathy (TIC). While tissue injury, shock and other variables play a role in this complex and incompletely understood phenomenon, a key contributor is extensive hemodilution resulting from prehospital administration of saline or other crystalloid solutions.[2]

Crystalloid resuscitation has been confirmed in several large case series to be an independent risk factor for coagulopathy.[3,4] In an analysis of 8,700 multiply injured patients, increasing amounts of intravenous fluids administered prior to ER admission were associated with an increasing incidence of coagulopathy. Coagulopathy was observed in more than 40 percent of patients who had received greater than 2,000 mL of intravenous fluids, in more than 50 percent of those who had received greater than 3,000 mL and in more than 70 percent in those administered greater than 4,000 mL.[3]

Particularly concerning is the effect of crystalloid hemodilution on the circulating levels of fibrinogen. Fibrinogen is the most abundant coagulation factor in blood, whose conversion to fibrin clots and facilitation of platelet aggregation at bleeding sites is crucial for hemostasis. Despite its high circulating concentrations, fibrinogen is the first coagulation factor to reach critically low levels in severely bleeding patients.[5] Blood loss, consumption of fibrinogen by clot formation at wound sites and increased degradation due to acidosis all act to reduce circulating fibrinogen. Hemodilution resulting from large-volume administration of crystalloids also drives down the fibrinogen level, but in this case there is an alternative: transfusing fibrinogen-rich donor human plasma instead.

* We are naturally equipped with a large reserve of oxygen-delivering RBCs and other compensatory mechanisms, so that partial arterial oxygen pressure remains largely unaffected in otherwise healthy individuals who have lost nearly half of their RBCs through blood loss — as long as their blood volume can be restored with crystalloid blood volume replacement. Assuming the heart and lungs are functioning normally, the patient may be able to tolerate further hemodilution down to as little as 5 g/dL or even lower with preservation of adequate oxygen perfusion while en route to the trauma operating room where blood can be promptly transfused.

The Superiority of Early Prehospital Plasma

Recently with support from the U.S. Army Medical Research Command, the concept of transfusing plasma in the prehospital setting was put to the test. Its landmark multicenter, cluster-randomized PAMPer trial compared the administration of two units of thawed plasma plus standard-care resuscitation with standard-care resuscitation only during air medical transport of 501 hypotensive, tachycardic trauma patients. Mortality at 30 days was sharply lower in the plasma group than the standard-care group: 23.2 percent vs. 33.0 percent. Notably, the median prothrombin-time ratio was also lower in the plasma group after arrival at the trauma center, indicative of better overall hemostatic function.[6]

A body of research from experience in the Iraq and Afghanistan military conflicts has also shown that early transfusion of plasma together with RBCs in a ratio approaching 1:1 also improves long-term outcomes in severely bleeding combat casualties. A chart review of 246 patients requiring massive transfusion at a U.S. Army combat support hospital documented dramatically lower overall and hemorrhage-related mortality rates in patients transfused at a higher plasma-to-RBC ratio (Figure 1).[7]

A separate review of 708 patients admitted to a combat support hospital who received blood products similarly found that each transfused unit of plasma was independently associated with increased survival (odds ratio 1.17; 95 percent confidence interval 1.06 to 1.29; p = 0.002).[8]

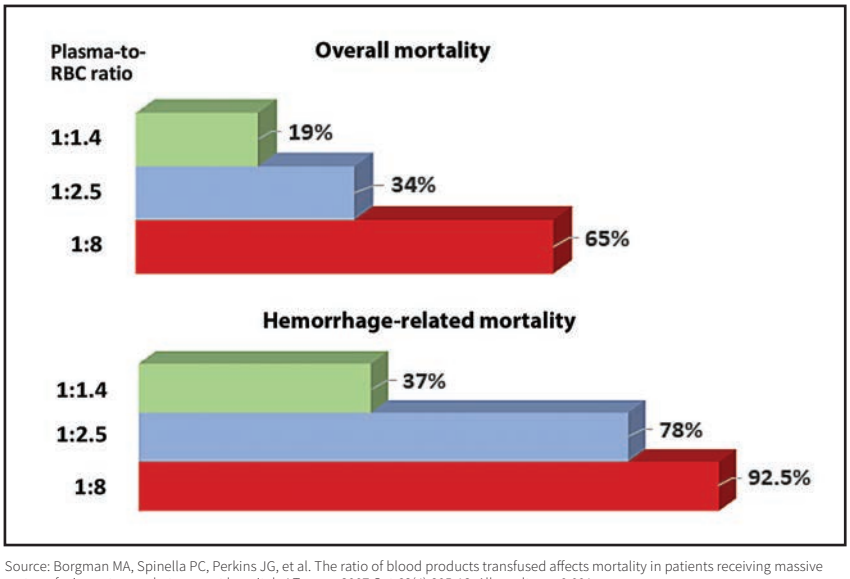
But a number of logistical constraints have limited the number of regional trauma systems that have incorporated thawed plasma on their evacuation helicopters. Prehospital transfusion is even more problematic for civilian ground ambulances, as well as rural or remote hospitals without blood banks.[9] Plasma stored in the frozen state takes about 30 minutes to thaw using conventional equipment, then must be stored in the refrigerated state and transfused within five days; most of this plasma must be rotated back to the hospital blood bank before expiry or discarded. Consequently, the transport, storage and inventory management requirements to routinely carry thawed plasma on helicopters or ground ambulances is very costly, and payment policies for these services rarely compensate blood product costs.

Past Experience with Dried Plasma

A far better option for carrying plasma on air or ground ambulances is a dried plasma product that can be stored for an extended period without refrigeration, and rapidly reconstituted with the appropriate volume of sterile water. But this idea is not new. Decades before most specific coagulation factors were even discovered, it was intuited that the protein-rich plasma running through our arteries and veins was the ideal early resuscitative fluid to give to severely bleeding trauma victims during transport to the hospital.

Recently with support from the U.S. Army Medical Research Command, the concept of transfusing plasma in the prehospital setting was put to the test.

Figure 1. Mortality in Massively Transfused Trauma Patients as a Function of Plasma-to-Red Blood Cell (RBC) Transfusion Ratio



Source: Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* 2007 Oct;63(4):805-13. All results p < 0.001.

Methods to lyophilize plasma were first developed and successfully tested in animals and humans in the 1930s.[10,11] Large-scale production and use of freeze-dried plasma began in World War II with the distribution of more than six million units of pooled, lyophilized plasma to U.S. fighting personnel. However, attempts with different pathogen reduction strategies to resolve the inevitable problem of hepatitis transmission by these pooled units were unsuccessful, and by the 1960s, dried pooled plasma was essentially abandoned.[12]

But beginning in the 1990s, improved donor screening and the advent of effective pathogen reduction technologies gave new life to the possibility of dried plasma. Today, three modern dried plasma products are manufactured and available in France, Germany and South Africa (Table). The German and French products are stable for 15 months and two years, respectively, at room temperature, and require just a few minutes to reconstitute. Limited quantities of the dried plasma product manufactured by the French Military Blood Institute have been purchased by the U.S. military since 2018 under an emergency use authorization.[7]

Investigational Products in the Pipeline

While no dried plasma products are approved for civilian use, several companies are actively developing investigational lyophilized or spray-dried plasma products, including Teleflex, Velico Medical, Terumo Blood and Cell Technologies and Octapharma. To facilitate their efforts, the U.S. Food and Drug Administration (FDA) recently published a guidance document providing specific recommendations for plasma sourcing, manufacturing and product quality assurance.[13]

Two companies in particular — Velico Medical and Teleflex — have advanced their dried plasma products into clinical testing on healthy volunteers. If proven safe and shown to have acceptable coagulant and anticoagulant activities, one or both could be approved for marketing in the very near future.

EZ-PLAZ Freeze Dried Plasma (Teleflex). With annual sales of $3 billion, Teleflex manufactures and sells a diverse range of medical technologies for use in surgery, vascular access, anesthesia, emergency medicine and other areas. Its investigational single-donor, freeze-dried plasma (FDP) product was originally developed by researchers at Vascular Solutions, which Teleflex acquired in 2017.

In collaboration with the U.S. Army Medical Research and Materiel Command, the safety and tolerability of up to three units of this FDP, produced from each study participant's own plasma, was evaluated in a Phase I clinical trial involving 24 healthy subjects; the comparator was autologous fresh frozen plasma (FFP) administered to the same study participants.[14]

FDP coagulation factors, clotting times and product quality following lyophilization were all preserved, with slight prolongation of mean clotting times and minimal or modest reductions in the mean content of fibrinogen, factors I, V, VII, VIII, IX, XI, XII, protein C, protein S, plasmin inhibitor, plasminogen, antithrombin III and von Willebrand factor antigen compared with the FFP control. Infusions of up to 810 mL per subject were found to be safe, with no instances of serious adverse events. Remarkably, the average time to reconstitute FDP with sterile water supplied with the product was just over one minute (67 ± 15 seconds) (Figure 2). Based on findings from this study, Teleflex submitted a biologics license application to FDA in early 2021; the product's current regulatory status is uncertain.

If approved, Teleflex intends to acquire plasma from type AB donors and/or type A donors with low anti-B titers and manufacture its FDP at its own facility for commercial sale.

FrontlineODP Spray Dried Plasma (Velico Medical). In contrast to Teleflex' manufacturing and commercialization strategy, Massachusetts-based Velico Medical has designed its proprietary technology — the FrontlineODP system — for use by regional blood centers to manufacture dried plasma along with

Table. Dried Plasma Products Commercially Available Outside the U.S.

Brand Name	Manufacturer	Process Highlights
FLYP	French Military Blood Institute (Centre de Transfusion Sanguine des Armees)	Lyophilized Pooled apheresis FFP (<11 donors) Leukocyte reduced Donor screening Amotosalen/UV light pathogen reduction
Lyoplas N-w	German Red Cross	Lyophilized Single donor units Leukocyte reduced Donor screening Frozen ≥4 months for donor retesting
Bioplasma FDP	National Bioproducts Institute (South Africa)	Lyophilized Pooled (up to 1,500 donors) Donor screening Solvent/detergent-based pathogen reduction

FFP: fresh frozen plasma
UV: ultraviolet

Figure 2. Teleflex' Investigational Freeze-Dried Plasma Kit Including Sterile Water and Administration Kit

other blood components they routinely distribute. Velico is developing the FrontlineODP system with support from the federal government's Biomedical Advanced Research and Development Authority.

The spray-dried FrontlineODP product is rapidly reconstituted with 200 mL of sterile water and stable for extended periods in ambient conditions. A Phase I dose-escalation study in healthy adult volunteers is currently in progress to assess FrontlineODP's safety, quality and hemostatic function indicators. This trial is expected to be completed in May. If the results are good, it is possible that FDA will accept these findings as acceptable to review an application for marketing approval of Velico's FrontlineODP system.

While the process of securing approval for a dried plasma product might seem straightforward at first blush, in reality it is not. Development of these products has been slowed or stymied by a number of regulatory and logistical challenges, among which are the following:[15]

- Uncertainty regarding clinical trial requirements to gain approval
- Need to demonstrate container integrity over a one- to two-year shelf life in a range of environmental conditions
- Limited availability of universal type AB plasma, the ideal blood type for prehospital administration
- Need for sufficient investment capital to fund scale-up and commercialization phases through initial product launch
- Testing of single-donor units for potency, purity and other product parameters that is not unduly burdensome or costly

Some experts in the field had anticipated that the first dried plasma product might be licensed and available by now,[11] but that projection has proven too optimistic. Nevertheless, it now appears likely that one or more dried plasma products will be approved and available commercially in the near future.

The Eagerly Awaited Return of Dried Plasma

It is now well-established that prehospital transfusion of plasma, with its balanced mix of coagulation proteins, counters the hemodilution and progressive derangement of hemostatic mechanisms caused by crystalloid-based resuscitation, improving the chances of survival in severely bleeding trauma victims.

Thanks to its long shelf life in lyophilized form and its readiness for reconstitution and transfusion in minutes, dried plasma is conceptually ideal to meet this need. Eight decades ago, dried plasma worked to save the lives of severely hemorrhaging servicemen in WWII, and with its return in the form of new pathogen-safe dried plasma products, it will work again on air and ground ambulances to save lives here at home. ❖

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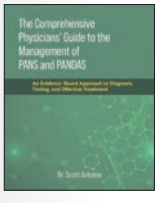
The Comprehensive Physician's Guide to the Management of PANS and PANDAS: An Evidence-Based Approach to Diagnosis, Testing, and Effective Treatment

Author: Scott Antoine, DO

Pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with strep (PANDAS) infections are complex disorders that demand a rich, multifaceted response with novel treatment approaches. The material in this book is assembled from the peer-reviewed medical literature, in combination with more than 30 years of clinical experience caring for the sickest patients, both in and out of the hospital. Physicians will find conclusive evidence for the existence and pathophysiology of PANS and PANDAS, alongside testing and treatment interventions the author has successfully used in his own practice with hundreds of children. The book concludes with rich appendices, including commonly used labs, doses of medications and supplements, a sample flare protocol, extensive support for parents, sample intravenous immune globulin orders and more.



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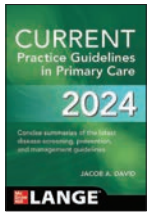
CURRENT Practice Guidelines in Primary Care 2024, 21st Edition

Author: Jacob A. David, MD, FAAFPU



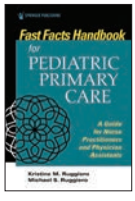
This go-to guide converts the tremendous amount of information on the web into a practical, relevant collection of usable data for busy clinicians. Each topic is carefully selected for relevance to the office practice of ambulatory medicine, and the text is presented in a convenient, easy-to-navigate outline and tabular format. Content is drawn from a wide array of recommendations from government agencies, expert panels, medical specialty organizations and other professional and scientific authorities. New in this year's edition are updates reflecting the review of more than 150 guidelines; updates to guidelines for screening/prevention of ASCVD; anxiety disorders in children; pediatric obesity; chronic pain; neonatal hyperbilirubinemia; osteoarthritis; and numerous additional topics, including screening and prevention of eating disorders, COVID vaccination in pregnancy, prevention of pelvic floor dysfunction, management of chest pain, left ventricular thrombus and delirium.

www.amazon.com/CURRENT-Practice-Guidelines-Primary-Care/dp/1265690162

Fast Facts Handbook for Pediatric Primary Care: A Guide for Nurse Practitioners and Physician Assistants, 1st Edition

Authors: Kristine Ruggiero, PhD, MSN, RN, CPNP, and Michael Ruggiero, DHA, MHS, PA-C

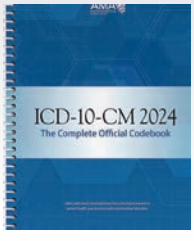
This quick-access reference guide encompasses all key diagnostic and management essentials needed for safe and effective pediatric practice. By incorporating the most current literature and evidence-based practice, this guide explains how to best assess, diagnose and treat common pediatric disorders in an ambulatory care setting. This practical, pocket-sized resource is presented in concise paragraphs, providing access to key information at a glance. Chapters consistently include focused assessment and diagnosis of the most common clinical problems and treatment options.



www.amazon.com/Fast-Facts-Pediatric-Primary-Care/dp/0826151833

ICD-10-CM 2024: The Complete Official Codebook

Authors: American Medical Association



ICD-10-CM 2024: The Complete Official Codebook provides the entire updated code set for diagnostic coding, organized to make the challenge of accurate coding easier. It is the cornerstone for establishing medical necessity, correct documentation, determining coverage and ensuring appropriate reimbursement. Each of the 22 chapters in the Tabular List of Diseases and Injuries is organized to provide quick and simple navigation to facilitate accurate coding. The book also contains supplementary appendices, including a coding tutorial, pharmacology listings, a list of valid three-character codes and additional information on Z-codes for long-term drug use and Z-codes that can be used only as a principal diagnosis. Official 2024 coding guidelines are included in this codebook.

www.amazon.com/ICD-10-CM-2024-Complete-Official-Codebook/dp/1640162909

Outpatient Albumin Infusions Reduce Hospitalizations in Decompensated Cirrhosis: Retrospective Cohort Study

While long-term human albumin administration improves survival in cirrhotic patients with diuretic-resistant ascites, a team of Australian investigators conducted a retrospective cohort study to determine whether there is a significant benefit in more severely affected cases regularly infused with albumin at their institution.

The study population included patients seen at the Royal Melbourne Hospital with a diagnosis of cirrhosis complicated by any of the following: diuretic-refractory (or intolerant) ascites requiring large-volume paracentesis, hepatic hydrothorax or severe peripheral edema. Of a total of 30 patients referred for outpatient albumin infusion between April 1, 2017, and June 30, 2021, 24 patients met the inclusion criteria. The median age was 59.5 years, and etiologies of liver disease included alcohol (n = 12), nonalcoholic steatohepatitis (NASH) (n = 4), hepatitis B or C (n = 2) or other causes

(n = 6). Comorbidities include chronic kidney disease. Assessed outcomes includes transjugular intrahepatic portosystemic shunt (TIPS)/transplant-free survival (TTFS) and biochemical and prognostic outcomes. The median follow-up time was 16 months.

Hospital admissions over the six months after initiating albumin infusions fell to 1.04, from a mean of 2.25 hospital admissions prior to albumin therapy. A particularly steep reduction in portal hypertensive-related admissions was observed (relative risk 0.39; 95% confidence interval [CI] 0.21 – 0.69, P = 0.003). The median TTFS significantly improved in patients with a change in the median model for end-stage liver disease-sodium (MELD-Na) ≤1 at one month: 29.4 months versus 7.7 months (P = 0.011). There was also a statistically significant reduction in the median Child-Pugh Score from 9 at baseline to 7.5 (P = 0.017) at 12 months.

This investigation additionally found that presence of type 2 diabetes mellitus (T2DM) significantly increased the risk of TIPS, liver transplant and death. The study authors concluded that T2DM "should be considered as an important factor when assessing patients for human albumin therapy." ❖

Hannah, N, Tjandra, D, Patwardhan, A, et al. Outpatient Albumin Infusions Reduce Hospitalizations and Improve Outcomes in Decompensated Cirrhosis: A Real-World Cohort Study. *JGH Open*, 2023 Jul 27;7(8):537-44.

Hyaluronidase-Facilitated Subcutaneous Immune Globulin Effective as Maintenance Therapy for CIDP: Pivotal Trial Results

Comprising recombinant human hyaluronidase and 10% human immune globulin (Gammagard Liquid), Takeda Pharmaceuticals' facilitated subcutaneous immune globulin (fSCIG; HyQvia) enables self-infusion of a full therapeutic dose on a less frequent schedule than conventional 16% or 20% SCIG. The Phase III, double-blind, placebo-controlled ADVANCE-CIDP 1 trial was conducted at 54 sites in 21 countries to evaluate whether fSCIG could prevent relapse in patients with definite or probable chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) who had received stable intravenous immune globulin (IVIG) for ≥12 weeks before screening.

A total of 132 patients received fSCIG 10% (n = 62) or placebo (n = 70). fSCIG 10% was administered at the same dose (or matching placebo volume) and interval as pre-randomization IVIG. The primary outcome was patient proportion experiencing CIDP relapse (defined as a ≥1-point increase in adjusted INCAT score from pre-subcutaneous treatment baseline) in the modified intention-to-treat population.

CIDP relapse was reduced with fSCIG 10% versus placebo (9.7% versus 31.4%, respectively) for an absolute difference of -21.8% (p = 0.0045). The probability of relapse was higher with placebo versus fSCIG 10% over time (p = 0.002). Adverse events were more frequent with fSCIG 10% (79.0% of patients) than placebo (57.1%), but severe (1.6% vs. 8.6%) and serious adverse events (3.2% vs. 7.1%) were less common.

The study investigators concluded that "fSCIG 10% more effectively prevented CIDP relapse than placebo, supporting its potential use as maintenance CIDP treatment." ❖

Bril, V, Hadden, RDM, Brannagan, TH, et al. Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% as Maintenance Therapy for Chronic Inflammatory Demyelinating Polyradiculoneuropathy: The ADVANCE-CIDP 1 Randomized Controlled Trial. *Journal of the Peripheral Nervous System*, 2023 Sep; 28(3):436-49.

Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2024, through March 31, 2024

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$982.81	$967.05
	BIVIGAM	ADMA Biologics	J1556	$145.92	$143.58
	GAMMAGARD SD	Takeda	J1566	$157.00	$154.48
	GAMMAPLEX	BPL	J1557	$110.31	$108.54
	OCTAGAM	Octapharma	J1568	$89.96	$88.51
	PANZYGA	Octapharma/Pfizer	J1576	$132.88	$130.75
	PRIVIGEN	CSL Behring	J1459	$96.58	$95.03
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$88.30	$86.89
	GAMMAKED	Kedrion	J1561	$99.57	$97.98
	GAMUNEX-C	Grifols	J1561	$99.57	$97.98
SCIG	CUTAQUIG	Octapharma	J1551	$138.88	$136.65
	CUVITRU	Takeda	J1555	$159.22	$156.67
	HIZENTRA	CSL Behring	J1559	$129.45	$127.37
	HYQVIA	Takeda	J1575	$170.85	$168.11
	XEMBIFY	Grifols	J1558	$141.83	$139.56

Calculate your reimbursement online at www.FFFenterprises.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
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	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	1 g, 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

2023-2024 Influenza Vaccines

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	90685
AFLURIA (IIV4)	Seqirus	5 mL MDV	6 months and older	90685
FLUAD (IIV4)	Seqirus	0.5 mL PFS 10-bx	65 years and older	90694
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-bx	6 months and older	90686
FLUBLOK (ccIIV4)	Sanofi	0.5 mL PFS 10-bx	18 years and older	90682
FLUCELVAX (ccIIV4)	Seqirus	0.5 mL PFS 10-bx	6 months and older	90674
FLUCELVAX (ccIIV4)	Seqirus	5 mL MDV	6 months 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	0.5 mL PFS 10-bx	6 months and older	90686
FLUZONE (IIV4)	Sanofi	5 mL MDV	6 months and older	90685
FLUZONE HIGH-DOSE (IIV4)	Sanofi	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

* Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

COVID-19 Vaccines

Product	Manufacturer	Presentation	Age Group	Code
SPIKEVAX COVID-19 Vaccine, mRNA	Moderna	0.5 mL PFS Blister 10-pk	12 years and older	91322
SPIKEVAX COVID-19 Vaccine, mRNA	Moderna	0.5 mL SDV 10-pk	12 years and older	91322
COVID-19 Vaccine, mRNA	Moderna	0.25 mL SDV 10-pk	6 months to 11 years	TBD
NOVAVAX COVID-19 Vaccine, Adjuvanted	Novavax	0.5 mL SDV 10-pk	12 years and older	TBD

Respiratory Syncytical Virus (RSV) Vaccines

Product	Manufacturer	Presentation	Age Group	Code
ABRYSVO	Pfizer	0.5 mL Kit 1-ctn	60 years and older	90678
ABRYSVO	Pfizer	0.5 mL Kit 5-ctn	60 years and older	90678
AREXVY	Pfizer	0.5 mL SDV 10-bx	60 years and older	90679

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