WINTER 2021

biosupply trends

QUARTERLY

SPECIAL FOCUS:
CRITICAL CARE

COVID-19

Changing the Future of Healthcare

Plasma Therapies:
COVID-19 TREATMENTS?

Pandemic Preparedness:
EVALUATING THE U.S. RESPONSE

Using PPE Properly
IN HEALTHCARE SETTINGS

MYTHS AND FACTS
About Alzheimer's

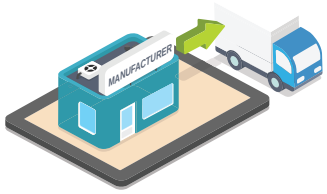
Hyperimmune Globulins: A Promising COVID-19 Therapeutic? p.46

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

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



STEP 2

Storage

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

STEP 3

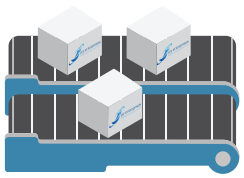
Specialty Packaging

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

STEP 4

Interactive Allocation

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



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

800.843.7477 | Emergency Ordering 24/7

STEP 5

Delivery

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

STEP 6

Methods of Delivery

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

STEP 7

Verification

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

STEP 8

Tracking

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

biosupply trends QUARTERLY

Features

Up Front

BioTrends Watch

BioFocus

BioSources

About BioSupply Trends Quarterly

BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

BioSupply Trends Quarterly (ISSN 1948-2620) is a national publication, with quarterly themed issues.

Publisher: FFF Enterprises, Inc., 44000 Winchester Road, Temecula, CA 92590

Subscriptions to *BioSupply Trends Quarterly* are complimentary. Readers may subscribe by calling (800) 843-7477 x1351.

BioSupply Trends Quarterly accepts manuscript submissions in MS Word between 600 and 2,500 words in length. Email manuscripts to or request submission guidelines at editor@BSTQuarterly.com. *BioSupply Trends Quarterly* retains the right to edit submissions. The contents of each submission and their accuracy are the responsibility of the author(s) and must be original work that has not been, nor will be, published elsewhere, without the written permission of *BioSupply Trends Quarterly*. A copyright agreement attesting to this and transferring copyright to FFF Enterprises will be required.

Advertising in BioSupply Trends Quarterly

BioSupply Trends Quarterly has a circulation of 40,000, with an approximate readership of more than 100,000 decision-makers who are comprised of general practice physicians, hospital and clinic chiefs of staff and buyers, pharmacy managers and buyers, specialist physicians and other healthcare professionals.

For information about advertising in *BioSupply Trends Quarterly*, you may request a media kit from Ronale Tucker Rhodes at (800) 843-7477 x1362, rrhodes@bstquarterly.com.

Enduring a Persistent Pandemic and Preparing for the Next

IT'S ALMOST a year since the pandemic first began ravaging the U.S., leaving healthcare providers grappling with how to care for the millions of Americans who have contracted the coronavirus. Still, scientists do not fully understand how to prevent or treat It. What's more, the healthcare industry is challenged to reframe how it conducts operations to meet the health and safety needs of patients while keeping its businesses afloat.

Clearly, there will be no return to business as normal as we knew it. As we outline in our article "How COVID-19 Is Changing the Future of Healthcare" (p.18), the pandemic has introduced significant scientific, clinical and financial challenges. For starters, the lack of personal protective equipment has shifted medical facilities' priority toward supply chain optimization and analytics to prepare for future scenarios. In addition, the reduction in visitation rates and elective procedures has dramatically decreased healthcare spending, prompting providers to reevaluate how to improve healthcare efficiency.

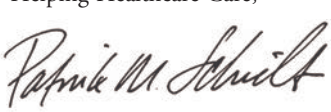
Now, with a second wave of the coronavirus sweeping across the nation, people remain anxious about when scientists will find effective preventive and treatment strategies. Taking a promising place among treatments being investigated as pre-existing therapeutic options are plasma therapies. To shed some light on the three types of plasma therapies — intravenous immune globulin, convalescent plasma and hyperimmune globulins — our article "Plasma Therapies: Effective COVID-19 Treatments?" (p.26) highlights some of the more notable research in progress.

Hyperimmune globulin therapies show considerable potential, as Keith Berman, MPH, MBA, a blood product expert, points out in his article "The Promise of COVID-19 Hyperimmune Globulin Therapy" (p.46). According to Berman, the impetus behind the development of this therapy is to create postexposure prophylaxis for patients, especially those more susceptible for lethal risk. Administering a hyperimmune globulin can protect individuals during the known 14-day lapse between infection and seroconversion, as has been shown to be effective against other diseases.

The overarching question remains, however, beyond a transformation in business practices and the development of effective therapies: What will this pandemic have taught us? Is there a reason the U.S. was so woefully unprepared for this pandemic, and what can be done to ensure this doesn't happen in the future? Our article "Pandemic Preparedness: Ensuring the U.S. Is Ready for the Next One?" (p.32) details how, despite the numerous pandemic preparedness plans created by health organizations, bureaucracy interference obstructed their effectiveness. We must do better.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

biosupply trends QUARTERLY

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.

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

Art Director
Allan Bean

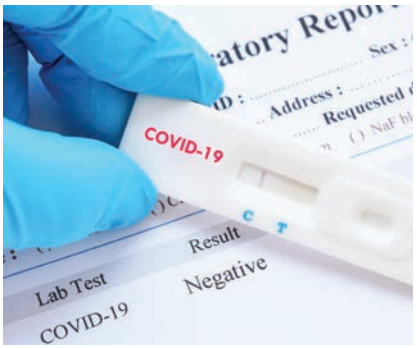
Contributing Writers
Keith Berman, MPH, MBA
Diane L.M. Cook
Bonnie Kirschenbaum, MS, FASHP, FCSHP
Trudie Mitschang
Jim Trageser

MarCom Awards

CISION TOP 10 2010

Please direct editorial, advertising and marketing communications to
44000 Winchester Road
Temecula, CA 92590
Ph: (800) 843-7477
Email: editor@BSTQuarterly.com

HHS and The Rockefeller Foundation to Share Best Practices for Increased COVID-19 Testing



The U.S. Department of Health and Human Services (HHS) and The Rockefeller Foundation have signed an agreement to identify and share effective approaches for using rapid point-of-care (POC) antigen tests to screen for COVID-19 in communities, with a focus on safely reopening K-12 schools. The partnership establishes a pilot program with select cities and states in The Rockefeller Foundation's Testing Solutions Group (TSG), a network of public officials devoted to rapidly scaling COVID-19 testing, tracing and tracking in their communities.

HHS will provide at least 120,000 Abbott BinaxNOW COVID-19 Ag Card POC SARS-CoV-2 diagnostic tests to pilot sites in Louisville, Ky, Los Angeles, New Orleans and Tulsa, Okla. In addition, Rhode Island has been selected as a pilot state.

BinaxNOW is a unique testing option to provide support to K-12 teachers and students, higher education, critical infrastructure, first responders and other priorities as governors deem fit. The rapid test is easy to use and produces COVID-19 test results in 15 minutes. BinaxNOW is the only antigen rapid POC test authorized by the U.S. Food and Drug Administration that does not require a laboratory-based instrument to test the samples; instead, negative or positive COVID-19 results are determined through a test card.

HHS will distribute the tests through its established approach leveraging the logistics expertise of the Department of Defense. The Rockefeller Foundation will help communities define problems, set policy goals, explore options and craft solutions to help them fight the pandemic in a science-based manner. The pilot program will provide essential information on the policies, practices and behaviors that public sector entities need to successfully adopt practices that enable communities to be more resilient.

The POC testing pilot program will also provide data on how testing strategies can be operationalized in laboratories, retail pharmacies and other community entities. In addition, the partnership will help build the capacity of communities across the United States to better prepare for future pandemics, especially in low-income and vulnerable communities.

"This pilot program will generate real-world evidence and identify best practices and lessons learned, as well as metrics on how to effectively integrate testing into school opening and reopening for K-12 students and teachers," said Admiral Brett Giroir, MD, HHS assistant secretary for health. "Our collaboration with The Rockefeller Foundation will inform states and territories on how to develop their own roadmaps for safely keeping children in the classroom, which is critical for their physical, emotional, mental and developmental health." ❖

HHS Teams Up with The Rockefeller Foundation to Share Best Practices for Increased COVID-19 Testing. U.S. Department of Health and Human Services press release, Oct. 1, 2020. Accessed at www.hhs.gov/about/news/2020/10/01/hhs-teams-up-with-the-rockefeller-foundation-to-share-best-practices-for-increased-covid-19-testing.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=october-04-2020.

HHS Launches Initiative to Track Physician Use and Burdens of Health IT

The U.S. Department of Health and Human Services (HHS) launched an initiative to measure health information technology (health IT) use among office-based physicians across the country. The HHS' Office of the National Coordinator for Health Information Technology (ONC) awarded a cooperative agreement to the American Board of Family Medicine (ABFM) to measure the use and potential burdens experienced by office-based physicians. The results of the effort will provide ONC with national-level data on how office-based physicians use health IT, including key measures on interoperability and burden.

This effort builds on prior research that found, in 2017, approximately 80 percent of office-based physicians used a certified electronic health record (EHR), but only one in 10 of those physicians reported they were able to electronically send, receive, find and integrate health data from EHRs outside of their networks. Under the three-year cooperative agreement, the American Board of Family Medicine will:

- Develop key measures related to health IT use and the interoperability of health information;
- Collect data from a nationally representative sample of office-based physicians to support national level progress; and
- Collaborate with ONC on the analysis and interpretation of the survey results.

ONC expects the data will help identify disparities or unintended consequences due to the use of health IT and the impacts of federal health IT policies to guide future policy decisions. ❖

HHS Launching Initiative to Track Physician Use and Burdens of Health IT ONC Awards Cooperative Agreement to American Board of Family Medicine. U.S. Department of Health and Human Services press release, Sept. 29, 2020. Accessed at www.hhs.gov/about/news/2020/09/29/hhs-launching-initiative-to-track-physician-use-and-burdens-of-health-it-onc-awards-american-board-of-family-medicine.html?utm_source=news-releases-email&utm_medium=e-mail&utm_campaign=october-04-2020.

CMS Releases New Tools to Streamline Certification for Labs Testing for COVID-19

The Centers for Medicare and Medicaid Services (CMS) released new tools to reduce burdensome paperwork and authorization delays for laboratories seeking Clinical Laboratory Improvement Amendments (CLIA) certification to test for COVID-19. CMS's quick-start guide helps laboratories with the application process for CLIA certification and includes information on the expedited review process implemented at the beginning of the pandemic that allows labs to start COVID-19 testing before the official paper certificate arrives by postal mail. Laboratories also have a new option to pay CLIA certification fees on the CMS CLIA Program website. Online payments are processed overnight, which is substantially faster than hard-copy checks.

CMS regulates all laboratory testing performed on humans for the purposes of diagnosis, prevention or treatment in the U.S. through the CLIA program. To become CLIA-certified, laboratories must meet performance and quality assurance requirements aimed at ensuring they are able

to deliver reliable and accurate test results for the purpose of proper diagnosis, prevention and treatment of diseases like COVID-19. This new guide provides laboratories with the resources they need to reduce paperwork and streamline the CLIA application and certification process. This quick-start guide outlines the steps laboratories must follow to apply for and receive CLIA certification, including ensuring the form is submitted to the correct state agency.

Prior to receiving certification, laboratories must also pay a user fee to cover the costs of administering the CLIA program, which also includes inspection costs. Laboratories can now pay CLIA certification fees through a secure platform hosted by the Treasury Department on the CMS CLIA Program website. CLIA fees are based on the certificate requested by the laboratory (i.e., Certificate of Waiver, Provider-Performed Microscopy, Accreditation or Compliance) and, in some instances, the annual volume and types of testing performed. The CLIA Certificate Fee Schedule contains detailed information on costs.

"CMS has left no stone unturned in helping fight this highly contagious, dangerous disease," said CMS Administrator Seema Verma. "An obscure process and outdated modes of payment have too often caused needless delays in certifying lab testing facilities. Today's announcement will allow testing laboratories to promptly and painlessly register with CMS so they can get to work, focusing on providing reliable information to combat the spread of this disease." ❖

CMS Releases New Tools to Streamline Certification for Labs Testing for COVID-19. Centers for Medicare and Medicaid Services press release, Sept. 25, 2020. Accessed at www.cms.gov/newsroom/press-releases/cms-releases-new-tools-streamline-certification-labs-testing-covid-19.

CMS Updates COVID-19 Testing Methodology for Nursing Homes

The Centers for Medicare and Medicaid Services (CMS) has updated the methodology it employs to determine the rate of COVID-19 positivity in counties across the country. Counties with 20 or fewer tests over 14 days will now move to "green" in the color-coded system of assessing COVID-19 community prevalence. Counties with both fewer than 500 tests and fewer than 2,000 tests per 100,000 residents, and greater than 10 percent positivity over 14 days — which would have been "red" under the previous methodology — will move to "yellow."

This information is critical to nursing homes, which are required to test their staff for COVID-19 at a frequency based on the positivity rate of their respective counties. Under guidance CMS issued on Aug. 26, 2020, nursing homes must test staff at a frequency of once monthly if the facility's county positivity rate is less than 5 percent. Staff testing frequency increases to once weekly if the county positivity rate is between 5 percent and 10 percent. Finally, testing frequency increases to twice weekly if the county positivity rate exceeds 10 percent. ❖

CMS Updates COVID-19 Testing Methodology for Nursing Homes. Centers for Medicare and Medicaid Services press release, Sept. 29, 2020. Accessed at www.cms.gov/newsroom/press-releases/cms-updates-covid-19-testing-methodology-nursing-homes.

COVID-19 Business Recovery

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

LIFE DURING the COVID-19 pandemic is surreal even after a year. Healthcare organizations are being pressured to do more with less while at the same time contribute revenue to whittle away at staggering losses. The definition of "recover" is to return to normal. Yet certainly, patients are not returning as anticipated. The pandemic has caused a downturn in elective procedures, fewer non-COVID-19 admissions and decreased clinic/office visits, impacting margins and creating technological struggles. And, while some practices have succeeded in reinforcing existing revenues, other haven't.

But beyond recovery, systemic issues predating the pandemic need solutions. Most importantly, providers must evaluate whether they have the tools to generate new revenue streams. This necessitates giving top priority to improved infrastructure, addressing data accuracy and completeness, and knowing who the payers are and their requirements for reimbursing drugs and biologicals either as separate line items or as part of a bundle or package.

Combating Revenue Loss

As the coronavirus continues to plague the country, hospitals may continue to face lower patient volumes, so they must respond to and plan for this possibility. Some are taking drastic measures, including slashing budgets and furloughing workers. Others are cutting specialty care that wasn't previously profitable but provided a continuum of care. Some are developing their own insurance plans since the pandemic has reduced expenses for payers.

However, more strategic approaches include enhanced new revenue streams, integrated systems that bring payers and providers together and improved medication use for Medicare patients. Most importantly, providers need to adapt and avoid missteps often caused by freezing innovation and relying only on what has worked in the past.

As patients become increasingly involved in their healthcare decisions, patient-centricity has become a common goal. Therefore, providers must support positive patient outcomes by prioritizing patient experiences, understanding how they live with their conditions and openly responding to feedback and analytics.

Managing Healthcare Environments

There are numerous environments in the healthcare setting, including acute/inpatient, outpatient, clinics, infusion center, diagnostic areas, the emergency department, observation patient areas, home infusion, ambulatory pharmacy, ambulatory surgery centers (ASCs), physician offices, retail, mail order and specialty pharmacy. And, each has its own payer relationships, requirements, federal manuals and resources. Accordingly, these

settings will determine how compliance and data, clinical documentation, pharmacy and therapeutics committees, electronic health records, charge masters and coding, billing and claims clearinghouses are structured and managed. And, it will require a new focus on billing and reimbursement to optimize the revenue cycle.

Evaluating Site of Care

There are dramatic differences in costs associated with site-of-care choice, with the inpatient setting the most expensive, followed by hospital-based outpatient areas and free-standing ambulatory clinics/ASCs, care in the home either by a home health service or self-care, and telehealth, the latter of which could evolve to hospital-at-home programs that will require communications technology, portable medical equipment and teams of doctors, nurses, X-ray technicians, paramedics and pharmacy services.

When site-of-care expenses decrease, co-pays also decrease, which benefits patients directly. Pandemics, payer mandates and the availability of subcutaneous versus intravenous drugs and biologicals are all reasons for fast pacing site-of-care changes.

An embedded theme in 2021 reimbursement rule sets is increasing choice and encouraging site neutrality. The rationale is to continue to give beneficiaries more affordable choices about where to obtain care with the potential for lower out-of-pocket expenses, including those for surgeries.

The Centers for Medicare and Medicaid (CMS) 2021 rule sets allow hospitals and ASCs to operate with better flexibility and patients to make informed decisions about where they receive care. CMS expanded the number of procedures Medicare will pay for in hospital outpatient settings by eliminating the inpatient-only list over three years. CMS stresses that hospital outpatient departments are subject to the same quality and safety standards as inpatient settings under Medicare rules.

CMS also removed regulatory barriers to give beneficiaries the choice to receive services in a lower-cost setting and the convenience to go home as early as the same day after a procedure when clinicians decide the setting is appropriate. These changes gradually allow more than 1,700 additional services to be paid for when furnished in the hospital outpatient setting, including approximately 300 newly payable musculoskeletal services (e.g., certain joint replacement procedures).

The Centers for Medicare and Medicaid 2021 rule sets allow hospitals and ASCs to operate with better flexibility and patients to make informed decisions about where they receive care.

Because services in ASCs are paid at a lower rate than hospital outpatient departments, patients can potentially lower their out-of-pocket costs even more when receiving care in an ASC. For example, on average, a Medicare beneficiary pays $101 for a common cataract surgery if the procedure is performed in a hospital outpatient department compared to $51 if performed in an ASC.

CMS added 11 procedures Medicare will pay for when provided in an ASC, including total hip arthroplasty. Expanding the number of procedures Medicare will pay for when performed in an ASC gives patients more choices about where they receive care and ensures CMS does not favor one type of care setting over another.

Site-neutral payments were first introduced in the 2019 Medicare outpatient prospective payment system final rule when CMS made payments for clinic visits site-neutral, reducing the payment rate for evaluation and management services provided at off-campus provider-based departments by 60 percent. However, this prompted complaints and legal action, and several lawsuits later, a final decision was made July 20, 2020, when a federal appeals court ruled the U.S. Health and Human Services Department has the authority to cut Medicare payments to off-campus clinics to bring them in line with independent physician practices. ❖

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.

Combating Stress in the Healthcare Workspace

By Ronale Tucker Rhodes, MS

EVEN PRIOR to the COVID-19 pandemic, healthcare workers experienced psychological burdens associated with work, resulting in approximately three times higher rates of depression than the general public; however, experts say the strain of treating coronavirus patients and the impossible decisions many doctors and nurses are being forced to make will likely worsen their mental health.[1]

According to a study published in *JAMA Network Open* in March, healthcare workers in China reported experiencing declining mental health as a result of treating patients with COVID-19. Of 1,257 survey responses, the study found approximately 50 percent of participants experienced depressive symptoms, 45 percent experienced anxiety, 34 percent experienced insomnia and 72 percent experienced distress.[1] In another study at the University of Rome, which surveyed more than 1,300 healthcare providers through Italy's pandemic, researchers found nearly half reported symptoms of post-traumatic stress syndrome (PTSD).[2] And, according to Meredith Mealer, a professor at the University of Colorado's Clinical and Translational Sciences Institute who worked on a 2013 study of intensive care unit (ICU) nurses that found between 21 percent to 28 percent of them exhibited symptoms of PTSD, "I would anticipate we start to see nurses and physicians who have PTSD as a result of [the coronavirus] up closer to 40 percent to 50 percent."[1]

So, what can be done to help combat this crisis in the healthcare workspace?

Understanding Workers' Concerns

A viewpoint published in *JAMA Network* summarized key considerations for supporting healthcare workers based on experience, direct requests from healthcare professionals and common sense. During the first week of the COVID-19 pandemic, the authors held eight listening sessions with 69 healthcare professionals, including physicians, nurses, advanced practice clinicians, residents and fellows, to explore three key concerns: what healthcare professionals were most concerned about, what messaging and behaviors they needed from their leaders and what other tangible sources of support they believed would be most helpful to them. The discussions revealed eight sources of anxiety: "1) access to appropriate personal protective equipment, 2) being exposed to COVID-19 at work and taking the infection home to their family, 3) not having rapid access to testing if they develop COVID-19 symptoms and concomitant fear of propagating infection at work, 4) uncertainty that their organization will support/take care of their personal and family needs if they develop infection, 5) access to childcare during increased work hours and school closures, 6) support for other personal and family needs as work hours and demands increase (food, hydration, lodging, transportation), 7) being able to provide competent medical care if deployed to a new area (e.g., non-ICU nurses having to function as ICU nurses) and 8) lack of access to up-to-date information and communication."

In short, say the authors, "Healthcare professionals want unambiguous assurance that their organization will support them and their family. This includes the organization listening to their concerns, doing all that is possible to protect them and prevent them from acquiring COVID-19 infection, and assuring them that if they do become infected, the organization will support them and their family on all fronts, both medically and socially."[3]

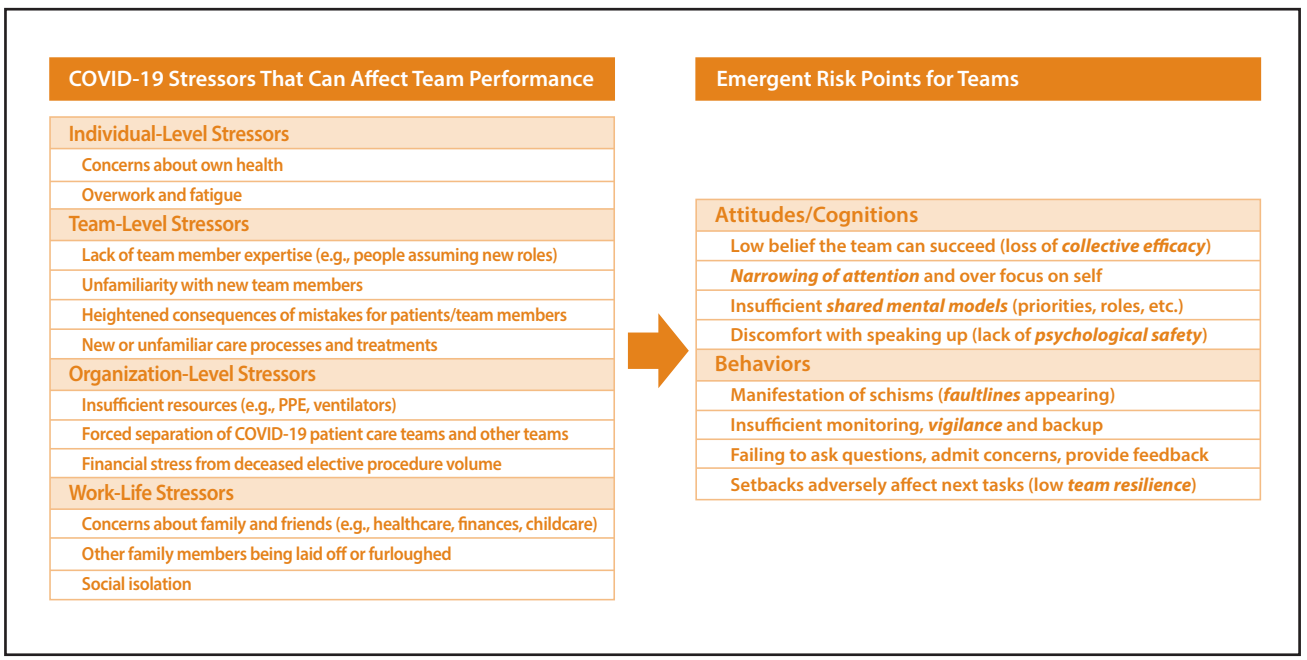
Addressing Workers' Concerns

To address healthcare workers' concerns, leadership is needed to develop approaches that mitigate them.

For instance, at the individual level, the World Health Organization has urged hospitals to think of the pandemic as a long-term situation, and give workers breaks and rotate them out of high-stress positions. Hospitals have begun offering support groups for frontline health workers, and the American Medical Association is urging them to use Headspace, a meditation app, to take breaks from news and social media. At Mount Sinai, New York City's Studio Elsewhere launched "recharge rooms" that immerse workers in music, sound, scent and lighting. And, Mealer rolled out a national program to allow up to 100 nurses and doctors to tell "trauma narratives" of what they have experienced.[1]

A team-based approach can also be extremely effective. In May, four individuals who have spent 30 years studying and advising teams in different workplace settings, published seven recommendations based on meta-analytic findings about how to counteract prevalent stressors and overcome risks that can adversely affect teamwork during the COVID-19 pandemic. Their recommendations are in response to individual, team, organizational and work-life stressors that will likely result in poor teamwork that can negatively affect patient safety and quality of care (Figure 1):[4]

Figure 1. Individual, Team, Organizational and Work-Life Stressors That Can Impact Frontline Patient Care Teams[4]



1) *Recognize wins and successes.* Research shows teams perform better when they possess collective efficacy, the belief their team is likely to successfully perform specific tasks under the current circumstances. Therefore, during the pandemic, when there is a high patient volume and numerous deaths, it's important to communicate the team's small and large wins.

2) *Ensure the team sustains shared mental models (SMM).* SMM refers to a team's shared, accurate and complementary understanding of their domain. During the pandemic, it's easy to develop different understandings about the purpose of an action or about responsibilities. Therefore, to sustain a shared perspective, team members should ask questions when they are unsure about a priority or a new process.

3) *Don't forget the people behind the scenes.* While frontline healthcare workers are rightfully referred to as heroes, it's important to recognize others who work behind the scenes to ensure enough supplies are procured, families are updated, information systems remain functional, non-COVID patients are cared for, etc.

4) *Emphasize and promote team mutual monitoring.* Teams need to focus consciously on monitoring, which can be accomplished, for example, with prebriefs prior to shifts that emphasize being ready to back up one another if someone appears overwhelmed or fatigued.

5) *Take actions that build and sustain psychological safety.* Psychological safety means team members can take interpersonal risks such as speaking up or admitting a mistake.

6) *Help team members address concerns with their 'home team.'* Crisis management teams can help to alleviate members' concerns about bringing home the virus or dealing with financial or childcare concerns by devoting attention to the needs of team members' families.

7) *Consciously boost team resiliency.* Highly resilient teams take intentional actions to minimize, manage and mend from stressful events by guiding team members to and from "normal" and "emergency" modes and providing timely updates.

"Honor Me"

According to the authors of the listening sessions, a "final overarching request of healthcare workers — even if only implicitly recognized — is 'honor me.' The genuine expression of gratitude is powerful. It honors and thereby could serve to reinforce the compassion of healthcare workers who risk their lives to help patients infected with this deadly disease. Reinforcing healthcare professional compassion helps them overcome empathetic distress and fear to provide care under extraordinarily difficult clinical circumstances every day."[3] ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly* magazine.

References

1. Ao B. Treating Coronavirus Takes Serious Toll on Health-Care Workers' Mental Health, Study Finds. *The Philadelphia Inquirer*, March 27, 2020. Accessed at www.inquirer.com/health/coronavirus/coronavirus-covid19-mental-health-doctors-20200327.html.
2. Glenza J. What Coronavirus Is Doing to Stressed U.S. Health Workers — and Why It Will Be Felt For Years. The Guardian, May 15, 2020. Accessed at www.theguardian.com/us-news/2020/may/15/us-nurses-doctors-mental-health-coronavirus.
3. Shanafelt T, Ripp J, and Trockel M. Understanding and Addressing Sources of Anxiety Among Health Care Professionals During the COVID-19 Pandemic. *JAMA Network*, April 7, 2020. Accessed at jamanetwork.com/journals/jama/fullarticle/2764380.
4. Tannenbaum SI, Traylor AM, Thomas EJ, and Salas E. Managing Teamwork in the Face of Pandemic: Evidence-Based Tips. *BMJ Quality & Safety*, published online May 29, 2020. Accessed at quality safety.bmj.com/content/early/2020/05/28/bmjqs-2020-011447.

Medicines

FDA Approves Updated PI for Octapharma's NUWIQ

The U.S. Food and Drug Administration (FDA) has approved an updated prescribing information (PI) for NUWIQ, Octapharma's human cell line-derived recombinant factor VIII (FVIII). NUWIQ is approved for the prevention and treatment of bleeding in people with haemophilia A.

The updated NUWIQ PI includes data from the NuProtect study, which was the largest prospective study of a single FVIII product in true previously untreated patients (PUPs). Patients received NUWIQ for prophylaxis or on-demand

treatment and were followed for 100 exposure days or five years. Of the 105 PUPs assessed for inhibitor development, 17 (16.2 percent) developed high-titre inhibitors and 11 (10.5 percent) developed low-titre inhibitors, five of whom had transient inhibitors. Of the 28 patients who developed an inhibitor, 25 did so within 20 days of treatment exposure, and no patients developed inhibitors after 34 exposure days. ❖

Octapharma Announces FDA Approval of Updated NUWIQ® Prescribing Information to Include Immunogenicity Data in Previously Untreated Patients. Octapharma press release, Oct. 19, 2020. Accessed at www.oaoa.com/news/business/octapharma-announces-fda-approval-of-updated-nuwiq-prescribing-information-to-include-immunogenicity-data-in-previously/article_7c2870cf-8349-534d-aa28-aca9b2ec9e9b.html.

Research

Study Finds Once-Per-Week Regimen of Selinexor, Bortezomib and Dexamethasone Effective for Treating Multiple Myeloma Patients

A Phase III study has found a once-per-week regimen of selinexor (XPOVIO; Karyopharm), bortezomib (Velcade; Takeda) and dexamethasone is an effective and convenient treatment option for patients with multiple myeloma who have received one to three previous lines of therapy.

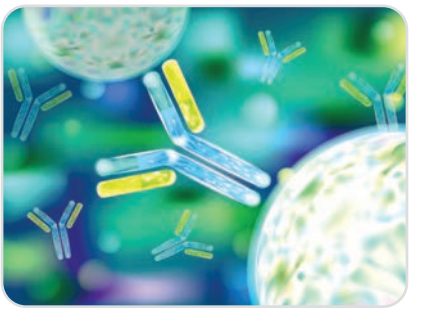
In the randomised, open-label BOSTON (**bo**rtezomib, **s**elinexor and dexamet**h**as**one**) study conducted at 123 sites in 21 countries, 402 multiple myeloma patients were randomly allocated to receive selinexor (100 mg once per week), bortezomib (1.3 mg/m once per week) and dexamethasone (20 mg twice per week) (49 percent) or bortezomib (1.3 mg/m twice per week for the first 24 weeks and once per week thereafter) and dexamethasone (20 mg four times per week for the first 24 weeks and twice per week thereafter) (51 percent) between June 6, 2017, and Feb. 5, 2019. Median follow-up durations were 13.2 months for the selinexor, bortezomib and dexamethasone group and 16.5 months for the bortezomib and dexamethasone group. Findings showed median progression-free survival was 13.93 months with selinexor, bortezomib and dexamethasone and 9.46 months with bortezomib and dexamethasone. The most frequent grade 3 to grade 4 adverse events were thrombocytopenia (39 percent of patients in the selinexor, bortezomib and dexamethasone group versus 17 percent in the bortezomib and dexamethasone group), fatigue (13 percent versus 1 percent), anemia (16 percent versus 10 percent) and pneumonia (11 percent versus 11 percent). Peripheral neuropathy of grade 2 or above was less frequent with selinexor, bortezomib and dexamethasone (21 percent) than with bortezomib and dexamethasone (34 percent). And, 24 percent of patients in the selinexor, bortezomib and dexamethasone group and 30 percent of patients in the bortezomib and dexamethasone group died.

"The results from the BOSTON study published in *The Lancet* demonstrate that the once-weekly regimen of XPOVIO and Velcade, with low-dose dexamethasone (SVd) reduced the risk of disease progression or death by 30 percent and induced a higher rate of overall and deep responses compared to patients receiving a standard twice-weekly Velcade and low-dose dexamethasone regimen (Vd). This was observed despite approximately 40 percent less Velcade, 25 percent less dexamethasone and approximately 35 percent fewer clinic visits on the SVd arm as compared with the standard Vd therapy arm. Encouragingly, the efficacy of the SVd regimen was consistent and noteworthy across several key subgroups, including patients who were frail or 65 years and older, patients with high-risk cytogenetics, patients with moderate renal impairment and patients who had either prior bortezomib or lenalidomide treatment," said Paul Richardson, MD, clinical program leader and director of clinical research at the Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute and co-senior author of the manuscript. ❖

Grosicki S, Simonova M, Spicka I, et al. Once-Per-Week Selinexor, Bortezomib, and Dexamathasone Versus Twice-Per-Week Bortezomib and Dexamethasone in Patients with Multiple Myeloma: A Randomized, Open-Label Phase 3 Trial. *The Lancet*, Nov. 14, 2020. Accessed at www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32292-3/fulltext.

Research

Some People's Immune Systems May Generate Faster and Stronger Response to COVID-19



A study shows some people who have never been exposed to the coronavirus (the virus that causes COVID-19) have helper T cells that may provide a stronger and faster recognition and response to the virus. The researchers believe this may be the case due to cross-reactivity, which occurs when helper T cells developed in response to another virus react to a similar but previously unknown pathogen. In the case of the coronavirus, these T cells may be left over from people's previous exposure to one of four different coronaviruses that cause common colds.

In the study, researchers examined the immune systems of 20 people who were infected with the coronavirus and recovered, only two of whom had severe cases and the other 90 percent had either mild or moderate infections, as well as blood samples collected from 20 people between 2015 and 2018 when there was no chance of being exposed to the virus. The coronavirus patients were selected so researchers could measure immune responses in average COVID-19 patients rather than hospitalized people (an estimated 20 percent of coronavirus cases are severe). Results showed that during the course of their infections, all 20 patients made antibodies and helper T cells capable of recognizing the coronavirus and responding accordingly, and 70 percent made killer T cells in response to the virus. Among those whose blood samples were collected prior to the pandemic, 50 percent had a type of white blood cell called CD4+ — T cells that help the immune system create antibodies capable of recognizing the new coronavirus and prompting the immune system to fight back right away. This suggests the body will be able to identify and defend itself against the coronavirus in the future. However, more research is needed to determine whether or to what degree this cross-reactivity influences the severity of an infection. ❖

Woodward A. Some People May Have a Head Start Against Coronavirus, Surprising Evidence Shows. Science Alert, June 4, 2020. Accessed at www.sciencealert.com/surprise-finding-suggests-some-people-are-already-primed-to-fight-the-coronavirus.

Research

Clinical Trial Seeks to Find Long-Term Treatment for Hemophilia A Using Gene Therapy

A Phase 1 clinical trial to assess a potential long-term treatment for severe hemophilia A using a gene therapy that targets synthesis of coagulation factor VIII (FVIII) has begun at Froedtert and Medical College of Wisconsin. The trial, which will recruit five patients, uses a lentiviral vector-based gene therapy known as Pleighlet that modifies bone marrow stem cells to drive synthesis of a normal FVIII replacement gene leading to storage specifically within the patients' platelets. The platelets would then act as the FVIII carrier and delivery vehicle within the body to stop uncontrolled bleeding.

"This treatment approach is expected to avoid exposure of FVIII to the patient's immune system by hiding FVIII within blood platelets until released directly at injured blood vessels, thus restoring normal clotting activity even in patients with immune reactions to FVIII," said David A. Wilcox, PhD, associate professor of pediatrics within the division of hematology, oncology and blood marrow transplant at the Medical College of Wisconsin. "Not only does it allow us to provide care to patients who previously were difficult to be treated due to complications they experienced from replacement FVIII, but also because it enables the patient's own body to produce normal FVIII protein. We believe this could be a potential long-term treatment for hemophilia A, and success of this gene therapy research could lead to significantly improved disease management for people who make antibodies following infusion of conventional FVIII products."

The clinical trial will receive approximately $1.6 million in funding from the National Institutes of Health National Heart, Lung and Blood Institute this year for a total of $8.2 million over five years. ❖

Researchers to Test Innovative Gene Therapy in Hemophilia-A Clinical Trial. Medical College of Wisconsin, June 15, 2020. Accessed at www.mcw.edu/newsroom/recent-news.

Research

National Cancer Institute to Launch a Study of HPV Self-Tests

The National Cancer Institute (NCI) will launch a multisite study in 2021 involving approximately 5,000 women to assess whether self-sampling for human papillomavirus (HPV) — the virus that causes virtually all cervical cancers — at home is comparable to screening in the office by a clinician. The hope is the research will fast-track a test approved by the U.S. Food and Drug Administration (FDA) that could be part of screening guidelines if self-sampling is proved effective. Rather than wait for self-sampling studies to be done by individual companies that make HPV tests for clinicians, federal officials will team up with the companies, academic institutions and others in a public-private partnership. NCI officials expect to spend about $6 million in federal funds and will oversee the study's data and analysis.

While NCI hasn't settled on the precise self-sampling approach it will use, the technique generally requires a woman to insert a tiny brush into her vagina and rotate it several times to collect the cells. The brush is then inserted into a specimen container that has a preservative solution, which is then returned for HPV analysis. According to a review of studies published in 2018 in the medical journal *BMJ*, the accuracy of identifying HPV was similar when samples were collected by women at home as when collected by clinicians. A urine-based HPV test, which may prove easier for women to perform, also is being studied, said Jennifer Smith, a professor of epidemiology at the University of North Carolina's Gillings School of Global Public Health.

Before companies can pursue applications for an FDA-approved home test, self-sampling by women has to be shown comparable to detect HPV, although it may not be quite as accurate as when a clinician is involved. NCI officials are still finalizing study details, but the plan is to invite four companies that already manufacture HPV tests for clinicians to participate. Those companies will pay for the cost of the tests, as well as future fees related to pursuing license applications through FDA. Study results are expected to be available by 2024, if not sooner. ❖

Huff C. NIH Spearheads Study to Test At-Home Screening For HPV and Cervical Cancer. *Kaiser Health News,* July 1, 2020. Accessed at khn.org/news/nih-spearheads-study-to-test-at-home-screening-for-hpv-and-cervical-cancer/?utm_campaign=KHN%3A%20Daily%20Health%20Policy%20Report&utm_medium=email&_hsmi=90579334&_hsenc=p2ANqtz-8UmICZcbbHBuTNujZST1eibdEnjm9TtiyeX2nlZLkRo39HAVVPSKE35-uddvyMP-FRCN7HgpULvw9zDYsgkEfyypCuUQ&utm_content=90579334&utm_source=hs_email.

Guidelines

National Hemophilia Foundation Revises Treatment Guidelines for Factor 1 Deficiency

The National Hemophilia Foundation (NHF) has revised its treatment recommendations for congenital fibrinogen (factor 1) deficiency to include fibryga, fibrinogen (human) lyophilized powder for reconstitution, for intravenous use. Fibryga is a highly purified, virus inactivated, human plasma-derived fibrinogen concentrate produced by Octapharma.

During manufacture, fibryga (previously called fibryna) undergoes solvent/detergent treatment for virus inactivation and nanofiltration for virus removal. The efficacy of fibryga was demonstrated in a recent Phase III clinical study with 25 afibrinogenemia patients who received 131 infusions for treatment of 89 bleeding episodes or prophylaxis for 12 surgeries. Fibryga demonstrated adjudicated hemostatic efficacy (treatment success) for 98.9 percent of bleeding episodes and 100 percent of surgical procedures.

"The NHF recommendations are great news for patients and providers who must manage the life-altering challenges of bleeding in congenital fibrinogen deficiency," said Octapharma USA President Flemming Nielsen. "We are committed to providing life-saving treatment options to people with rare bleeding disorders, including factor 1 deficiency."

"The MASAC recommendations previously noted that fibrinogen concentrates can be used to treat patients with congenital hypofibrinogenemia and afibrinogenemia, but not dysfibrinogenemia," said MASAC Member Michael D. Tarantino, MD, founder, medical director and president of the Bleeding & Clotting Disorders Institute in Peoria, Ill. "Dysfibrinogenemia patients are excluded from clinical trials, but the absence of regulatory approval does not preclude consideration for use by individual practitioners based on their medical judgment. The treatment recommendations have been changed to indicate that fibrinogen concentrates have not received regulatory approval for use in patients with dysfibrinogenemia." ❖

National Hemophilia Foundation Revises Treatment Guidelines for Factor 1 Deficiency to Include Octapharma's Fibryga. Octapharma press release, Oct. 7, 2020. Accessed at news.yahoo.com/national-hemophilia-foundation-revises-treatment-130300468.html.

Research

New Therapy Improves Multiple Sclerosis Treatment

Researchers at the Pritzker School of Molecular Engineering at the University of Chicago have developed a new therapy for multiple sclerosis (MS) by fusing a cytokine. When tested in mice, the combination prevented destructive immune cells from infiltrating the central nervous system and decreased the number of cells that play a role in MS development, leading to fewer symptoms and disease prevention.

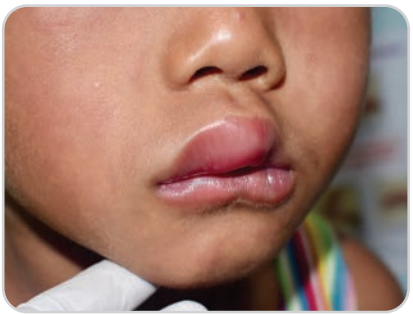
Recent studies have shown Th17 cells, immune cells that are activated in the body's secondary lymphoid organs, migrate to the brain and play a role in the severity of MS. While several drugs that treat MS work by sequestering these cells in the lymph nodes and preventing them from targeting tissue, these drugs have adverse side effects. Since it is known that interleukin-4 (IL-4) suppresses the genes that cause MS and suppresses the reactivation of Th17 cells, the researchers bound IL-4 to a blood protein and injected it into mice that had experimental autoimmune encephalomyelitis (the mouse model of MS) and found it caused the IL-4 to stay within the secondary lymphoid organs, which reduced infiltration of Th17 cells into the spinal cord, suppressed the disease and resulted in fewer symptoms. The researchers also found the therapy prevented MS from developing in a majority of mice. Jeffrey Hubbell, Eugene Bell professor in tissue engineering and co-author of the paper, said the treatment could potentially be self-administered by MS patients at home with an injector pen. Although the therapy produced few negative effects, it will need to be formally studied in human clinical trials.

"This is the first time anyone has shown how the fusion of this protein to immunosuppressive cytokines can treat and prevent multiple sclerosis," said Jun Ishihara, a former postdoctoral research and corresponding author of the study. ❖

Ayshford E. UChicago Researchers Find Way to Improve Multiple Sclerosis Treatment. UChicago News, Oct. 12, 2020. Accessed at news.uchicago.edu/story/uchicago-researchers-find-way-improve-multiple-sclerosis-treatment.

Medicines

FDA Approves Haegarda for Prevention of HAE Attacks in Pediatric Patients



The U.S. Food and Drug Administration has approved CSL Behring's Haegarda (C1 esterase inhibitor subcutaneous [human]) for routine prophylaxis to prevent hereditary angioedema (HAE) attacks in patients 6 years of age and older. Haegarda is now the first and only subcutaneous treatment option for prevention of HAE attacks in these patients. In addition to the expanded pediatric indication, the updated label now includes clinical safety data regarding Haegarda use in pregnant women.

Approval was based on results from two CSL Behring-sponsored COMPACT (Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy) trials: COMPACT Pivotal Study and COMPACT Open Label Extension (OLE) Study. COMPACT, an international, prospective multi-center, randomized, double-blind, placebo-controlled Phase III pivotal study, included six subjects aged 17 years or younger with symptomatic HAE. In the COMPACT pivotal study, the FDA-approved dose of 60 IU/kg of Haegarda reduced the number of HAE attacks by a median of 95 percent relative to placebo. Use of rescue medication was reduced by a median of greater than 99 percent versus placebo. COMPACT OLE featured 126 subjects, including nine patients ages 17 years or younger. In this trial, all nine pediatric subjects experienced greater than 50 percent reduction in number of attacks per month versus the pre-study period, with a median of 97 percent reduction in the median number of attacks per month. All subjects had less than one attack per four-week period and four had less than one attack per year (one subject was attack-free). No subject discontinued treatment due to a treatment-related adverse event. Safety and effectiveness results of subgroup analysis by age was consistent with overall study results.

The new label now includes results from the randomized, open-label, active treatment controlled study regarding four patients who became pregnant during the study, and received treatment until pregnancy was identified. These patients ranged in age from 19 years to 32 years and received nine to 15 doses of Haegarda for four to eight weeks during the first trimester. These women reported no complications during delivery, and all women delivered healthy babies.

"Since 2017, Haegarda has been a trusted and effective option for patients seeking to prevent HAE attacks, but until now preventative options for younger children living with the condition have been limited," said Debra Bensen-Kennedy, MD, vice president of North America Medical Affairs at CSL Behring. "With this expanded indication, we are able to offer pediatric patients as young as 6 years of age an effective preventative subcutaneous solution and deliver on our promise of addressing the unmet needs of people living with HAE." ❖

U.S. Food and Drug Administration Approves HAEGARDA® (C1 Esterase Inhibitor Subcutaneous [Human]) for Prevention of Hereditary Angioedema (HAE) Attacks in Pediatric Patients. CSL Behring press release, Sept. 28, 2020. Accessed at www.tiogapublishing.com/news/state/u-s-food-and-drug-administration-approves-haegarda-c1-esterase-inhibitor-subcutaneous-human-for-prevention/article_406bc66d-34e3-56c9-aea3-8e0b65c3bb2c.html.

Research

New Universal Flu Vaccine Provides Protection Against Six Influenza Viruses in Mice

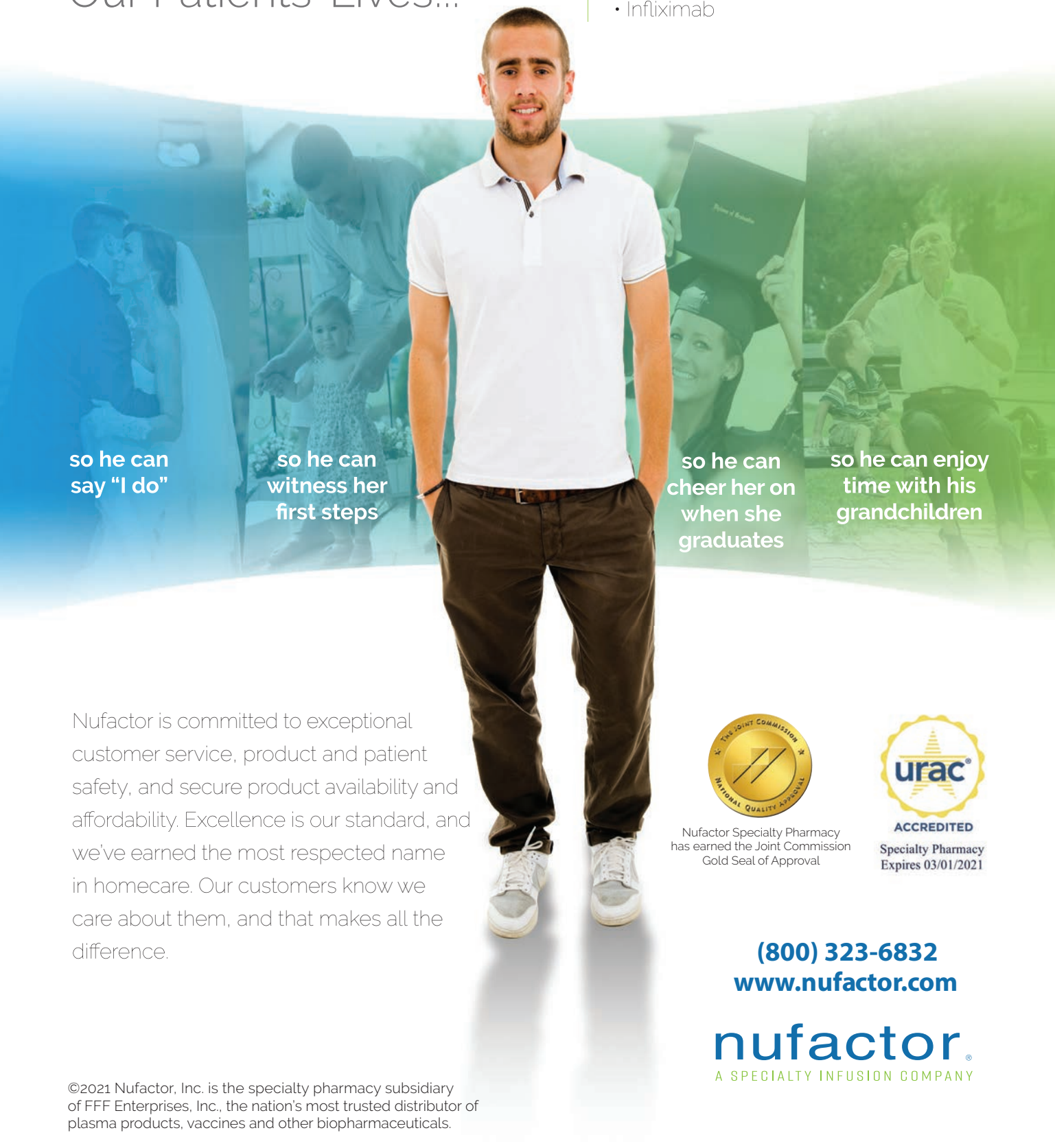
Researchers at the Georgia State University Institute for Biomedical Sciences have developed a novel nanoparticle vaccine that combines two major influenza proteins effective in providing broad, long-lasting protection against six different influenza viruses in mice. The double-layered vaccine contains the influenza virus proteins matrix protein 2 ectodomain (M2e) and neuraminidase (NA). In the study, mice were exposed to one of six influenza virus strains after receiving the vaccine by intramuscular injection, which proved to have long-lasting immune protection that was unchanged against viral challenges up to four months later.

"It's important to mention that a lot of flu vaccines haven't focused on NA before," said Gilbert Gonzalez, co-author of the study and manager in the lab of Bao-Zhong Wang, PhD, at the Institute. "NA is becoming a more important antigen for influenza vaccine research. Previously, it had been ignored or discounted because hemagglutinin (HA) is much more dominant. When you get a flu infection, your body reacts to the HA." However, since the HA protein mutates quickly, the seasonal flu vaccines must be changed every year. The next step is for the researchers to load the double-layered nanoparticle vaccine onto microneedle patches for skin vaccination. ❖

Georgia State University Institute for Biomedical Sciences. Researchers Develop Universal Flu Vaccine with Nanoparticles That Protects Against Six Different Influenza Viruses in Mice, Jan. 6, 2020. Accessed at news.gsu.edu/2020/01/06/researchers-develop-universal-flu-vaccine-with-nanoparticles-that-protects-against-six-different-influenza-viruses-in-mice.

Making a Difference in Our Patients' Lives...

Specialty Solutions in Chronic Care
- Immune Globulin
- Factor
- Infliximab



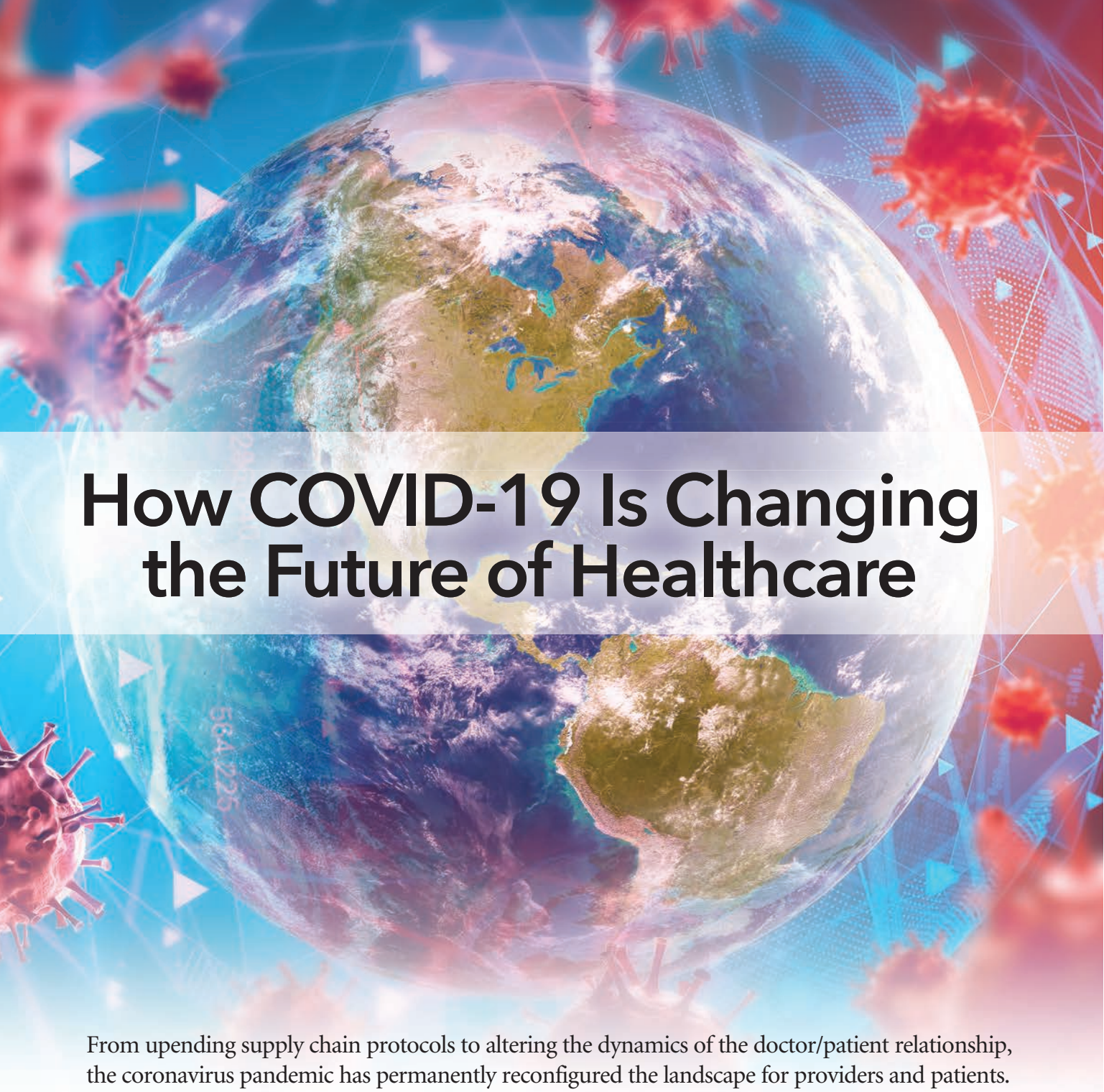
Nufactor is committed to exceptional customer service, product and patient safety, and secure product availability and affordability. Excellence is our standard, and we've earned the most respected name in homecare. Our customers know we care about them, and that makes all the difference.

Nufactor Specialty Pharmacy has earned the Joint Commission Gold Seal of Approval

urac ACCREDITED Specialty Pharmacy Expires 03/01/2021

(800) 323-6832
www.nufactor.com

nufactor®
A SPECIALTY INFUSION COMPANY



How COVID-19 Is Changing the Future of Healthcare

From upending supply chain protocols to altering the dynamics of the doctor/patient relationship, the coronavirus pandemic has permanently reconfigured the landscape for providers and patients.

By Trudie Mitschang

THE COVID-19 PANDEMIC has impacted every sector of public life, with some of the most significant and perhaps long-reaching effects surfacing within the healthcare industry. During the early months of the outbreak, the rapid spread of the virus left health industry leaders scrambling to find effective ways to address the crisis, as unprecedented demands for care overwhelmed emergency rooms and hospitals across the nation. And, as the crisis drags on, it seems increasingly clear there will be no return to business as usual when it comes to traditional healthcare models. Experts say the industry is in a state of flux, and many predict ongoing challenges and financial pressures.

"It's an emphasis on the haves and have-nots of healthcare providers," said Justin Gernot, vice president at healthcare advisory firm Healthbox. Gernot outlined a number of issues during a

virtual media event on the impact of the pandemic on the future of healthcare that was sponsored by the Healthcare Information and Management Systems Society. "The organizations that had a tight digital strategy, that were good at telehealth, had money in the bank, by and large, those healthcare systems, unless they are in hard-hit areas, those systems will do well and emerge with an eye toward acquisitions and advancing the position of strength they have," he said. "The smaller, rural, less financially healthy systems will come out of this crisis in a bad way." Gernot went on to say that COVID-19 also led to myriad financial pressures for hospitals: "There are a lot of cracks in the system that have been exposed, from supply chain for personal protective equipment (PPE) to how underserved populations are more exposed and much more at risk for COVID than others."[1]

In fact, the COVID-19 pandemic surfaced critical flaws in hospital supply chains for vital equipment like PPE. Many health systems struggled with shortages and often competed with one another for necessary supplies.[2] In addition (at the time of this writing), hospitals across the country are bracing themselves for a potential second wave of the virus, with the potential to put even more strain on limited supplies and financial resources.

Turning an Eye Toward Supply Chain Optimization

As hospitals have struggled to maintain proper levels of PPE, ventilators and medications, hospital leaders have shifted their priorities toward supply chain optimization. A survey of 138 hospital leaders[3] found supply chain optimization has become hospital leaders' second-highest priority, right behind patient safety. The survey also found supply chain analytics ranked second out of nine technologies that hospital leaders said has increased in importance.

Because the coronavirus that causes COVID-19 is spread primarily through droplets in the air, PPE is critical to protect medical staff and other patients from contracting the respiratory disease. As medical facilities all over the world required more PPE, equipment vendors were pushed well beyond their normal capacity. The sudden and unexpected demand forced hospitals to look at the sources for their equipment supply; many took for granted that products manufactured overseas would always be available.

While it is not possible to control external factors that affect the healthcare supply chain (such as one caused by a global pandemic), what hospitals can do is instigate changes now to ensure they are more prepared for future disruptions. Experts suggest some key areas to focus on include:

- *Updating and automating current systems.* Healthcare significantly lags behind other industries when it comes to supply chain management technologies. To close the gap, transitioning to automated processes will make it easier for hospitals to track and analyze data efficiently. This includes data related to inventory, which will enable faster responses to shortages and more informed use of limited resources.
- *Investing in demand forecasting technology.* Supply chain management technology is available that can help hospitals plan for, better manage and more quickly recover from supply chain disruptions. For example, incident and peak demand forecasting tools can support inventory planning and management during disruption periods and during periods of normalcy.
- *Prioritizing contingency plans with increased scope and duration.* COVID-19 was novel in many ways, including illustrating that hospitals must have stronger contingency plans in place. Sourcing plans for secondary and tertiary resources should be included in these plans, and hospitals should consider forming coalitions with other organizations to enhance resource-sharing when necessary and possible.

As hospitals have struggled to maintain proper levels of PPE, ventilators and medications, hospital leaders have shifted their priorities toward supply chain optimization.

The Rapid Rise of Telemedicine

COVID-19 and the subsequent and immediate need for social distancing quickly put the spotlight on digital health tools like telehealth and remote monitoring as healthcare providers pivoted to technology-led patient care. Almost overnight, digital health platforms went from being an interesting idea to a fundamental necessity. According to the Centers for Disease Control and Prevention (CDC), while telehealth technology and its uses are not new, widespread adoption among healthcare providers and patients beyond simple telephone correspondence had been relatively slow — until 2020.[4] In this rapidly evolving landscape, even professional medical societies now endorse telehealth services and provide guidance for medical practices.

CDC outlines several telehealth modalities that are currently being successfully implemented:

• Synchronous: This model includes real-time telephone or live audio-video interaction typically with a patient using a smartphone, tablet or computer. In some cases, peripheral medical equipment (e.g., digital stethoscopes, otoscopes, ultrasounds) can be used by a nurse or medical assistant who is physically with the patient, while the consulting medical provider conducts a remote evaluation.

• Asynchronous: A "store and forward" technology where messages, images or data are collected at one point in time and interpreted or responded to later. Patient portals can facilitate this type of communication between provider and patient through secure messaging.

• Remote patient monitoring: This allows direct transmission of a patient's clinical measurements from a distance to their healthcare provider. The transmission may or may not be in real time.

In addition to supporting social distancing guidelines, telehealth services can reduce the strain on healthcare systems by minimizing patient demand on facilities, and reduce the use of PPE by healthcare providers, putting less pressure on the supply chain.

COVID-19 and Behavioral Health

From isolation and economic setbacks to the very real fear of contracting the coronavirus, the pandemic fallout has negatively affected many people's mental health and created new complications for people already suffering from mental illness and substance use disorders.

A poll conducted by the Kaiser Family Foundation (KFF) found nearly half (45 percent) of adults in the United States reported their mental health has deteriorated due to worry and stress over the virus.[6] As the pandemic wears on, it's likely the mental health burden will increase as measures taken to slow the spread of the virus such as social distancing, business and school closures, and shelter-in-place orders lead to greater isolation and potential financial distress. Though necessary to prevent loss of life due to COVID-19, these public health measures expose many people to experiencing situations linked to poor mental health outcomes.

Although recognition that behavioral health is a crucial component of whole-person care and positive health outcomes, it remains underfunded and inaccessible for many. Many mental health experts are concerned the country is on the verge of another healthcare crisis as isolation, fear and desperation around financial concerns generate widespread psychological trauma.

Yet, allocation of resources for mental health comprises only a small portion of the trillions of dollars Congress passed in emergency coronavirus funding. Therapists have struggled to bring their practices online and to reach vulnerable groups because of restrictions on licensing and reimbursement. Community behavioral health centers treating some of the most vulnerable populations are struggling to stay financially solvent and have begun closing programs.

Assessing the Advantages of Value-Based Care

As the coronavirus crisis continues to reshape healthcare delivery, advocates, payers and providers are grappling with how best to navigate dramatic shifts in the system.

In a joint webinar, experts from the University of Michigan's Center for Value-Based Insurance Design (V-BID) and the Smarter Health Care Coalition outlined challenges providers face amid the pandemic and the benefits of increased access to high-value care during the outbreak and beyond.[7]

The webinar pointed out that in early April, visits to ambulatory practices fell nearly 60 percent below the pre-COVID-19 baseline before rebounding in mid-June. However, rates plateaued at around 10 percent below baseline from then through the end of July, according to data presented by Michael Chernew, PhD, a founding partner of V-BID Health and co-editor-in-chief of the *American Journal of Managed Care* (*AJMC*).

In addition, rebounds in visitation rates in June and July varied by specialty. In areas such as pulmonology, orthopedics and neurology, for example, the drop remained very significant, with the potential for resulting in clinical ramifications. "I'm not sure

we have yet sorted out what those clinical ramifications are, and I think there's going to be … a lot of interest in understanding what we're losing in terms of health when all these visits went down," Dr. Chernew explained.[7]

And, despite the large uptick in hospital admissions for COVID-19 patients, data show these visits did not make up for the loss of routine procedures and other visits postponed or cancelled due to the pandemic. COVID-19 admissions also skew toward those with Medicare coverage, which results in lower payment rates for hospitals compared with commercially insured patients. Meanwhile, hospitals face increased costs due to reconfigurations of floors, excess need for PPE and staffing shortages.

In total, Dr. Chernew predicts total healthcare spending will be about 5 percent below where it otherwise would have been in 2020. Due to a large national deficit and a looming recession, employers may also reduce their generosity when it comes to providing coverage. And although insurers are spending less money, not all of those funds will be refunded to customers and most will likely go back to employers. Insurers could also face increased costs in the future as new treatments and tests for COVID-19 are developed.

Looking to create a more efficient healthcare system in the wake of COVID-19, Mark Fendrick, MD, director of V-BID and co-editor-in-chief of *AJMC*, explained the importance of reallocating money already within the healthcare system. "There are more clinically nuanced ways of coming out of the COVID-19 pandemic," he said. To transform the pandemic into a potential path to improve healthcare efficiency, he recommended the following strategies:[7]

- Build on existing alternative payment models that base reimbursement on patient-centered outcomes, increase reimbursement for high-value services and reduce or cease payment for known low-value care.
- Leverage the widespread adoption of electronic health records to make it easier to order high-value care with simplified processes and discourage the use of low-value care with alerts.
- Align patient cost-sharing with the value of the underlying services, reduce out-of-pocket cost on high-value services and increase patient cost on low-value care.

The concept has received bipartisan support over the years, noted Katy Spangler, co-director of the Smarter Health Care Coalition, who also spoke during the webinar. For example, in March 2020, Internal Revenue Service notice 2020-15 was published, which allows health savings account-eligible high-deductible health plans to provide predeductible coverage of "medical care services and items purchased related to testing for and treatment of COVID-19." In addition, both the Families First Coronavirus Response Act and the Coronavirus Aid, Relief and Economic Security Act have encouraged high-value care during the pandemic.

A Catalyst for Change

The coronavirus introduced significant scientific, clinical and financial challenges that will permanently change the healthcare industry and the way we live our lives. Without question, how we manage our physical and mental health and obtain healthcare services have to evolve to become increasingly innovative and efficient going forward.

Almost overnight, digital health platforms went from being an interesting idea to a fundamental necessity.

While COVID-19 has created unprecedented social and economic challenges, it also has provided a unique catalyst for meaningful change. Access to more complete, timely and accurate healthcare information, collaborating across boundaries and using advanced predictive models are keys to addressing the challenges presented by a global pandemic. They are also foundational for improving outcomes, enhancing patient experiences and reducing the cost of care. ❖

References

1. Landi H. The COVID-19 Pandemic Will Have a Long-Term Impact on Healthcare. Fierce Healthcare, May 18, 2020. Accessed at www.fiercehealthcare.com/tech/4-ways-healthcare-will-change-from-impact-covid-19-experts-say.
2. Grimm CA. Hospital Experiences Responding to the COVID-19 Pandemic: Results of a National Pulse Survey March 23-27, 2020. U.S. Department of Health and Human Services Office of Inspector General, April 2020. Accessed at oig.hhs.gov/oei/reports/oei-06-20-00300.pdf.
3. Sage Growth Partners. Evolving U.S. Healthcare Needs and Attitudes During COVID-19. Accessed at medcitynews.com/uploads/2020/05/SGP_Hosp_Exec_Pulse_Survey_200421-1.pdf.
4. Centers for Disease Control and Prevention. Using Telehealth to Expand Access to Essential Health Services During the COVID-19 Pandemic, June 10, 2020. Accessed at www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html.
5. Amit J, Punya J, and Shruti A. SARS-CoV-2 Impact on Elective Orthopaedic Surgery. *The Journal of Bone and Joint Surgery*, July 1, 2020, Volume 102, Issue 13, p.e68. Accessed at journals.lww.com/jbjsjournal/Fulltext/2020/07010/SARS_CoV_2_Impact_on_Elective_Orthopaedic_Surgery_.10.aspx.
6. Kirzinger A, Kearney A, Hamel L, and Brodie M. Poll Findings: The Impact of Coronavirus On Life In America. Kaiser Family Foundation, April 2, 2020. Accessed at www.kff.org/coronavirus-covid-19/report/kff-health-tracking-poll-early-april-2020.
7. Melillo G. Experts Argue COVID-19 Provides Opportunity to Implement Value-Based Care Practices. *American Journal of Managed Care*, Aug. 13, 2020. Accessed at www.ajmc.com/view/experts-argue-covid-19-provides-opportunity-to-implement-value-based-care-practices.

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

Proper Use of Personal Protective Equipment in Healthcare Settings

It's not enough for healthcare facilities to have PPE on hand; it must be consistently and properly used.

By Jim Trageser

WHILE OUTBREAKS OF infectious diseases have always required access to personal protective equipment (PPE) in the healthcare workplace, the COVID-19 pandemic has elevated its proper use to a top priority in every practice. Any employee who is onsite — from top management to custodian — as well as vendors and patients are required to use PPE in nearly all jurisdictions. And even where not legally compelled, medical ethics and legal liability have led most medical facilities to implement rules requiring the use of PPE.

In normal times, large corporate practices have the resources necessary to develop and deploy protocols for safely and effectively utilizing PPE provided to staff. But the rapidly shifting landscape of the current pandemic — and the severity of a seasonal influenza season yet to be determined — has led to even large respected institutions scrambling to not only source increasingly scarce PPE, but to quickly develop instructions and training for using the equipment.

Shortages of N95 respirators, for instance, have left many frontline medical workers with only basic cloth masks — the design and efficacy of which can vary widely, even more so if they aren't properly worn.

And, of course, today there is more to PPE than respirators, gowns and gloves: Check-in desks may now have plexiglass shields between patients and staff; credit-card readers may have a clear plastic cover over the keypad. Goggles or safety glasses may be required for everyone onsite, including nurses performing temperature checks at the entrance. And new cleaning protocols for all exam rooms and even restrooms have support staff as engaged in the use of PPE as nurses and doctors.

The Three-Headed Monster

David Lo, MD, PhD, senior associate dean of research at the University of California, Riverside, School of Medicine, says every practice faces three distinct challenges for ensuring the proper use of PPE to protect both patients and staff:

- Procuring reliable equipment
- Training staff in its proper use
- Following up to ensure staff is complying with protocols

Procurement is the area where a medical practice is most vulnerable to the whims of outside forces, he says. "There's so much variability in terms of what's available, as well as whether you can trust the source," says Dr. Lo. "That's an ongoing issue." As Dr. Lo points out, no matter how good a facility's training and compliance protocols, if it's using defective goods, they're not going to protect anyone from infection.

What's more, with the surge in demand for PPE, there has

been a global shortage. A recent survey of more than 21,000 nurses in the U.S. found that as we were heading into autumn, 42 percent were still reporting shortages of PPE.[1] Due to these shortages, a healthcare facility's normal suppliers may be unable to source needed equipment, leaving staff to look to unfamiliar providers. And, in some cases, long-trusted suppliers may, while trying to serve its customers, procure equipment of questionable origin.

Indeed, the entire supply chain is susceptible to fraud. *The Wall Street Journal* reported on Sept. 15 that a growing number of the 70 billion medical gloves imported each year are substandard and do not offer the protection they promise.[2] Then, on Sept. 17, U.S. Customs and Border Protection agents in Boston seized more than 20,000 counterfeit N95 respirators.[3] Similarly, customs agents at O'Hare International Airport are finding record numbers of counterfeit protective gear. And, as a customs agent told a reporter, there is no dog on Earth that can sniff out counterfeit respirators.[4]

The counterfeiting situation has become so rampant that the Centers for Disease Control and Prevention (CDC) has issued an alert through the National Personal Protective Technology Laboratory. The site (www.cdc.gov/niosh/npptl/usernotices/counterfeitResp.html) includes tips for spotting potentially counterfeit goods, as well as photographic samples of dozens of seized counterfeits that have recently appeared on the market, to help purchasing agents identify fraudulent supplies.

Security consultant Pinkerton also has published an online checklist to help healthcare providers navigate the increasingly murky waters of procuring legitimate PPE (pinkerton.com/our-insights/blog/identifying-and-combating-counterfeit-ppe).

Training Staff

After legitimate, quality protective gear is acquired, it is imperative staff are trained to properly use it. Improperly used equipment can be just as ineffective at stopping the spread of infection as using no gear at all, and merely having the equipment can give people a false sense of safety. "You can get a high-quality respirator, and if you wear it improperly, then it's useless," says Dr. Lo. "Similarly, if you wear just a regular face mask — not an N95 — and if you don't cover your nose or if you have a heavy beard, it won't be effective." Dr. Lo also points out that PPE is not difficult to learn to use correctly: "It's not heavy training on how to use it. Technically, it's not challenging; it's people being consistent."

PPE providers should include illustrated instructions on the proper use of each item. If they don't, most manufacturers have user manuals and instructions posted on their websites for download. And, any reputable supplier or manufacturer will gladly provide additional copies of user documents if they weren't included in the shipment.

But, facilities should be sure the source providing instructions for using PPE products is credible. While there are thousands of how-to instructional videos on YouTube, Vimeo and other video-sharing services, many are created by hobbyists or other end users and may not represent proper, effective usage. Despite what they say, the videos may also not be illustrating the exact same model or variant of the PPE obtained. In fact, YouTube is great for instructions on assembling your 12-year-old's new backyard trampoline, but not so much for the appropriate use of respirators or face guards.

For standard equipment of all makes and models, particularly equipment used in an infection isolation environment, CDC has step-by-step instructions both for putting it on before entering an infection-control room and removing it before exiting at www.cdc.gov/coronavirus/2019-ncov/hcp/using-ppe.html. Also found on this site are printable posters in PDF format providing visual guides for the instructions, as well as proper wear of respirators and masks, all of which are in English and Spanish and are appropriate for posting either in nurses' stations, changing/locker rooms or outside isolation rooms where they can be referenced by staff as they don the equipment.

A recent survey of more than 21,000 nurses in the U.S. found that as we were heading into autumn, 42 percent were still reporting shortages of PPE.

According to Dr. Lo, many trade groups and associations serving a variety of healthcare facilities also offer PPE training materials and videos. The clinics he works with at the University of California, Riverside Health System, for instance, have access to materials from the Association of American Medical Colleges. And, various state and county health departments may have training materials that can be obtained from local public health offices or association representatives.

What's most important is training should be delivered

consistent with an organization's existing training program, and new employees should receive PPE training along with their onboard training.

Measuring Compliance

Staff can be provided all the training in the world, but if they don't follow that training consistently on a daily basis, it won't do any good. For example, one need look no further than the issue of healthcare acquired infections. CDC reports nearly every one of these infections would have been preventable if standard protocols had been followed. Floor staff know how to disinfect an exam room and instruments, and they have received training and follow-up reinforcement. Yet, each year, some two million Americans get infected at a medical facility[5] because the training wasn't followed.

The first step to ensuring compliance is keeping accurate records of PPE training for all staff. Some PPE training is already covered by Occupational Safety and Health Administration requirements for bloodborne pathogens training.[6] Including airborne PPE training into an existing training regimen will help ensure no employees are falling through the cracks, putting themselves, their co-workers and patients at heightened risk of spreading the novel coronavirus.

Periodic retesting is also a useful tool to determine whether employees are retaining and implementing the training. In addition, unannounced audits, in which employees are observed in their normal duties to see if they are following the training, are an effective method for measuring compliance.

But Lo says the single biggest factor in whether employees consistently follow safety protocols regarding PPE is the workplace culture: "Whether or not we had a pandemic, there are a lot of team mentalities operating all the time." He points out that the procedures in properly using PPE are well-known to all healthcare workers, and they've been in place for decades. "In clinical settings, in patient settings, even when you had isolation wards for tuberculosis, nothing's really significantly changed," Dr. Lo explains. "When I was back in medical school when HIV was getting out there, and you had a lot of isolation, not a lot has had to change. All of this was true before you had COVID."

Dr. Lo says the biggest changes in infection control and the use of PPE over the decades haven't been technological so much as cultural — an increasing emphasis on consistently following protocols every single time: "Over the years, there's been so much more attention to just washing your hands! Doing rounds, we didn't used to wash our hands between patients when I was first starting."

The Wildcard

The biggest wildcard, says Dr. Lo, is whether patients follow the posted rules when visiting a clinic or office. Administrators and supervisors have far less control over patient behavior than they do over staff. "The patients don't get the training," he points out. "I think it's a question of how the culture is going to change over the next months and years, where the patients are going to be more attentive to these things. A lot depends on the psychology [of an organization]. In our research labs on campus, we still haven't had a case of COVID traced to our labs, which is really impressive."

As an example of how an organizational culture can affect patient compliance with behavioral expectations, Dr. Lo points to the experience of medical professionals in some Asian countries where patients have been wearing masks in healthcare settings for so many years that it has become ingrained habit.

Moving Forward

Dr. Lo warns that healthcare supervisors are going to have to be vigilant about training and compliance regarding PPE for the foreseeable future: "I think we're going to be dealing with this for at least another year or two."

Unfortunately, as the novelty of life with COVID-19 has worn off, Dr. Lo says the biggest challenge for administrators will be to watch for staff burnout and people letting their guard down over time. "I think the whole shutdown has its whole psychiatric overlay. People are to the point of, 'Oh, who cares if I get infected.'"

On reflection, though, everything being done to stop the spread of the novel coronavirus is what has been done in short stretches to stop particularly heavy outbreaks of influenza or other airborne infectious diseases in years past. "The precautions they've been pushing every year for the flu are just as valid for COVID," explains Dr. Lo. "That's also true for the common cold. If you don't wash your hands, you touch everything and then you touch your face: That's how you get it." ❖

JIM TRAGESER is a freelance journalist in the San Diego area.

References

1. Kronemyer B. Protect Yourself From Counterfeit PPE. *Infectious Disease* Special Edition, Sept. 25, 2020. Accessed at www.idse.net/Covid-19/Article/09-20/Protect-Yourself-From-Counterfeit-PPE/60661.
2. Forrest B, Grimaldi J, and Pulliam S. Brokers Peddle Fake Medical Gloves Amid Coronavirus Shortages. *The Wall Street Journal*, Sept. 15, 2020. Accessed at www.msn.com/en-us/news/us/brokers-peddle-fake-medical-gloves-amid-coronavirus-shortages/ar-BB194a5B.
3. 20,000 Counterfeit N95 Masks Seized By CBP In Boston. WBZ Channel 4, Sept. 17, 2020. Accessed at boston.cbslocal.com/2020/09/17/counterfeit-n95-masks-ppe-boston-cargo-port-customs.
4. Hickey M. Surge in Illegal Drugs and COVID-19 Counterfeits During Pandemic Shipments. CBS 2 Chicago, Sept. 24, 2020. Accessed at chicago.cbslocal.com/2020/09/24/surge-in-illegal-drugs-and-covid-19-counterfeits-during-pandemic-shipments.
5. PatientCareLink. Healthcare-Acquired Infections (HAIs). Accessed at patientcarelink.org/improving-patient-care/healthcare-acquired-infections-hais.
6. U.S. Department of Labor. Bloodborne Pathogens and Needlestick Prevention. Accessed at www.osha.gov/bloodborne-pathogens/resources.

BioSupply®
Helping Healthcare Care

BioSupply® is the online product ordering platform by FFF Enterprises, Inc., the largest and most trusted distributor of plasma products, vaccines, biosimilars and other specialty pharmaceuticals and biopharmaceuticals.

Visit www.fffenterprises.com to learn more about us.

Point, Click, Confidence.

BioSupplyOnline.com

makes ordering your products easy, fast and convenient!

Available Products

Adult Vaccines
Albumin/Plasma Protein Fraction
Ancillaries
Antithrombin
BioSurgical
Coagulation Factor
Essential Medicines
Hyperimmune Globulin Immune Globulin
Influenza Vaccines
Oncology
Pediatric Vaccines
Pharmaceuticals

We are proud to be an accredited NABP® Verified-Accredited Wholesale Distributor for all authorized U.S. plasma products manufacturers.

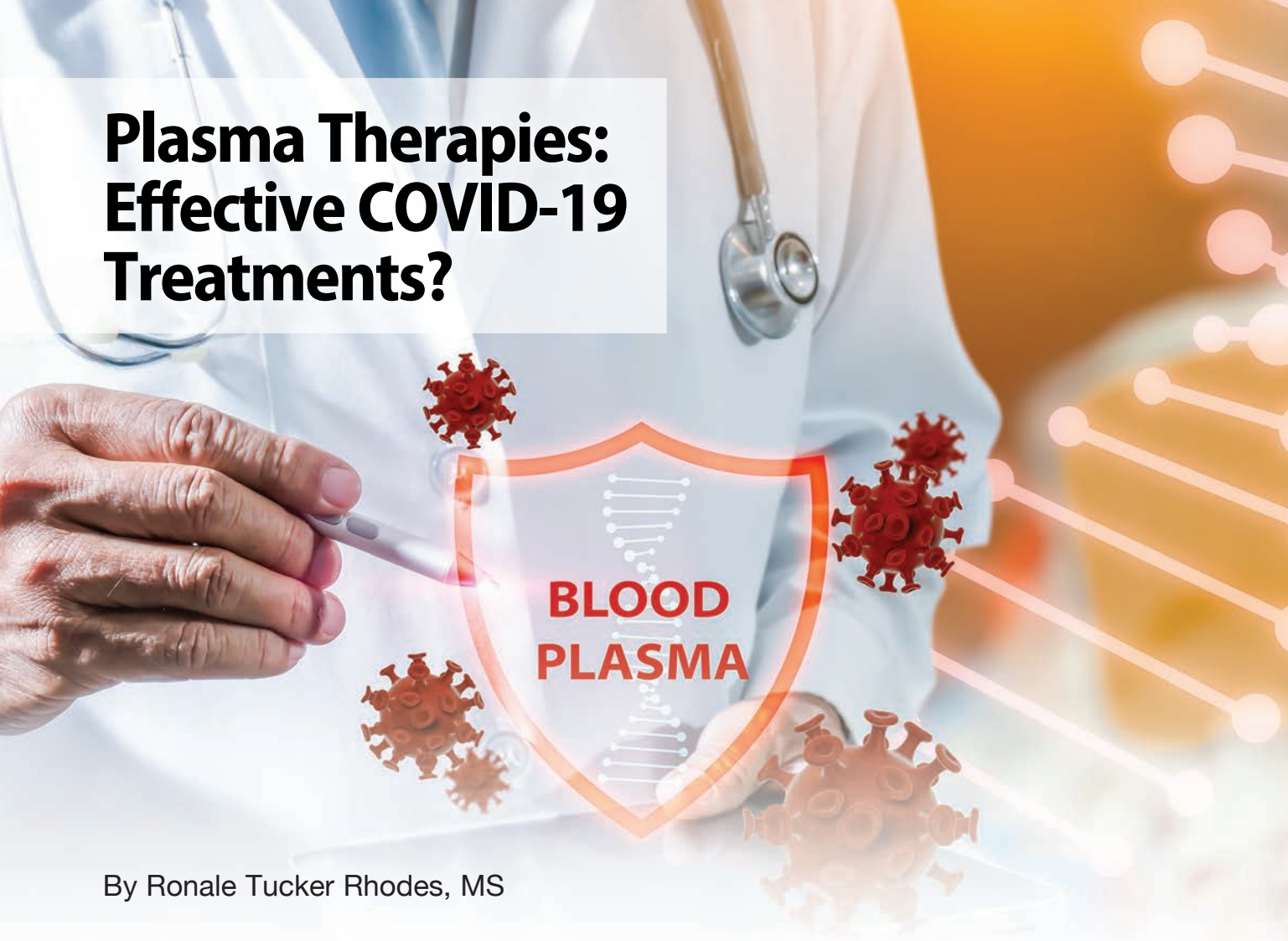
BioSupply is a quick and easy-to-use e-commerce platform offering instant access to the critical-care products you need when you need them. Our customer-driven online portal empowers you to order what you want, when you want it, so you can better manage your inventory. With over 32 years of safe, counterfeit-free product distribution, you can purchase through us with confidence and peace of mind. BioSupply offers:

- At-a-glance access to your account information
- Links to view open orders and ordering history
- Shortcuts to frequently purchased products
- FFF Sales Team contact information
- Detailed product pages
- Product alternatives if products are back-ordered or unavailable
- Convenience and accessibility to drop-ship products
- Shopping Cart feature displays account number and shipping address to minimize purchasing errors
- My Favorites feature for frequently ordered products
- BioVision reporting tool provides analysis of purchasing patterns

For ordering support, contact our Wow! Customer Care team:
P: (800) 843-7477 | Emergency Ordering available 24/7/365
F: (800) 418-4333
E: customerservice@fffenterprises.com

FFF enterprises
Helping Healthcare Care®

Plasma Therapies: Effective COVID-19 Treatments?



By Ronale Tucker Rhodes, MS

Studies shed light on whether high-dose intravenous immune globulin, convalescent plasma and hyperimmune globulin will be effective therapeutic options for the novel coronavirus.

THE RACE IS on to find remedies to prevent and treat the COVID-19 virus that has infected more than 38 million and killed more than one million people worldwide. While much focus has been on a preventive vaccine, numerous other treatments to reduce the severity of infection and reverse the course of disease are being studied. Plasma therapies have taken a seat among these investigational treatments as pre-existing therapeutic options, including high-dose intravenous immune globulin (IVIG), convalescent plasma and hyperimmune globulin. And, although there is a great deal of hope for the promise of plasma therapies to treat COVID-19 patients, their effectiveness is still unknown, and other challenges remain, most notably the availability of plasma to manufacture them.

IVIG, Convalescent Plasma and Hyperimmune Globulin: The Difference?

IVIG, derived from the plasma of thousands of donors from the general population, provides passive immune protection against a broad range of pathogens. It is used to treat primary and secondary immunodeficiencies, autoimmune/inflammatory conditions, neuroimmunologic disorders and infection-related sequelae. Currently, seven manufacturers commercially market nine different IVIG products. And, while it may provide immunomodulatory effect in a hyperinflammation state such as can occur with COVID-19, it is absent any specific neutralizing antibody titers against novel pathogens such as the SARS-CoV-2 virus that causes COVID-19.[1]

Convalescent plasma, collected from recovered patients, can be transfused directly into people experiencing serious complications from COVID-19. It is an individualized therapy, which means the plasma comes from one or several donors and is transfused directly to one patient, which makes it difficult to scale to the levels needed globally. However, since there is limited processing and faster availability, it can be ready for use the same day plasma is collected, but it must be infused or frozen within 24 hours. To ensure its safety, donated plasma must be evaluated to ensure it does not contain other viruses, and the blood needs to be tested

to ensure it is compatible with the recipient's blood. However, its effectiveness varies since the amount and range of antibodies in a unit of plasma varies by donor. In addition, because plasma is 90 percent water and convalescent plasma is minimally processed, it contains fewer virus-specific antibodies per unit of volume.[2]

Hyperimmune globulin is derived from convalescent plasma that has been pooled, processed and purified to concentrate antibodies with the potential to treat people at high risk for serious complications from COVID-19. A mass-produced therapy from donors who have recovered from COVID-19, it is sent to manufacturing facilities where it is pooled together, processed to remove or inactive viruses and toxins, and purified to concentrate antibodies. Requiring more processing and clinical trials, it takes longer to become available; however, it has a longer shelf-life (24 months to 36 months), making it easier to distribute and store for use in future outbreaks. Unlike convalescent plasma, blood-type matching is not required. Because hyperimmune globulin is pooled from convalescent plasma donors and then purified and concentrated, it can be standardized to have a minimum level of antibodies in each unit, which means the effectiveness of different batches should not vary therapeutically. And, because it is highly concentrated, it contains more virus-specific antibodies per unit of volume.[2]

High-Dose IVIG Studies

To date, one randomized placebo-controlled, double-blind clinical trial, as well as data from retrospective, case series and open-label randomized controlled trials have indicated IVIG immunotherapy could benefit severe and critically ill COVID-19 patients.

Results from the first randomized placebo-controlled double-blind clinical trial were published at the end of October in the journal *BMC Infectious Diseases*. In the study, 59 patients with severe COVID-19 infection who did not respond to initial treatments were randomly assigned to two groups: 30 patients who received four vials of IVIG daily for three days (in addition to initial treatment), and 29 patients who received a placebo. Patients' demographic, clinical and select laboratory test results were recorded and deemed to not be statistically different between the two groups. In addition, the occurrence of in-hospital mortality was recorded, which found the mortality rate was significantly lower in the IVIG group compared to the control group (6 [20.0 percent] vs. 14 [48.3 percent], respectively). Multivariate regression analysis demonstrated administration of IVIG did indeed have a significant impact on mortality rate.[3]

In an article published in *Clinical & Translational Immunology*, researchers presented a multicenter retrospective cohort study

that evaluated the efficacy of IVIG in 325 severe and critically ill COVID-19 patients admitted to hospitals in southern China between December 2019 and March 2020. In the study, 174 patients (64 percent male, median age 61 years) received a dose of 0.1 g/kg to 0.5 g/kg of IVIG per day for between five and 15 days, while 151 patients (51 percent male, median age 56 years) did not receive this therapy. Additional therapies included antibiotics, antiviral drugs and steroids per guidelines in China. Results showed early administration (less than or equal to seven days postadmission) of high-dose (greater than 15 g per day) IVIG improves the prognosis of critical-type patients with COVID-19. However, the researchers cautioned the study had limitations since it was a retrospective study, there was a wide range of IVIG dose and varying duration of treatment, and there was a lack of analyses of various inflammatory cytokines and immune cells. There are also data from six other studies that were mostly case series or retrospective, with an exception of one study that was a randomized open-label trial. Most of these studies combined corticosteroids with IVIG, making it difficult to evaluate the therapeutic benefits of IVIG. However, all did show some therapeutic benefit.[4]

Because studies suggest convalescent plasma is effective in treating other coronaviruses, researchers are studying its use for treating COVID-19.

Perhaps one of the most promising of the other six studies that evaluated high-dose IVIG for treating COVID-19 patients in the U.S. is Octapharma's first study of its Octagam 10% (immune globulin intravenous [human]) plus standard of care (SOC) compared to SOC alone to prevent mechanical ventilation in COVID-19 patients requiring high-flow oxygen. That study enrolled 33 COVID-19 patients experiencing hypoxia who were at risk of requiring mechanical ventilation. Sixteen patients with a median age of 51 years received 0.5 g/kg/day for three days with 40 mg of methylpredisolone 30 minutes prior to infusion, and 17 patients with a median age of 58 years received SOC alone. Findings revealed the use of IVIG reduced the rate of progression of respiratory failure requiring mechanical ventilation (13 percent with IVIG versus 41 percent without IVIG). According to lead investigator George Sakoulas, MD, of Sharp Memorial Hospital and the Sharp Rees-Stealy Medical Group in San Diego, Calif., "While this [study] did not achieve statistical significance among the collective subject cohorts, the reduced rate of progression to mechanical ventilation with IVIG achieved statistical significance among the subset with a calculated or estimated Alveolar-arterial gradient of greater than 200 mm Hg (14 percent with IVIG versus 58 percent without IVIG)."[5]

Dr. Sakoulas is also leading a larger multicenter, randomized, double-blind placebo-controlled study to determine if high-dose Octagam 10% therapy will slow or stop respiratory deterioration in patients with severe COVID-19. Secondary objectives of this study are to measure the effects of the treatment on slowing or stopping the clinical progression of COVID-19 by improving pulmonary function, quality of life and correlated impact on metabolic factors. The study is estimated to enroll more than 200 patients and is currently enrolling.[6]

Grifols Therapeutics is conducting a study to determine if a high dose of IVIG plus standard medical treatment (SMT) can reduce all-cause mortality versus SMT alone in hospitalized participants with COVID-19 requiring admission to the intensive care unit (ICU) through day 29. Participants receiving IVIG plus SMT will receive the first IVIG infusion of Gamunex-C on day one up to a total net dose of 2 g/kg, based on participant's body weight (maximum dose = 160 g for participants over 80 kg), administered in divided doses as infusions of 500 mg/kg, based upon participant's body weight, over four days, or 400 mg/kg, based upon participant's body weight, over five days. Participants will also receive all SOC interventions while hospitalized from day one to day 29. The primary outcome measure is all-cause mortality rate at day 29. The study is currently recruiting, and there is no scheduled end date.[7]

Grifols is also conducting a study to determine if high-dose IVIG plus SMT can reduce the proportion of participants dying or requiring ICU admission on or before day 29 or who are dependent on high-flow oxygen devices or invasive mechanical ventilation on day 29 versus SMT alone in hospitalized patients with COVID-19. This study will enroll an estimated 100 patients who will receive Flebogamma (immune globulin [human] liquid) at the same dosing as its Octagam study.[8]

Although why IVIG seems to have beneficial effect is not yet precisely understood, it is believed to be due to a reduction in the inflammatory mediators following IVIG therapy, which suggests IVIG might target cytokine storm in severe and critically ill COVID-19 patients by complement scavenging, inhibition of innate immune cells and effector T-cell activation, and expansion of Tregs.[4]

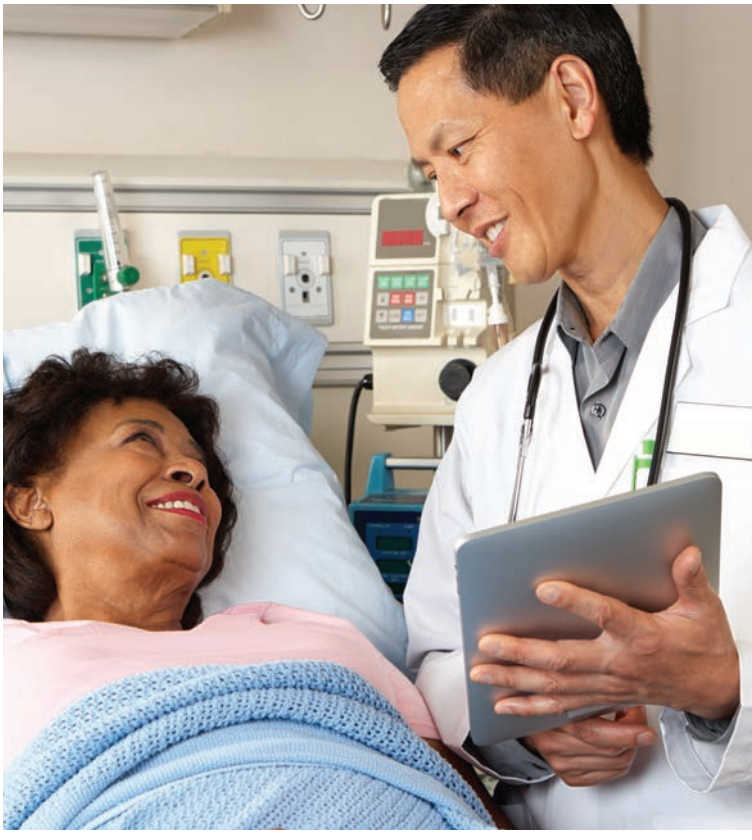
Convalescent Plasma Studies

Because studies suggest convalescent plasma is effective in treating other coronaviruses, researchers are studying its use for treating COVID-19. For instance, a study conducted in 2004 in Hong Kong showed patients with SARS who were given convalescent plasma earlier in the infection process were discharged from the hospital sooner and were less likely to die than patients who were given it later. And, in 2014, the World Health Organization published guidance on convalescent plasma donor selection and treatment after research showed positive results for Ebola.[9]

Unfortunately, most current research does not show convalescent plasma is effective in treating SARS-CoV-2. One study in China that was reported in *JAMA* in June found convalescent plasma in addition to standard treatment didn't significantly improve patients with severe or life-threatening COVID-19.[8] In June, a meta-analysis was conducted of 20 studies (one randomized controlled trial, three controlled nonrandomized studies of interventions [NRSIs], and 16 noncontrolled NRSIs) with 5,443 participants, 5,211 of whom received convalescent plasma. Results were very uncertain whether convalescent plasma has any effect on 1) all-cause mortality at hospital charge, 2) prolonged time to death and 3) improvement of clinical symptoms at seven days.[10]

Some research does show convalescent plasma seems to reduce the risk of dying from COVID-19. An analysis of 35,000 hospitalized patients who received convalescent plasma to treat severe COVID-19 within three days of diagnosis were less likely to die than patients who received convalescent plasma later in their illness. But, that study had no control group.[11] In another safety study of convalescent plasma, there was a trend toward fewer deaths in 145 patients who received plasma versus 435 patients who did not. However, the researchers reported the results were not statistically meaningful. But, when they broke the data down to look at people who received plasma treatment with high levels of antibodies within 72 hours of being admitted to the hospital, they did see a statistically meaningful difference: About 7 percent of those who didn't get plasma died within 28 days of hospitalization, compared with 1.2 percent of patients who were treated with plasma with high levels of antibodies within a couple of days of hospitalization. The researchers stressed, though, that only results from randomized, controlled trials will be able to determine how well the treatment works.[12]

While convalescent plasma is generally considered safe, it is not without some risks. In a Johns Hopkins University study of more than 16,000 Americans with COVID-19 who were infused with plasma from recovered patients, no major safety issues were reported.[7] In another study of 5,000 patients published in the



Journal of Clinical Investigation, researchers found serious adverse events such as allergic reactions or transfusion-related lung injury occurred less than 1 percent of the time.[12] And, in the meta-analysis discussed previously, the researchers concluded they are very uncertain whether convalescent plasma affects the number of serious adverse events. Other studies have reported on possible grade 3 or grade 4 adverse events, the majority of which were allergic or respiratory events. However, those researchers were unsure whether convalescent plasma affects the risk of moderate to severe adverse events. Lastly, one study reported 15 deaths, four of which they classified as potentially, probably or definitely related to transfusion of convalescent plasma.[9]

What's important to note is there are no randomized controlled trials yet that have shown convalescent plasma works against the SARS-CoV-2 virus. Nevertheless, on Aug. 23, as part of the U.S. Food and Drug Administration's ongoing efforts to fight this pandemic, the agency issued an emergency use authorization (EUA) for the use of investigational convalescent plasma to treat hospitalized patients with serious or life-threatening COVID-19 infection.[13] Indeed, it's important to understand that while outcomes were tracked of the some 70,000 COVID-19 patients who were treated with convalescent plasma prior to the EUA,

those outcomes were not intended to be a formal clinical trial since there was no control arm.[14]

Even so, EUA gives physicians permission to use an experimental therapy in certain circumstances. And, while it's not the same as FDA approval (there are no approved therapies for COVID-19), researchers can test convalescent plasma in clinical trials of COVID-19. And, use of survivors' plasma can also be extended to people with serious or immediately life-threatening COVID-19 who aren't eligible for clinical trials.[12]

Hyperimmune Globulin Studies

Hyperimmune globulin, which provides passive immunity to COVID-19, could be used for both prevention and treatment. As part of a collaboration with FDA, the National Institutes of Health and the Biomedical Advanced Research Development Authority, among others, hyperimmune globulin products are being developed to undergo clinical trials to evaluate their safety and efficacy:

Perhaps one of the greatest obstacles for plasma therapies is supply.

• Since April, Grifols has been collecting COVID-19 convalescent plasma for its anti-SARS-CoV-2 hyperimmune globulin in more than 245 Grifols U.S. donation centers. The donors' plasma has high levels of anti-SARS-CoV-2 neutralizing antibodies. In July, Grifols delivered the first manufactured batches of its anti-SARS-CoV-2 hyperimmune globulin for clinical trials. Its hyperimmune globulin, which is derived from blood plasma of healthy donors recovered from COVID-19, has the potential to be a highly specific, pure and safe medicine that delivers a high and consistent concentration of protective antibodies against the novel coronavirus. As of this writing, FDA had approved the protocol to start the clinical trial that will evaluate its safety and efficacy.[15]

• Patients are now being enrolled in the Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) Phase III clinical trial that will evaluate the safety, tolerability and efficacy of an investigational anti-coronavirus hyperimmune intravenous immune globulin (H-Ig) medicine for treating hospitalized adults at risk for serious complications of COVID-19 disease. If successful, the CoVIg-19 Plasma Alliance's H-Ig may become one of the earliest treatment options for hospitalized COVID-19 patients. The investigational H-Ig materials for the trial will be provided by CSL Behring and Takeda on behalf of the Alliance, as well as by two other companies.[16]

Another trial listed on the clinicaltrials.gov website is being sponsored by Green Cross Corp., which began recruiting in September. The company's study will evaluate the efficacy and safety of its 5131A hyperimmune globulin for hospitalized patients of COVID-19.[17]

Interestingly, while the aforementioned trials are all testing hyperimmune globulin products manufactured from donated human plasma, there have been published news reports about investigational treatments for COVID-19 using hyperimmune serum developed with antibodies from horses. For example, Immunova developed its hyperimmune globulin product by injecting a SARS-CoV-2 protein into horses to generate a large amount of neutralizing antibodies. Plasma is then extracted from the horses, purified and processed. After positive results in laboratory tests, its clinical trial will be tested in 242 people diagnosed with moderate to severe COVID-19 symptoms.[18] The Indian Council of Medical Research (ICMR) is also developing horse sera containing antibodies against COVID-19 as a potential alternative to plasma therapy after a study conducted in India showed the latter does not prevent deaths in moderate and severe COVID-19 patients. According to ICMR, plasma recovered from patients experiencing COVID-19 has a varying profile of antibodies, efficacy and concentrations, which makes it unreliable as a clinical tool for patient management. But, it says, the standardization of antibody-rich plasma can be achieved using animals. After completing animal trials, ICMR received clearance to begin a clinical trial in humans.[19]

For more information on hyperimmune globulin, see "The Promise of COVID-19 Hyperimmune Globulin Products" on p.46.

The Uncertainty of Plasma Supply

Perhaps one of the greatest obstacles for plasma therapies is supply. Inherently, since IVIG is manufactured from human plasma donated by the general population, there is potentially ample supply. However, that assumes people will donate. And, during this pandemic, plasma donations have significantly declined due to impacts of social distancing measures and other mobility restrictions. According to the Plasma Protein Therapeutics Association (PPTA), considering the complex manufacturing of plasma-derived therapies can take seven to 12 months, any decline in plasma donations could impact patients' ability to access this therapy. In response, PPTA

and other organizations such as the Immune Deficiency Foundation and the Immunoglobulin National Society have launched campaigns to raise awareness of source plasma collection, recognize the contributions of plasma donors in saving and improving lives, and increase understanding about lifesaving plasma therapies.[20]

But, even more of a challenge is obtaining enough donated plasma from people who have recovered from COVID-19. The American Red Cross announced in July that it's facing an emergency shortage of convalescent plasma since it is being distributed faster than donations are coming in. When COVID-19 cases spiked, the American Red Cross saw hospital demand for convalescent plasma more than double, reducing the supply by more than 70 percent. Currently, the agency is collecting convalescent plasma at more than 170 locations throughout the U.S. to help meet patient needs. But more donations are needed to keep up with immediate and future patient needs.[21]

Clinicians and hospitals can help with convalescent plasma collection. In partnership with FDA, the American Red Cross has developed a process to identify and qualify individuals who have recovered from COVID-19 and collect their COVID-19 convalescent plasma. The program is working with clinicians to enable rapid access to a new experimental plasma treatment for the most seriously ill patients. However, because this is still an investigational new drug (IND) program, requesting and receiving convalescent plasma occurs outside the routine product ordering processes. FDA has allowed for three pathways through which hospitals can acquire convalescent plasma: the Expanded Access Protocol (EAP), a Single Patient Emergency Investigational New Drug (eIND) application or another Investigator-Initiated Research IND. Specific information can be found at Recommendations for Investigational COVID-19 Convalescent Plasma (www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma). Clinicians participating via the EAP and eIND pathways to receive COVID-19 convalescent plasma for their currently ill patients can register them at www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients/clinician-registration.html.[22]

Interventions Are Needed Now

Until a preventive vaccine is developed to protect against the SARS-CoV-2 virus, the urgent need for other effective interventions such as plasma therapies remains. While there is no clear indication plasma is effective, studies of the use of high-dose IVIG have shown it may be helpful in severe COVID-19 cases. It is also believed convalescent plasma could be a highly effective treatment since it has shown promise in other diseases. Practically speaking, it is unknown whether hyperimmune globulin will be effective since no clinical trials have yet been completed. Nevertheless, even if plasma therapies show promise for treating COVID-19 patients, plasma collection and processing remain a challenge. ❖

References

1. Nguyen AA, Habiballah SB, Platt CD, et al. Immunoglobulins in the Treatment of COVID-19 Infection: Proceed with Caution! *Clinical Immunology*, Volume 216, July 2020. Accessed at www.sciencedirect.com/science/article/pii/S1521661620303557.
2. CoVIg-19 Plasma Alliance. Convalescent Plasma Transfusion and Hyperimmune Globulin: Understanding the Difference. Accessed at www.cslbehring.com/vita/2020/convalescent-plasma-and-hyperimmune-globulin.
3. Gharebaghi N, Nejadrahim R, Mousavi SJ, et al. The Use of Intravenous Immunoglobulin Gamma for the Treatment of Severe Coronavirus Disease 2019: A Randomized Placebo-Controlled Double-Blind Clinical Trial. *BMC Infectious Diseases*, Volume 20, Article number: 786 (2020). Accessed at bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05507-4.
4. Galeotti C, Kaveri SV, and Bayry J. Intravenous Immunoglobulin Immunotherapy for Coronavirus Disease-19 (COVID-19). *Clinical & Translational Immunology*, Oct. 16, 2020. Accessed at onlinelibrary.wiley.com/doi/full/10.1002/cti2.1198.
5. ClinicalTrials.gov. Study to Evaluate the Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) Plus Standard Medical Treatment (SMT) Versus SMT Alone in Participants in Intensive Care Unit (ICU) with Coronavirus Disease (COVID-19). Accessed at clinicaltrials.gov/ct2/show/NCT04480424.
6. ClinicalTrials.gov. Octagam 10% Therapy in COVID-19 Patients with Severe Disease Progression. Accessed at clinicaltrials.gov/ct2/show/NCT04400058?term=High-dose+intravenous+immune+globulin&cond=Covid19&draw=2&rank=3.
7. Coronavirus Disease (COVID-19). Accessed at clinicaltrials.gov/ct2/show/NCT04480424.
8. ClinicalTrials.gov. Study to Evaluate the Safety and Efficacy of High Dose IVIG in Hospitalized Participants with Coronavirus Disease (COVID-19). Accessed at clinicaltrials.gov/ct2/show/NCT04432324?term=High dose+intravenous+immune+globulin&cond=Covid19&draw=2&rank=2.
9. Rodriguez A. What Is Plasma Therapy, and How Does It Work to Treat the Coronavirus? Everything You Need to Know. *USA Today*, June 8, 2020. Accessed at www.usatoday.com/story/news/health/2020/06/08/coronavirus-plasma-therapy-covid-19-what-and-how-works/3143045001.
10. Piechotta V, Chai KL, Valk SJ, et al. Convalescent Plasma or Hyperimmune Immunoglobulin for People with COVID-19: A Living Systematic Review. *Cochrane Database Systematic Review*, July 10, 2020; 7(7). Accessed at pubmed.ncbi.nlm.nih.gov/32648959.
11. Harvard Medical School. Treatments for COVID-19, Aug. 24, 2020. Accessed at www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19.
12. Lambert J and Saey TH. COVID-19 Plasma Treatments May Be Safe, But We Don't Know If They Work. Science News, Aug. 25, 2020. Accessed at www.sciencenews.org/article/coronavirus-covid-19-patient-convalescent-plasma-treatment.
13. FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration's Fight Against Pandemic. U.S. Food and Drug Administration press release, Aug. 23, 2020. Accessed at www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment.
14. Feldscher K. Decision on Convalescent Plasma for COVID-19 Raises Questions. Harvard School of Public Health, Aug. 28, 2020. Accessed at www.hsph.harvard.edu/news/features/decision-on-convalescent-plasma-for-covid-19-raises-questions.
15. Grifols Delivers First Manufactured Batches of Its Anti-SARS-CoV-2 Hyperimmune Globulin for Clinical Trials. Grifols press release, July 28, 2020. Accessed at www.grifols.com/en/view-news/-/news/grifols-delivers-first-manufactured-batches-of-its-anti-sars-cov-2-hyperimmune-globulin-for-clinical-trials.
16. First Patient Enrolled in NIH Phase 3 Trial to Evaluate Potential COVID-19 Hyperimmune Medicine. CSL Behring press release, Oct. 8, 2020. Accessed at www.cslbehring.com/newsroom/2020/first-patient-enrolled-in-nih-covid19-phase-3-trial.
17. Clinicaltrials.gov. COVIDIG (COVID-19 Hyper-ImmunoGlobulin). Accessed at clinicaltrials.gov/ct2/show/NCT04555148?term=Hyper+Immunoglobulin&cond=SARS-CoV-2&draw=2&rank=2.
18. Argentina Starts Trials on Hyperimmune Equine Serum to Treat COVID-19. Reuters, July 30, 2020. Accessed at timesofindia.indiatimes.com/life-style/health-fitness/health-news/argentina-starts-trials-on-hyperimmune-equine-serum-to-treat-covid-19/articleshow/77254025.cms.
19. Basu M. ICMR Sets Sights on Horse Sera for COVID as Therapy with Human Plasma Found 'Ineffective.' The Print, Oct. 6, 2020. Accessed at theprint.in/health/icmr-sets-sights-on-horse-sera-for-covid-as-therapy-with-human-plasma-found-ineffective/518208.
20. International Plasma Awareness Week 2020: Be a Hero, Donate Plasma Today. Plasma Protein Therapeutics Association press release, Oct. 5, 2020. Accessed at www.prnewswire.com/news-releases/international-plasma-awareness-week-2020-be-a-hero-donate-plasma-today-301145146.html.
21. American Red Cross. National Coronavirus Surge Leads to Emergency Convalescent Plasma Shortage, July 22, 2020. Accessed at www.redcross.org/about-us/news-and-events/press-release/2020/national-coronavirus-surge-leads-to-emergency-convalescent-plasma-shortage.html.
22. American Red Cross. Coronavirus (COVID-19) Convalescent Plasma Clinician Information. Accessed at www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients/clinician-registration.html.

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly*.

Pandemic Preparedness:
Ensuring the U.S. Is Ready for the Next One?

After several federal agencies spent two decades and tens of billions of dollars preparing for the next pandemic, critics were not shy about pointing out how unprepared the United States was for the current SARS-Cov-2 pandemic.

By Diane L.M. Cook

PANDEMICS HAVE BEEN on record as far back as the 1600s. In the last 100 years, there have been four pandemics. In the United States, each pandemic has resulted in hundreds of thousands of illnesses and tens of thousands of deaths, including devastating effects on the nation's economy. And, after each pandemic, the nation's many agencies developed new pandemic preparedness plans or, at the least, incorporated lessons learned into existing plans.

If there is one lesson learned from the current pandemic, it is the illumination of shortcomings and gaps in pandemic preparedness plans. What started as a misrepresented pneumonia outbreak in 44 patients in Wuhan, China — reported to the World Health Organization (WHO) China Country Office on Dec. 31, 2019[1] — quickly morphed into one of the world's worst pandemics on record. On March 11, 2020, WHO finally judged the SARS-CoV-2 virus, which causes the novel corona influenza virus (COVID-19), could be characterized as a pandemic.[2]

This two-and-a-half-month delay in announcing the pandemic resulted in the world's countries delaying their own responses that would have involved calling states of emergencies while the pandemic rapidly unfolded. The adverse effects of this delay were especially profound in the United States where, even after invoking its many agencies' multifaceted pandemic preparedness plans, there have been more than eight million cases and more than 250,000 deaths as a result of COVID-19 as of this writing.[3]

However, critics say, notwithstanding WHO's delay in declaring a pandemic, it was the bureaucracy surrounding the United States' pandemic preparedness plans that resulted in millions of cases of COVID-19 and hundreds of thousands of deaths, rather than the government's unpreparedness.

Historically, only one global-based health agency and a few main health agencies in the United States existed in the last two decades to develop pandemic preparedness plans intended as guidance documents for government, healthcare systems and hospitals. And, since many of these agencies work in conjunction with each other, additional information or material has been created that overlaps these plans.

World Health Organization (WHO)

WHO, in working to promote worldwide health, keep the world safe and serve the vulnerable, has developed several guidance documents on pandemic preparedness to help countries plan and prepare for a pandemic. According to WHO, "The objective of pandemic planning is to enable countries to be prepared to recognize and manage an influenza pandemic. Planning may help to reduce transmission of the pandemic virus strain, to decrease cases, hospitalizations and deaths, to maintain essential services and to reduce the economic and social impact of a pandemic."[4]

WHO's Pandemic Influenza Phases comprise an alert system developed to help inform the world about the seriousness of a pandemic. It has six phases, with Phase 1 having the lowest risk of human cases and Phase 6 posing the greatest risk. The system also includes a post-peak period, possible new wave period and post-pandemic period. The phases are applicable globally and provide a framework to aid countries in pandemic preparedness and response planning.[5]

Since 1952, global influenza surveillance has been conducted through WHO's Global Influenza Surveillance and Response System (GISRS), which has fostered global confidence and trust for more than half a century through effective collaboration and sharing of viruses, data and benefits based on member states' commitment to a global public health model. The mission of GISRS is to protect people from the threat of influenza by continuously functioning as a global mechanism of surveillance, preparedness and response for seasonal, pandemic and zoonotic influenza; global platform for monitoring influenza epidemiology and disease; and global alert for novel influenza viruses and other respiratory pathogens.[6]

In 2005, WHO published its Checklist for Influenza Pandemic Preparedness Planning. In 2009, the agency published its Pandemic Influenza Preparedness and Response Guidance. In 2011, it published its Pandemic Influenza Preparedness (PIP) framework whose purpose is to share information about influenza viruses with member states and stakeholders to increase access to vaccines during pandemics, particularly for developing countries.[7] And in 2017, WHO published its Pandemic Influenza Risk Management: A WHO Guide to Inform and Harmonize National and International Pandemic Preparedness and Response guidance document.

However, even with these guidance documents, WHO admits the world is not prepared for any pandemic. According to a report of the Review Committee on the Functioning of the International Health Regulations (2005) concerning the H1N1 pandemic H1N1 in 2009, "The world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public health emergency."[8]

United States Department of Health and Human Services (HHS)/Office of the Assistant Secretary for Preparedness and Response (ASPR)

In 2005, HHS developed a PIP plan to prevent, control and mitigate the effects of influenza viruses that have the potential to become pandemics. HHS has since published four updates to it, the latest of which was published in 2017 that consists of seven domains. According to HHS, "These domains reflect an end-to-end systems approach to improving the way preparedness and response are integrated across sectors and disciplines, while remaining flexible for the conditions surrounding a specific pandemic. This will allow HHS to respond more quickly to a future influenza pandemic and, at the same time, strengthen our response to seasonal influenza to mitigate the next influenza pandemic."[9]

HHS has also developed three tools to help guide different aspects of planning and response: the Pandemic Intervals Framework (PIF), the Influenza Risk Assessment Tool and the Pandemic Severity Assessment Framework.

WHO admits the world is not prepared for any pandemic.

Developed under HHS, the Hospital Preparedness Program (HPP) is a cooperative agreement administered by the ASPR that establishes a foundation for national healthcare preparedness. According to HHS, the HPP prepares the healthcare system to save lives through the development of regional healthcare coalitions (HCCs), which are groups of healthcare and response organizations that collaborate to prepare for and respond to medical surge events. HCCs, it says, incentivize diverse and often competitive healthcare organizations to work together. Since 2002, the HPP has invested

$5.9 billion in healthcare preparedness with 96 percent of HCCs reporting they feel HPP support has improved their ability to decrease morbidity and mortality during disasters.[10]

In fall 2013, HHS, the ASPR and the National Healthcare Preparedness Programs (NHPP) developed the Healthcare Coalition Checklist for Pandemic Planning, which assists HCCs in assessing, developing and improving their preparedness and response plans for a pandemic. The checklist follows the preparedness capabilities outlined in the Healthcare Preparedness Capabilities: National Guidance for Healthcare System Preparedness. It also recommends actions to develop and/or improve coalition-based emergency response plans for pandemic influenza.[11]

NHPP also developed performance measures, outlined in the 2017-2022 Hospital Preparedness Program: Performance Measures Implementation Guidance, to evaluate program performance and track progress. The guidance is framed for the primary users — awardees and HCCs — to ease comprehension, improve information aggregation and enable faster data collection.[12] In addition, the 2017-2022 Health Care Preparedness and Response Capabilities guidance describes what the healthcare delivery system (HCCs, hospitals and emergency medical services) needs to do to effectively prepare for and respond to emergencies that impact the public's health.[13]

More recently, the ASPR developed the COVID-19 Healthcare Planning Checklist, which identifies specific activities jurisdictions can implement to prepare for, respond to and be resilient in the face of COVID-19. The checklist is adapted from a variety of HHS influenza pandemic planning resources.[14]

In 2018, the ASPR began supporting the Regional Disaster Health Response System (RDHRS) pilot projects, which provide funding directly to hospitals and health systems to establish multistate regional partnerships that increase preparedness and response capability and capacity for hospitals and healthcare facilities in advance of, during or immediately following incidents, including emerging infectious diseases.[15]

Currently, the ASPR is developing a new RDHRS by leveraging and enhancing existing programs such as the HPP and the National Disaster Medical System to create a more coherent, comprehensive and capable healthcare disaster response system integrated into daily care delivery. The proposed RDHRS will be built on a tiered regional framework that emphasizes collaboration among local healthcare coalitions, trauma centers, public and private healthcare facilities, and emergency medical services to expand access to specialty clinical care expertise and increase medical surge capacity.[16]

In June 2019, the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 was passed to strengthen public health and healthcare readiness, bolster response and recovery programs, and increase transparency. There is now a formal authorization for annual funding for programs to develop medical countermeasures for pandemic influenza and other emerging infectious diseases.[16]

The Centers for Disease Control and Prevention (CDC)

CDC works to improve global control and prevention of seasonal and novel influenza, as well as improve influenza pandemic preparedness and response. CDC's response to the COVID-19 pandemic includes preparing first responders, healthcare providers and health systems; providing advice to businesses, communities and schools about how they can manage the pandemic; sharing what it has learned about COVID-19; maintaining safety at the nation's borders by issuing extensive travel guidance; and publishing a variety of communication resources that state and local governments and community organizations can use to support their own pandemic response.[17] According to CDC, "Since launching an agency-wide response to this pandemic on Jan. 21, 2020, CDC has been preparing healthcare workers, learning more about how the disease spreads, and supporting state, local, tribal and territorial governments on the front lines of this outbreak."[18]

Although CDC has not developed a pandemic preparedness framework specifically for COVID-19, it has developed influenza preparedness frameworks. And, since COVID-19 is caused by an influenza virus, the majority of the agency's PIF can be applied to this pandemic. CDC's PIF describes the progression of an influenza pandemic using six intervals to guide influenza pandemic planning and provides recommendations for risk assessment, decision-making and action in the United States.[19]

The Federal Emergency Management Agency (FEMA)

As an agency of the United States Department of Homeland Security, FEMA's mission is to help people before, during and after disasters.

In 2008, FEMA published a template guidance document titled Pandemic Influenza Continuity of Operations Annex Template (PICOAT), which was last updated in 2009, to address a pandemic influenza that focuses on a whole community response.[20]

In 2015, FEMA produced the second edition of its National Preparedness Goal that describes five mission areas (prevention, protection, mitigation, response and recovery) and 32 activities grouped under three core capabilities (planning, public information and warning, and operational coordination) that address the greatest risks to the nation.[21]

In 2017, FEMA published the Biological Incident Annex (BIA) to the Response and Recovery Federal Interagency Operations Plan. While BIA is not scenario-specific, there is significant discussion about federal coordination, response and recovery activities to a

pandemic influenza event that capitalizes on its existing plans for the H1N1 (2009) influenza virus, the emergence of MERS-CoV and H7N9 influenza, and the Pandemic Crisis Action Plan.[22]

In August 2019, FEMA participated in the HHS-led Crimson Contagion national level exercise that involved multiple federal and state agencies and major hospitals, which exercised a nationwide pandemic influenza response, testing current plans, policies and procedures, as well as the nation's core capability to respond. The exercise found that, in the event of a pandemic, the United States lacks sufficient domestic manufacturing capacity and/or raw materials for almost all pandemic influenza medical countermeasures, including vaccines and therapeutics, the needles and syringes needed to administer them, and personal protective equipment, including masks, needles and syringes.[22]

In October 2019, FEMA published the fourth edition of its National Response Framework (NRF), a guide to how the United States responds to all types of disasters and emergencies. The NRF is built on scalable, flexible and adaptable concepts identified in the National Incident Management System to align key roles and responsibilities. It is structured to help jurisdictions, citizens, nongovernmental organizations and businesses develop whole community plans; integrate continuity plans; build capabilities to respond to cascading failures among businesses, supply chains and infrastructure sectors; and collaborate to stabilize community lifelines and restore services. This edition includes lessons learned from previous disasters, new initiatives and enhances the unified effort between the government and the private sector through better coordination and collaboration.[23]

In May 2020, FEMA published its COVID-19 Pandemic Operational Guidance for the 2020 Hurricane Season to help states, tribes and territories address additional planning and safety considerations in the face of COVID-19.[24]

According to a FEMA spokesperson, "FEMA is continuously learning from past disasters and using those lessons learned to inform planning and response decisions. Disaster response cannot be conducted by FEMA alone, it is a whole-of-America effort involving coordination with and expertise from local, state and federal governments, as well as private sector and voluntary organizations."

United States' Nurses Unprepared for the COVID-19 Pandemic

Despite the HPP and a multitude of other pandemic preparedness plans, nurses in U.S. hospitals were woefully unprepared to meet COVID-19 patients' needs. They were acutely aware there was not enough medical PPE (masks, face shields, gloves and gowns), emergency beds or staff, ventilators or specific pandemic information.

Nurses cite a current lack of emergency preparedness education,

the public health system's lack of drilling nurses on emergency situations, staffing shortages, a lack of cross-training and a lack of adequate mental healthcare as reasons they were so unprepared for the pandemic. A recent survey of 32,000 nurses revealed 87 percent of nurses are afraid to go to work, and 36 percent reported having to care for an infectious patient despite inadequate PPE. They also reported an urgent need for education on caring for COVID-19 patients, PPE usage, personal safety and COVID-19 testing.[25]

The Failure of United States' Pandemic Preparedness Plans

Even before WHO officially announced the COVID-19 pandemic, many government officials, academics and media organizations criticized the federal government's handling of it. An article titled "Why Two Decades of Pandemic Planning Failed" outlines how many federal agencies during the past two decades prepared a multitude of pandemic preparedness plans, but when the COVID-19 pandemic occurred, it was not a lack of a pandemic preparedness plan, but rather the bureaucracy of the agencies and the plans that prevented the nation from responding to the pandemic effectively. "The failure of the United States government to respond to the coronavirus was not a failure of foresight," says the article's author. "It was a failure to create a coherent strategy and to provide clear lines of authority to implement it."[26]

In a remarkable case of foreshadowing, the author of a *Politico* magazine article titled "Inside America's 2-Decade Failure to Prepare for Coronavirus," says the HHS' Pandemic Influenza Plan, which was announced in November 2005, "includes tactics, models and other details that eerily resemble today's coronavirus crisis. One scenario, cut from the final report, even described how a respiratory

disease would swiftly move from sickening dozens in an Asian village to killing as many as 1.9 million Americans — a 'grimly compelling' vision, the *New York Times* reported at the time, and a framework that would have foreshadowed future discussions about the COVID-19 outbreak. Staff who worked on the plan say they can't remember why the Asian flu scenario was removed from the final plan."[27]

The headline in an article in *The Washington Post* that retraces the failures over the first 70 days of the coronavirus crisis and is based on 47 interviews with administration officials, public health experts, intelligence officers and others involved in fighting the pandemic, reads, "The U.S. Was Beset by Denial and Dysfunction as the Coronavirus Raged. From the Oval Office to the CDC, Political and Institutional Failures Cascaded Through the System, and Opportunities to Mitigate the Pandemic Were Lost."[28]

Although CDC has not developed a pandemic preparedness framework specifically for COVID-19, it has developed influenza preparedness frameworks.

Another article, in which a disaster response expert was interviewed, says, "While the United States is well-prepared to respond to some diseases, COVID-19 just isn't one of them." And "some clear missteps have hindered our ability to lessen the spread and severity of COVID-19 in the U.S."[29]

Yet another article that reviews a breakdown of federal government spending to prepare for health crises, says, "Over the past decade, the U.S. government spent nearly $100 billion on preparation for major health crises, including pandemics … though the coronavirus outbreak still had Washington and states across the country scrambling to muster supplies and respond when it hit. The sad truth is that the U.S. government did plan for just such a crisis as the one we now face. But we cannot count on planning to solve a future crisis. We need to simplify and clarify our federal bureaucracy so it can respond more nimbly to such a crisis in the future, even while we continue to rely on the wisdom of many thousands of Americans in state and local governments to lead."[30] ❖

DIANE L.M. COOK, B. Comm., is a Canadian freelance magazine writer with more than 330 articles published in several trade journals, including *Oilweek, Oilsands Review, Alberta Construction Magazine* and *Canadian Lawyer*.

References

1. World Health Organization. Pneumonia of Unknown Cause — China, January 9, 2020. Accessed at www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/#:~:text=On%2031%20December%202019%2C%20the,the%20national%20authorities%20in%20China.
2. World Health Organization. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19, March 11, 2020. Accessed at www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
3. Worldometer. United States Coronavirus. Accessed at www.worldometers.info/coronavirus/country/us.
4. World Health Organization. WHO Checklist for Influenza Pandemic Preparedness Planning, 2005. Accessed at www.who.int/csr/resources/publications/influenza/FluCheck6web.pdf.
5. World Health Organization. Current WHO Phase of Pandemic Alert for Pandemic (H1N1) 2009. Accessed at www.who.int/csr/disease/swineflu/phase/en.
6. World Health Organization. Global Influenza Surveillance and Response System. Accessed at www.who.int/influenza/gisrs_laboratory/en.
7. World Health Organization. Addressing Our Health Responsibilities for Pandemic Influenza Preparedness. Accessed at www.who.int/influenza/pip/WHO_PIP_brochure.pdf?ua=1.
8. World Health Organization. Pandemic Influenza Risk Management: A WHO Guide to Inform & Harmonize National & International Pandemic Preparedness and Response, May 2017. Accessed at apps.who.int/iris/bitstream/handle/10665/259893/WHO-WHE-IHM-GIP-2017.1-eng.pdf?sequence=1.
9. United States Department of Health and Human Services. Pandemic Influenza Plan: 2017 Update. Accessed at www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf.
10. United States Department of Health and Human Services/Office of the Assistant Secretary for Preparedness and Response. Hospital Preparedness Program. Accessed at www.PHE.gov/HPP.
11. United States Department of Health and Human Services/Office of the Assistant Secretary for Preparedness and Response. Interim Healthcare Coalition Checklist for Pandemic Planning/National Healthcare Preparedness Programs, Fall 2013. Accessed at www.phe.gov/Preparedness/planning/hpp/reports/Documents/pandemic-checklist.pdf.
12. Office of the Assistant Secretary for Preparedness and Response. 2017-2022 Hospital Preparedness Program: Performance Measures Implementation Guidance. Accessed at www.phe.gov/Preparedness/planning/hpp/reports/Documents/hpp-pmi-guidance-2017.pdf.
13. Office of the Assistant Secretary for Preparedness and Response. 2017-2022 Health Care Preparedness and Response Capabilities, November 2016. Accessed at www.phe.gov/Preparedness/planning/hpp/reports/Documents/2017-2022-healthcare-pr-capablities.pdf.
14. Office of the Assistant Secretary for Preparedness and Response. COVID-19 Healthcare Planning Checklist. Accessed at www.phe.gov/emergency/events/COVID19/Documents/COVID-19%20Healthcare%20Planning%20Checklist.pdf.
15. United States Department of Health and Human Services. Flu Season: U.S. Public Health Preparedness and Response, Statement of Robert Kadlec, MD, MTM&H, MS, Assistant Secretary for Preparedness and Response, Dec. 4, 2019. Accessed at docs.house.gov/meetings/IF/IF02/20191204/110278/HHRG-116-IF02-Wstate-KadlecMDMTMHMSR-20191204.pdf.
16. United States Department of Health and Human Services/Office of the Assistant Secretary for Preparedness and Response. Regional Disaster Health Response System. Accessed at www.phe.gov/Preparedness/planning/RDHRS/Pages/default.aspx.
17. Centers for Disease Control and Prevention. Coronavirus Disease 2019: CDC's Response, Aug. 31, 2020. Accessed at www.cdc.gov/coronavirus/2019-ncov/cdcresponse/index.html.
18. Centers for Disease Control and Prevention. Coronavirus Disease 2019: CDC in Action, July 8, 2020. Accessed at www.cdc.gov/coronavirus/2019-ncov/cases-updates/cdc-in-action.html.
19. Centers for Disease Control and Prevention. Updated Preparedness and Response Framework for Influenza Pandemics, Recommendations and Reports, Sept. 26, 2014. Accessed at www.cdc.gov/mmwr/preview/mmwrhtml/rr6306a1.htm.
20. Federal Emergency Management Agency. Pandemic Influenza Continuity of Operations Annex Template, 2009. Accessed at www.fema.gov/pdf/about/org/ncp/pandemic_influenza.pdf.
21. Federal Emergency Management Agency. National Preparedness Goal, Second Edition, September 2015. Accessed at www.fema.gov/sites/default/files/2020-06/national_preparedness_goal_2nd_edition.pdf
22. Federal Emergency Management Agency. Biological Incident Annex to the Response and Recovery Federal Interagency Operational Plans: Final — January 2017. Accessed at www.fema.gov/sites/default/files/2020-07/fema_incident-annex_biological.pdf.
23. Federal Emergency Management Agency. National Response Framework, Fourth Edition, Oct. 28, 2019. Accessed at www.fema.gov/sites/default/files/2020-04/NRF_FINALApproved_2011028.pdf.
24. Federal Emergency Management Agency. COVID-19 Pandemic Operational Guidance for the 2020 Hurricane Season, May 2020. Accessed at www.fema.gov/sites/default/files/2020-07/fema-2020-hurricane-pandemic-plan_english.pdf.
25. Veenema TG and Meyer D. Why America's Nurses Were Not Prepared for the Coronavirus Pandemic. *Forbes*, June 4, 2020. Accessed at www.forbes.com/sites/coronavirusfrontlines/2020/06/04/why-americas-nurses-were-not-prepared-for-the-coronavirus-pandemic/#50b6a0b0164b.
26. Glock J, Why Two Decades of Pandemic Planning Failed. Medium, April 9, 2020. Accessed at medium.com/cicero-news/why-two-decades-of-pandemic-planning-failed-a20608d05800.
27. Diamond D. Inside America's 2-Decade Failure to Prepare for Coronavirus. *Politico*, April 11, 2020. Accessed at www.politico.com/news/magazine/2020/04/11/america-two-decade-failure-prepare-coronavirus-179574.
28. Abutaleb Y, Dawsey J, Nakashima E, and Miller G. The U.S. Was Beset by Denial and Dysfunction as the Coronavirus Raged: From the Oval Office to the CDC, Political and Institutional Failures Cascaded Through the System and Opportunities to Mitigate the Pandemic Were Lost. *The Washington Post*, April 4, 2020. Accessed at www.washingtonpost.com/national-security/2020/04/04/coronavirus-government-dysfunction/?arc404=true.
29. Lewis W. Disaster Response Expert Explains Why the U.S. Wasn't More Prepared for the Pandemic. USC Dornsife, March 24, 2020. Accessed at dornsife.usc.edu/news/stories/3182/why-u-s-wasnt-better-prepared-for-the-coronavirus.
30. Olson T. Feds Spent Nearly $100B on Pandemic Readiness, Health Security in Decade Leading Up to Coronavirus Crisis. Fox News, May 11, 2020. Accessed at www.foxnews.com/politics/pandemic-preparedness-spending.

MINIBAR Rx®

A subsidiary of FFF Enterprises, Inc.

Schedule a live demo or webinar today:

(855) 544-2122

- **Ready to provide your patients treatment NOW**
- **Improve the quality care of your patients**
- **Improve the patient experience; no waiting or rescheduling of treatment**

Through our solution...

- Forward-Deployed Inventory (FDI)
- Reduce financial acquisition and inventory costs
- Invoice on dispense
- Right-sized inventory
- Effortless and seamless technology
- Enhanced data granularity
- State-of-the-art temperature control and monitoring
- Full suite of smart management tools

... and much more!

FFF enterprises
Helping Healthcare Care®

info@MinibarRx.com | MinibarRx.com

Myths and Facts: **Alzheimer's Disease**

Government and researchers continue to pursue plans and studies to gain a greater understanding of this devastating and deadly disease to prevent, treat and, ultimately, cure it.

By Ronale Tucker Rhodes, MS

IT'S AN ALARMING statistic: An estimated 5.8 million Americans age 65 and older were living with Alzheimer's disease (AD) in 2020, and 80 percent are age 75 or older. Indeed, one in 10 people age 65 and older (10 percent) has AD. It affects almost twice as many women as men. Older African-Americans are about twice as likely to have AD or other dementias as older whites. And, older Hispanics are about one and one-half times as likely to have AD or other dementias as older whites. Also, with the number of older Americans growing rapidly, so too will the number of new and existing cases.[1]

The sixth-leading cause of death in the U.S., 61 percent of those with AD are expected to die before age 80 compared with 30 percent of people without AD — a rate twice as high. And, it is a costly disease. In 2020, AD and other dementias cost the nation $305 billion, including $206 billion in Medicare and Medicaid payments. By 2050, AD is projected to cost more than $1.1 trillion (in 2020 dollars). This is more than four-fold increases both in government spending under Medicare and Medicaid and in out-of-pocket spending.[1] Sadly, how AD develops and how it impacts those living with it is clouded by many misconceptions about the disease, which stands in the way of helping those affected.

Separating Myth from Fact

Myth: AD and dementia are the same disease.

Fact: While the terms "Alzheimer's" and "dementia" are often used interchangeably, they are very different. Dementia describes a group of symptoms affecting memory, thinking and social abilities severely enough to interfere with daily life.[2] AD is only one form of dementia and the most common type, but it accounts for only 60 percent to 80 percent of all dementia cases.[3] And, dementia is caused by many things, including AD (it is the most common cause of dementia), Huntington's disease, Parkinson's disease and Creutzfeldt-Jakob disease. Some forms of dementia are temporary or they can be reversed, but with AD and some other forms of dementia, that is not the case.[2]

Myth: Memory loss is AD.

Fact: AD is much more than memory loss. AD causes brain cells to malfunction and ultimately die. When this happens, an individual may forget the name of a longtime friend or what roads to take to return to a home they've lived in for decades.[4]

With AD, damage to the brain starts a decade or more before memory and other cognitive problems become evident, when people seem to be symptom-free. But, during this time, toxic changes are taking place in the brain. Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain, and once-healthy neurons stop functioning, lose connections with other neurons and die. The damage initially appears to take place in the hippocampus, the part of the brain essential in forming memories, which can be one of the first signs of AD. But as more neurons die, additional parts of the brain are affected, and by the final stage of AD, damage is widespread, and brain tissue has shrunk significantly.[5]

The Alzheimer's Association has identified 10 early signs and symptoms of AD: 1) memory loss that disrupts daily life, 2) challenges in planning or solving problems, 3) difficulty with completing familiar tasks, 4) confusion with time or place, 5) trouble understanding visual images and spatial relationships, 6) new problems with words in speaking or writing, 7) misplacing things and losing the ability to retrace steps, 8) decreased or poor judgment, 9) withdrawal from work or social activities and 10) changes in mood and personality.[6]

Myth: All older adults develop AD.

Fact: While most people who develop AD are over age 65, AD isn't a normal part of aging. And, although a person's risk of developing AD doubles every five years after 65, nearly half of 85-year-olds don't have the disease. And, AD can start young. Symptoms in those with younger-onset AD, which is a rare inherited form, can start between 30 years old and 50 years old.[3]

Myth: Only seniors develop AD.

Fact: AD does most commonly occur in older adults, yet it can also affect people in their 30s, 40s and 50s. Approximately 90 percent of AD cases are called late-onset, meaning they occur after age 65. But, it is estimated 5 percent to 6 percent of people with AD develop symptoms before age 65. So, if 5.8 million Americans have AD, around 285,000 to 342,000 people have the early-onset form of the disease.[7]

Myth: AD is hereditary.

Fact: Less than 5 percent of all cases of AD are "familial Alzheimer's," a type that runs in families, but if a person has a parent or sibling with AD, he or she will have a higher chance of getting it.[3]

However, genes have been shown to play a role. Indeed, several genes associated with late-onset and early-onset AD have been identified in recent years. In late-onset AD, the most common gene is apolipoprotein E (APOE), which has three common forms: APOE e2 is the least common and appears to reduce the risk of AD; APOE e4 is more common and appears to increase the risk of AD; and APOE e3 is the most common and doesn't seem to affect the risk of AD. The APOE gene can be inherited from both the mother and father. Inheriting at least one APOE e4 gene increases risk of developing AD. With two APOE e4 genes, the risk is even higher. Yet, not everyone who has one or two APOE e4 genes develops AD. What's more, the disease develops in people with no APOE e4 gene.

In addition, with continuing research into the genetics of AD, seven other genes have been identified. These include:

- ABCA7, whose exact role isn't clear, but the gene seems to be linked to a greater risk of AD, and it appears to be linked to the gene's role in how the body uses cholesterol;
- CLU, which helps regulate the clearance of amyloid-beta (central to the development of AD) from the brain;
- CR1, which may contribute to chronic inflammation in the brain due to a deficiency of the protein this gene produces;
- PICALM, which is linked to the process by which brain nerve cells (neurons) communicate with each other;

With AD, damage to the brain starts a decade or more before memory and other cognitive problems become evident, when people seem to be symptom-free.

- PLD3 that has recently been linked to a significantly increased risk of AD, although not much is known about this gene;
- TREM2, which is involved in the regulation of the brain's response to inflammation; and
- SORL1 variants on chromosome 11, which appear to be associated with AD.

It should be noted that all of these genes are risk factors, not

direct causes, for developing AD. Not everyone who has one of these genes will develop the disease.[8]

Mutations in three genes that cause early-onset AD have also been identified: amyloid precursor protein (APP) on chromosome 21, presenilin 1 (PSEN1) on chromosome 14 and presenilin 2 (PSEN2) on chromosome 1. Mutations in these genes result in the production of abnormal proteins associated with the disease. Each of these mutations plays a role in the breakdown of APP that generates harmful forms of amyloid plaques, a hallmark of AD. However, APP's precise function is not yet fully understood. If a child's biological mother or father carries a genetic mutation for one of these three genes, that child has a 50/50 chance of inheriting that mutation, resulting in a very strong probability of developing early-onset AD.

Other genetic components have also been found to be associated with early-onset AD, and studies are ongoing to identify additional genetic risk variants.

In addition, Down syndrome increases the risk of developing early-onset AD, and many people with Down syndrome develop AD as they get older, with symptoms appearing in their 50s or 60s. It is believed this is because people with Down syndrome are born with an extra copy of chromosome 21, which carries the APP gene.[9]

AD does most commonly occur in older adults, yet it can also affect people in their 30s, 40s and 50s.

Myth: AD can be caused by influenza (flu) shots, depression, aluminum, silver fillings and aspartame.

Fact: The truth is experts don't really know what causes AD. It's likely a mixture of genes, environmental factors and lifestyle. And, some research suggests it might be related to health conditions such as heart disease, high blood pressure and diabetes.[10]

New research reported at the Alzheimer's Association International Conference in 2020 found risk factors for AD may be apparent as early as the teens and 20s, although many of these risk factors are disproportionately apparent in African-Americans.

In the Study of Health Aging in African Americans that included more than 714 African-Americans, researchers found high blood pressure, diabetes or two or more heart health risk factors in adolescence, young adulthood or midlife was associated with statistically significantly worse late-life cognition. And these differences persisted after accounting for age, gender, years since risk factors were measured and education.

Another study found a correlation between body mass index (BMI) and higher late-life dementia risk. Scientists analyzed 5,104 older adults from two studies, including 2,909 from the Cardiovascular Health Study (CHS) and 2,195 from the Health, Aging and Body Composition study (Health ABC), 18 percent of whom were black and 56 percent of whom were women. Using pooled data from four established cohorts spanning the adult life course, including the two cohorts under the study, scientists estimated BMI beginning at age 20 for all older adults of CHS and Health ABC. For women, dementia risk increased with higher early adulthood BMI. Compared to women with normal BMI in early adulthood, dementia risk was 1.8 times higher among those who were overweight, and 2.5 times higher among those who were obese. Analyses were adjusted for midlife and late-life BMI. They found no association between midlife BMI and dementia risk among women. For men, dementia risk was 2.5 times higher among those who were obese in early adulthood, 1.5 times higher among those who were overweight in midlife and 2.0 times higher among those who were obese in midlife in models also adjusted for late-life BMI. For both women and men, dementia risk decreased with higher late-life BMI.

In another study that followed a diverse group of more than 2,400 people for up to 21 years, higher-quality early-life education was associated with better language and memory performance and lower risk of late-life dementia. However, results were somewhat different between blacks and whites and men and women. The study included 2,446 black and white men and women age 65 and older enrolled in the Washington Heights/Inwood Columbia Aging Project who attended elementary school in the United States. A school quality variable based on historical measures included mandatory school enrollment age, minimum dropout age, school-term length, student-teacher ratio and student attendance. Those who attended school in states with lower-quality education had more rapid decline in memory and language as an older adult. Black women and men and white women who attended schools in states with higher-quality education were less likely to develop dementia. According to the scientists, the results were explained, in part, because people who attend higher-quality schools end up getting more years of education.[11]

The theory that flu shots cause AD may stem from statements by Hugh Fudenberg, MD, claiming the flu shot increases the risk

of AD because of the small amount of mercury in thimerosal, the preservative that is still contained in some flu vaccines. However, there has been no peer-reviewed research that supports this allegation, and Dr. Fudenberg's medical license was revoked in 1995. In fact, several studies debunk that theory and show flu shots and other vaccines actually reduce the risk of AD and lead to overall better health. One study conducted in 2001 with 4,392 participants showed there was a decreased risk of developing AD for those who had received influenza immunizations, as well as for those who received vaccinations for diphtheria or tetanus (which were grouped together in the research) or poliomyelitis (polio). While it didn't actually show the flu vaccine was what caused a lower risk of AD, it did indicate that those who received the vaccine were less likely to develop AD, and those who didn't were more likely to develop AD. In addition, a study published in the *Journal of the American Medical Association* in 2004 showed annual flu shots for older adults were associated with a reduced risk of death from all causes.[12]

Most recently, two new studies show the flu and pneumonia vaccines lessen the risk of developing AD in the future. The first study examined a large American health record data set of more than 9,000 patients over age 60 years and found having one flu vaccination was associated with a 17 percent reduction in AD. Further, those vaccinated more than once over the years saw an additional 13 percent reduction in incidence. The protective association appeared to be strongest for those who received their first vaccine at a younger age, for example at age 60 years versus 70 years. The second study, which examined the associations between pneumococcal vaccine with and without an accompanying flu shot and the risk of AD, analyzed more than 5,000 people over 65 years who were participating in the Cardiovascular Health Study, a long-term government-funded look at risk factors for cardiovascular disease. Some participants had a known genetic risk factor for AD: the rs2075650 G allele in the TOMM40 gene, which has also been linked to a higher risk for lifetime depression. The researchers found that getting a pneumococcal vaccine between the ages of 65 years and 75 years reduced risk of developing AD by 25 percent to 30 percent after adjusting for sex, race, birth cohort, education, smoking and genetic risk factors. However, the largest reduction in the risk of AD — up to 40 percent — was seen among people vaccinated against pneumonia who didn't have the risk gene.[13]

Mercury is also at the root of the theory that silver dental fillings increase the risk of AD. Silver fillings are made of an amalgam mixture that typically contains about 50 percent mercury, 35 percent silver and 15 percent tin. But, once again, studies show

no relationship to AD. The most recent study was conducted in 2003 and published in the *New England Journal of Medicine*, which found no connection between mercury-containing dental fillings and AD or other neurological diseases.

Lastly, in May 2006, the U.S. Food and Drug Administration (FDA) reported that of the more than 100 laboratory and clinical studies conducted to determine if aspartame causes memory loss, none had presented any scientific evidence of it.[4]

Myth: AD can be prevented.

Fact: It's really not yet known what can prevent AD, and there is certainly no single treatment to prevent it. It has been purported that taking supplements can help inhibit AD, but studies conducted on vitamins E, B and C, ginkgo biloba, folate and selenium have been inconclusive.[14]

The only conclusive diagnosis of AD is at death, when microscopic examination of the brain reveals the characteristic plaques and tangles.

Many things, however, can be done to protect the brain. A committee of experts from the National Academies of Sciences, Engineering and Medicine (NASEM) conducted a recent review of research that looked at the evidence on ways to prevent or delay AD or age-related cognitive decline and found "encouraging but inconclusive" evidence for three types of interventions: increased physical activity, blood pressure control for people with high blood pressure (hypertension) and cognitive training. While there isn't adequate research to recommend exercise as a way to prevent AD, years of observational studies show people who exercise have a lower risk of cognitive decline than those who don't. Exercise has also been associated with fewer AD plaques and tangles in the brain and better performance on certain cognitive tests. Many studies show a connection between high blood pressure, cerebrovascular disease and dementia, and there are many clinical trials underway to determine whether this is true. For instance, one large clinical trial called Systolic Blood Pressure Intervention Trial-Memory Cognition in Decreased Hypertension found lowering systolic blood pressure to less than 120 mmHg compared to a target of less than 140 mmHg didn't significantly reduce the risk of dementia. However, the multiyear study did show intensive blood pressure lowering significantly reduced the risk of mild cognitive impairment (MCI), a common precursor of AD. Finally, there is evidence that computer-based cognitive training may help delay or slow age-related cognitive decline. However, there is no evidence it can prevent or delay AD's-related cognitive impairment.[15]

Myth: There is a test for AD.

Fact: There is no test that can definitively diagnose AD. The only conclusive diagnosis of AD is at death, when microscopic examination of the brain reveals the characteristic plaques and tangles. However, to distinguish AD from other causes of memory loss, physicians rely on personal and medical history, blood tests, neurological tests and some imaging tests. The physical exam is used to determine overall neurological health by testing reflexes, muscle tone and strength, the ability to get up from a chair and walk across a room, sense of sight and hearing, coordination and balance. Blood tests help to rule out other causes of memory loss and confusion such as thyroid disorders or vitamin deficiencies. Neurophysical testing may include a brief mental status test or a more extensive assessment of thinking and memory. An MRI can be used to rule out other conditions and to assess whether there is shrinkage in brain regions implicated in AD. A CT is used to rule out tumors, strokes and head injuries. And, a PET scan can show which parts of the brain aren't functioning well, with new techniques able to detect the levels of plaques and tangles in the brain. In special circumstances, such as rapidly progressive dementia or very early-onset dementia, other tests may be used to measure abnormal beta-amyloid or tau in the cerebrospinal fluid.[16]

Unfortunately, better testing is needed since a diagnosis of AD can be delayed or missed because it is often associated with the normal aging process, and early symptoms develop gradually.[17] In fact, AD can develop 20-plus years before memory loss.[3] AD can also be overdiagnosed because it mimics other conditions such as transient ischemic attack, depression, vascular dementia, Creutzfeldt-Jacob disease, bovine spongiform encephalopathy, brain tumor, hydrocephalus or advanced syphilis or AIDS.[17]

This is why early detection is a key focus of research today. The earlier AD can be identified, the better the effectiveness of existing medications. Research investigating new tests include:[18]

• A biomarker test that can indicate the presence of two proteins, beta-amyloid and tau, which are found in the brains of people with AD and that can measure the fluid that surrounds the brain and spinal cord (cerebrospinal fluid), which is examined for evidence of abnormal development of beta-amyloid proteins that

FDA-Approved Treatments for AD[21]

Generic	Brand	Approved For	Side Effects
Donepezil	Aricept	All stages	Nausea, vomiting, loss of appetite, muscle cramps and increased frequency of bowel movements
Galantamine	Razadyne	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements
Memantine	Namenda	Moderate to severe	Headache, constipation, confusion and dizziness
Rivastigmine	Exelon	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
Memantine + Donepezil	Namzaric	Moderate to severe	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness.

form plaques, and tau proteins that form tangles.

• Brain imaging (neuroimaging) such as MRI and PET scans used with radiotracers (charged particles that "light up" when a person has dementia).

• Cognitive assessment technology that can detect cognitive changes and may be useful in the early diagnosis of AD.

• Loss of odor identification tests (olfactory impairment), which can indicate a decline in mild cognitive impairment and progression from MCI to AD.

Recently, two new studies have shown blood levels of a specific form of phosphorylated tau effectively identify AD, which could lead to a highly accurate diagnostic blood test with the potential to predict AD up to 20 years before disease onset. In the first study, researchers looked at whether CSF levels of tau phosphorylated at threonine 217 (p-tau217) could be a blood-based biomarker of AD using mass spectrometry to measure tau in blood samples from participants of previous AD studies, including a discovery cohort of 32 individuals and a validation cohort of 92 individuals. Low blood concentrations of tau meant the protein had to be purified and concentrated 800-fold to enable its detection with mass spectrometry, an approach that enabled reliable measurement of p-tau181 and p-tau217. They found blood levels of p-tau181 and p-tau217 correlated well with CSF levels, despite a lack of correlation between total tau levels in the two compartments. Blood levels of both tau isoforms were higher among AB-positive individuals than among AB-negative people, but the magnitude of change was greater for p-tau217.

In the second study, the value of p-tau217 as a blood biomarker was independently identified. The study involved samples from three different cohorts: one in which pathology had been determined post-mortem; one in which patients with dementia and other neurological disease were classified as AB-positive or AB-negative; and one comprising cognitively impaired and unimpaired carriers of a PSEN1 mutation that is known to cause AD. Across the three cohorts, measurement of p-tau217 enabled individuals with a diagnosis of AD to be distinguished from those with other neurodegenerative diseases, and allowed the identification of individuals with pathologically defined AD. The findings of the two studies suggest p-tau217 levels could form the basis of a diagnostic, and possibly even predictive, blood test for AD.[19]

Myth: AD can be treated.

Fact: Currently, there is no treatment to indefinitely delay or stop the progression of AD. However, there are two types of drugs approved by the U.S. Food and Drug Administration (FDA) that treat the symptoms of AD — temporarily helping memory and thinking problems. However, these medications do not treat the underlying causes of the disease or slow its progression.[20] The first type of drugs are cholinesterase inhibitors, and they include donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon), all of which curb the breakdown of a chemical in the brain called acetylcholine, which is important for memory and learning. They may slow down how fast symptoms get worse for about half of people who take them, and the effect lasts for a limited time, on average six to 12 months. The second type is memantine (Namenda), which treats moderate to severe AD. It works by changing the amount of a brain chemical called glutamate, which plays a role in learning and memory. Brain cells in people with AD give off too much glutamate, and Namenda keeps the levels of that chemical in check. Also available is

Namzaric, which is a mix of Namenda and Aricept, that is best for people with moderate to severe AD who already take the two drugs separately.[20,21]

Because of the progress in understanding healthy brain function and what goes wrong in AD, there are some promising targets for next-generation drug therapies under investigation. These include trials for drugs targeting beta-amyloid (the chief component of plaques), beta-secretase (the enzyme that makes it possible for beta-amyloid to form), tau protein (the chief component of tangles), inflammation (another key AD brain abnormality) and 5-HT2A receptor (found on some brain cells that can lock in chemicals called neurotransmitters).[21]

Since a variety of underlying causes can trigger chronic inflammation, there is no one way to prevent its onset.

There are also several clinical trials underway by the Alzheimer's Association:[21]

• The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study is examining the effectiveness of solanezumab, a drug targeting beta-amyloid, in 1,169 symptom-free volunteers whose PET scans show abnormally high levels of beta-amyloid in the brain. This drug could possibly prevent cognitive decline in individuals at increased risk of developing AD. The estimated completion date for the study is July 2022.

• The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) hopes to slow or stop the development of AD in individuals who have mutations on three genes known to cause a rare form of AD that accounts for less than 1 percent of cases. Currently being tested are two drugs, gantenerumab and solanezumab, that are designed to help remove excess beta-amyloid in the brain. The study is expected to conclude in March 2021.

• The Alzheimer's Prevention Initiative (API) includes both the Autosomal Dominant Alzheimer's Disease (ADAD) trial and the Generation Study. Like DIAN-TU, the API tests therapies in people who have a gene mutation that causes AD but who have not yet developed symptoms. The ADAD trial is studying the effects of crenezumab, an immune-based therapy that delivers antibodies against beta-amyloid in an effort to reduce the negative cognitive effects of excess beta-amyloid. The Generation Study includes cognitively healthy older adults who are at high risk of developing AD based on their age and having two copies of the AD risk gene APOE-e4. The study is expected to conclude in February 2022.

Over the years, unfortunately, many studies that evaluated treatments for AD failed. But, in August, FDA gave priority review status to Biogen and its Japanese partner Eisai for the approval of aducanumab, a controversial investigational treatment for AD. While trials of the drug were discontinued in March 2019 because they were unlikely to meet their primary endpoints, the companies renewed plans in October 2019 to pursue regulatory approval of aducanumab based on positive results of a new analysis that showed a different outcome. The new analysis of the EMERGE study showed patients treated with a high dose (10 mg/kg) of aducanumab experienced a statistically significant reduction in clinical decline of AD. While a group of analysts believe FDA may not approve the drug, a decision is expected on March 7, 2021.[22]

Myth: An AD diagnosis means life is over.

Fact: The progress of AD depends on the unique circumstances of each patient, and many people live years or even decades before the disease claims their lives. AD is commonly divided into three stages: 1) the mild stage in which the patient is able to live a mostly normal life, 2) the middle or moderate stage that requires more extensive care and 3) the late or severe stage that requires around-the-clock supervision and medical help. While life may never be the same after an AD diagnosis, it's far from over.[23]

Myth: AD isn't fatal.

Fact: AD is the sixth-leading cause of death in the U.S., and the average life expectancy after diagnosis is 10 years.[24] In fact, AD has no survivors because it destroys brain cells and causes memory changes, erratic behaviors and loss of body functions. Sadly, it slowly and painfully takes away a person's identity, ability to connect with others, think, eat, talk and walk.[4]

Myth: Caregivers don't need help to care for their loved ones with AD.

Fact: Eighty-three percent of caregivers are family members who don't ask for help for many reasons such as pride, sense of obligation or love. In 2020, AD and other dementias will cost the nation $305 billion. Caregivers provided an estimated 18.6 billion hours of care valued at nearly $244 billion. In fact, of the total lifetime cost of caring for someone with dementia, 70 percent is borne by families either through out-of-pocket health and long-term care expenses or from the value of unpaid care. Caring for a person with AD takes a devastating toll, with twice as many caregivers of those with dementia suffering substantial

emotional, financial and physical difficulties.[1]

The reality is caregivers can't do it alone. Federal and state programs offer many resources for caregivers that can be found at alz.org/help-support/caregiving. In addition, the Alzheimer's Association has a 24/7 support line at (800) 272-3900, which can help caregivers find local support groups in their areas.[25]

Dispelling the Myths Now

Developing treatments to slow or even cure AD is crucial. It is estimated by 2050 the number of people age 65 and older with AD may grow to a projected 13.8 million, and 50 percent of primary care physicians believe the medical profession is not ready for the growing numbers of people with it.[1]

In recent years, both international and national efforts have recognized the public health importance of AD. The Alzheimer's Association, working with and through the Alzheimer's Impact Movement (AIM), is leading the way to increase research funding at the federal and state level. Their efforts have resulted in a more than six-fold increase in federal AD and dementia research funding since 2011, including a $350 million increase for AD research at the National Institutes of Health (NIH) in 2020. With this increase, along with previous research investments, NIH was expected to spend $2.8 billion on AD research in 2020. The association and AIM are also working to encourage investment by state and local governments. In 2019, they secured more than $100 million in state funding for dementia-specific care and support services, research, public health activities, home and community-based services and other areas to meet the needs of individuals and families living with dementia.[26]

In 2011, President Obama enacted the National Alzheimer's Project Act, which called for a National Advisory Council on Alzheimer's Disease Research and resulted in the development of a national plan to address AD each year for the effective prevention and treatment of AD by 2025. The goals of the project are to create and maintain an integrated national plan to overcome AD; coordinate AD research and services across all federal agencies; accelerate the development of treatments that would prevent, halt or reverse the course of AD; improve early diagnosis and coordination of care and treatment of AD; decrease disparities in AD for racial and ethnic minority populations that are at higher risk for AD; and coordinate with international bodies to fight AD globally.[27]

In 2012, the World Health Organization (WHO) identified dementia as a public health priority. That same year, WHO and Alzheimer's Disease International published a report titled "Dementia: A Public Health Priority" to raise awareness of dementia as a public health priority, articulate a public health approach and advocate for action at international and national levels.[28]

Scientists have made remarkable progress in understanding AD, but there is much more to be accomplished. Through planning and research, it can only be hoped we discover how AD can be prevented, treated and even cured. Until that happens, though, it's important for those affected to know the signs of AD and where to get help. ❖

References

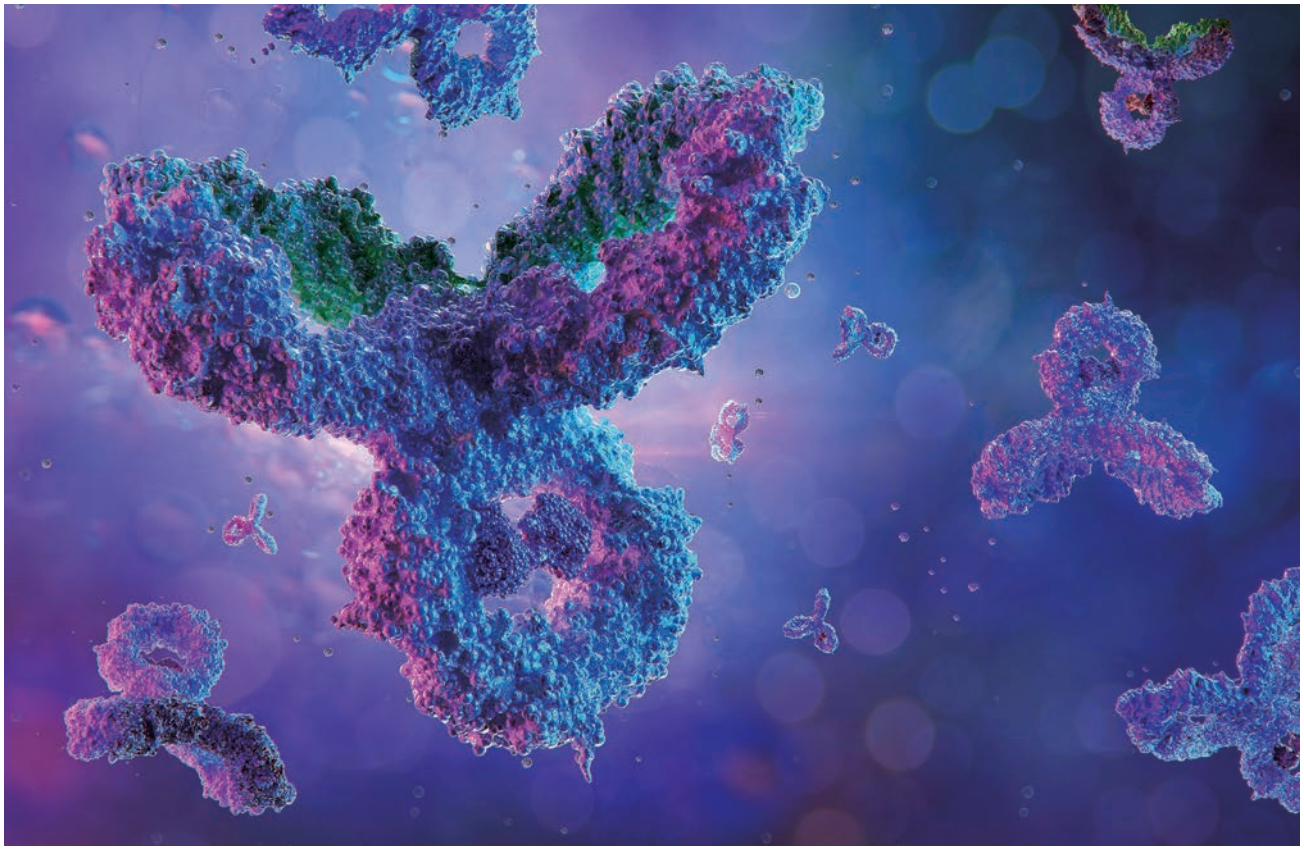
1. Alzheimer's Association. Facts and Figures. Accessed at www.alz.org/alzheimers-dementia/facts-figures#:~:text=An%20estimated%205.8%20million%20Americans%20of%20all%20ages,65%20and%20older%20%2810%20percent%29%20has%20Alzheimer%27s%20dementia.
2. Mayo Clinic. Dementia. Accessed at www.mayoclinic.org/diseases-conditions/dementia/symptoms-causes/syc-20352013.
3. WebMD. Quiz: Alzheimer's Myths and Facts. Accessed at www.webmd.com/alzheimers/rm-quiz-alzheimers-myths-facts.
4. Alzheimer's Association. Alzheimer's Myths. Accessed at www.alz.org/alzheimers_disease_myths_about_alzheimers.asp.
5. National Institute on Aging. About Alzheimer's Disease: Alzheimer's Basics. Accessed at www.nia.nih.gov/alzheimers/topics/alzheimers-basics.
6. Alzheimer's Association. 10 Early Signs and Symptoms of Alzheimer's. Accessed at www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp#signs.
7. Mayo Clinic. Young-Onset Alzheimer's: When Symptoms Begin Before Age 65. Accessed at www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048356.
8. Mayo Clinic. Alzheimer's Genes: Are You at Risk? Accessed at www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-genes/art-20046552.
9. National Institute on Aging. Alzheimer's Disease Genetics Fact Sheet. Accessed at www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet.
10. WebMD. 5 Myths About Alzheimer's Disease. Accessed at www.webmd.com/alzheimers/features/5-alzheimers-disease-myths?page=2.
11. Alzheimer's Association. Alzheimer's Risk Factors May Be Measurable in Adolescents and Young Adults. Medical Xpress, July 30, 2020. Accessed at medicalxpress.com/news/2020-07-alzheimer-factors-adolescents-young-adults.html.
12. Heerema E. Do Flu Shots Increase the Risk of Alzheimer's? VeryWell Health, April 5, 2020. Accessed at www.verywellhealth.com/flu-shots-and-alzheimers-disease-98672.
13. Kane A and LaMotte S. Flu and Pneumonia Shots May Lower Risk for Alzheimer's, Studies Find. CNN Health, July 27, 2020. Accessed at www.cnn.com/2020/07/27/health/flu-pneumonia-shot-lowers-alzheimers-risk-wellness/index.html.
14. Alzheimer Society of Canada. Myths and Realities of Alzheimer's Disease. Accessed at www.alzheimer.ca/en/About-dementia/Alzheimer-s-disease/Myth-and-reality-about-Alzheimer-s-disease.
15. National Institute on Aging. Preventing Alzheimer's Disease: What Do We Know? Accessed at www.nia.nih.gov/health/preventing-alzheimers-disease-what-do-we-know.
16. Mayo Clinic. Alzheimer's Disease Tests and Diagnosis. Accessed at www.mayoclinic.org/diseases-conditions/alzheimers-disease/basics/tests-diagnosis/con-20023871.
17. Right Diagnosis. Misdiagnosis of Alzheimer's Disease. Accessed at www.rightdiagnosis.com/a/alzheimers_disease/misdiag.htm.
18. Mayo Clinic. Alzheimer's Test: Detection at the Earliest Stages. Accessed at www.mayoclinic.org/diseases-conditions/alzheimers-disease/expert-answers/alzheimers-test/faq-20057850.
19. Fyfe I. Tau Species Has Potential for Alzheimer Disease Blood Test. *Nature Review Neurology*, Aug. 13, 2020. Accessed at www.nature.com/articles/s41582-020-0401-z.
20. WebMD. Treatments for Alzheimer's Disease. Accessed at www.webmd.com/alzheimers/guide/alzheimers-disease-treatment-overview#1.
21. Alzheimer's Association. Medications for Memory. Accessed at www.alz.org/alzheimers-dementia/treatments/medications-for-memory.
22. Shah K. Alzheimer's in Focus as Biogen's Aducanumab Gets Priority Tag. Yahoo Finance, Aug. 10 2020. Accessed at finance.yahoo.com/news/alzheimers-focus-biogens-aducanumab-gets-154803558.html.
23. Stewart T. Alzheimer's Disease: Five Common Myths, Busted. The Eagle, Oct. 4, 2018. Accessed at theeagle.com/news/health_fitness/alzheimer-s-disease-five-common-myths-busted/article_47823cc6-c759-11e8-9619-bf7abc21708b.html.
24. Development of a Life Expectancy Calculator for Alzheimer's & Dementia. Dementia Care Central, May 5, 2020. Accessed at www.dementiacarecentral.com/aboutdementia/life-expectancy-calculator.
25. Alzheimer's Association. Caregiving. Accessed at alz.org/help-support/caregiving.
26. Alzheimer's Association. Research Funding. Accessed at www.alz.org/get-involved-now/advocate/research-funding.
27. U.S. Department of Health and Human Services. National Plan to Address Alzheimer's Disease: 2019 Update, Oct. 18, 2019. Accessed at aspe.hhs.gov/report/national-plan-address-alzheimers-disease-2019-update.
28. World Health Organization. Dementia: A Public Health Priority. Accessed at www.who.int/mental_health/publications/dementia_report_2012/en.

Editor's note: This article has been updated from the original published in the Winter 2016 edition of BioSupply Trends Quarterly.

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly.*

The Promise of COVID-19 Hyperimmune Globulin Therapy

By Keith Berman, MPH, MBA



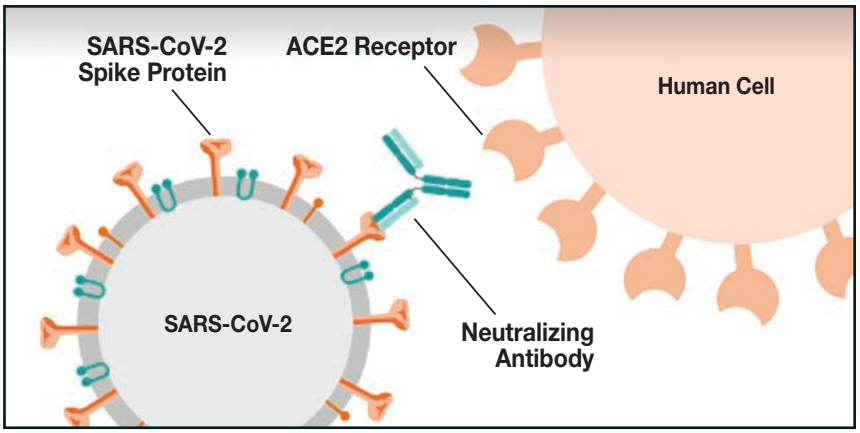
IN THE EARLY months of the COVID-19 pandemic, attention was understandably focused on three critical priorities: public health measures intended to prevent disease transmission, development of protective vaccines against the SARS-CoV-2 virus, and potential treatments to reduce severe complications and deaths, particularly for the roughly 40 percent of adults whose age or compromised health status places them at relatively high risk of hospitalization and death.

Among the more widely publicized investigational treatments is COVID-19 convalescent plasma (CCP) collected by apheresis from fully recovered COVID-19 patients. Just as they did for the plasma donor, anti-SARS-CoV-2 antibodies in CCP directly neutralize the virus or act to facilitate viral clearance. Anecdotal evidence from past acute respiratory viral disease pandemics — SARS, MERS, Argentine hemorrhagic fever, even the 1918 Spanish flu — suggest early transfusion of one to two units of CCP could potentially reduce mortality.[1]

To date, however, conflicting early findings from a number of matched-control and placebo-controlled trials have led to controversy over whether the roughly two grams to four grams of immune globulin G (IgG)* in a unit

** As well as smaller gram quantities of IgM and IgA*

Figure 1. Anti-Spike Protein Antibody Blockade of SARS-CoV-2 Entry Into Host Cell



Source: www.siemens-healthineers.com/en-ph/press-room/press-videos/im-202006020001shs.html

or two of CCP can confer meaningful survival benefit in hospitalized COVID-19 patients. Nevertheless, in August, the U.S. Food and Drug Administration (FDA) granted CCP emergency use authorization for essentially unrestricted use in hospitalized COVID-19 patients.[2]

Meanwhile, the National Institutes of Allergy and Infectious Diseases (NIAID) has joined with several companies in development of anti-SARS-CoV-2 monoclonal antibodies (MAbs), based on what agency director Anthony Fauci, MD, describes as "their direct antiviral effect" that acts to "block the virus from entering its target cell in the body and hence interrupt the course of infection." They do so by targeting the highly conserved receptor binding domain of the virus's critical spike protein that enables it to gain entry to targeted cells and commandeer their genetic apparatus to replicate itself (Figure 1).

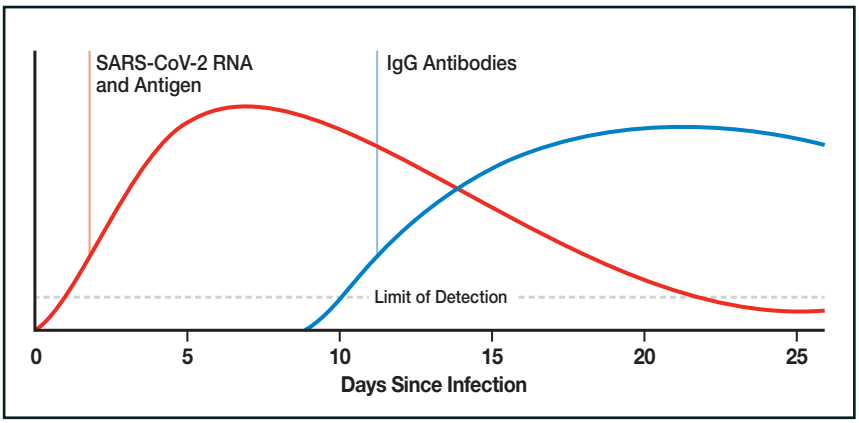
The first preparations to enter clinical trials comprise either a single MAb or "cocktails" of two potent anti-spike protein MAbs selected from thousands of anti-SARS-CoV-2 antibodies identified from recovered COVID-19 patients or produced in mice that have been genetically modified to have a human immune system. Furthest along in development are MAb candidates developed by Regeneron Pharmaceuticals and Eli Lilly. While results are not yet available from trials in hospitalized patients, both companies have reported highly encouraging preliminary findings from separate studies of two-MAb "cocktails" in symptomatic COVID-19 outpatients, including

significantly reduced viral load and lower rates of COVID-19 medical visits than those experienced in the placebo control groups.

The third class of investigational COVID-19 antibody preparations will have a familiar ring for emergency room and infectious disease specialists: concentrated COVID-19 hyperimmune IgG (COVID-Ig) prepared from large pools of high-titer CCP. In early October, NIAID announced the initiation of the multinational Phase 3 Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) trial to test the safety, tolerability and efficacy of high-dose intravenous COVID-Ig. Five hundred hospitalized patients are being randomized to receive COVID-Ig in conjunction with remdesivir, or remdesivir alone. In a first-of-its-kind collaboration, potent virus-neutralizing COVID-Ig is being supplied by four leading manufacturers of standard or hyperimmune polyvalent IgG therapies: Grifols, CSL Behring,

As of this writing, NIAID and industry collaborators are also finalizing the design of a large-scale trial to assess whether COVID-Ig can reduce the rate of hospitalization and other medical encounters in earlier-stage COVID-19 patients exhibiting mild to moderate symptoms.

Figure 2. Temporal Lag Between SARS-CoV-2 Viremia and IgG Antibody Response



Takeda Pharmaceuticals and Emergent BioSolutions.**

As of this writing, NIAID and industry collaborators are also finalizing the design of a large-scale trial to assess whether COVID-Ig can reduce the rate of hospitalization and other medical encounters in earlier-stage COVID-19 patients exhibiting mild to moderate symptoms. With support from the U.S. Department of Defense, at least one trial is planned as well to evaluate COVID-Ig as postexposure prophylaxis treatment for frontline healthcare and other high-risk populations at high risk of COVID-19 infection.[3]

So, with CCP, COVID-Ig and monoclonal antibody preparations, we have not one but three potential anti-SARS-CoV-2 antibody-based treatments currently or soon to be investigated for 1) hospitalized COVID-19 patients, 2) symptomatic nonhospitalized COVID-19 patients, in particular those at high risk for progressing to severe disease, and 3) populations exposed or at increased risk of exposure to COVID-19.

The much-anticipated NIAID-sponsored ITAC trial investigating high-dose (400 mg/kg body weight) COVID-Ig in hospitalized COVID-19 patients started subject enrollment in early October and is projected to be completed in July 2021.

Clinical trials will be completed and findings reported over the coming months. But in the meantime, can we surmise anything in advance about the real-world prospects for these three distinct antibody therapies in specific treatment settings? It turns out the answer is yes.

It's COVID-Ig or MAbs for COVID-19 Prevention and Early Treatment

In concert with cellular immune defenses, a humoral immune response is critical to help clear SARS-CoV-2 infection.[4] Neutralizing anti-SARS-CoV-2 antibodies act to block the spike protein receptor binding domain (RBD) that fuses with surface ACE2 receptors to enable viral entry into host cells.

But not unlike the pathogenesis of SARS, the first coronavirus pandemic that swept through southeast Asia in 2003, there is a weak link in our immune response: a median of roughly 14 days elapses between infection and seroconversion. A week after initial symptoms appear, most COVID-19 patients still have no detectable IgG antibodies against the virus. That extended time lag before humoral immunity finally kicks in, coupled with a lethargic cellular immune response in some infected individuals,[2] gives this novel coronavirus a big head start during its early viremic phase (Figure 2), resulting in a potentially serious or lethal disease course in more susceptible individuals.

The principle of closing that time gap and "nipping the infection in the bud" was

*** Other plasma products companies participating in this "COVIg-19 Plasma Alliance" include ADMA Biologics, Biotest, BPL, GC Pharma, LFB, Liminal BioSciences, Octapharma and Sanquin. Two other major plasma fractionators, Kedrion Biopharma and Kamada, are also collaborating to develop their own COVID-Ig preparation.*

the impetus for the development of multiple licensed hyperimmune IgG products for postexposure prophylaxis, including those for rabies (HyperRAB S/D, KEDRAB), hepatitis B (HyperHEP S/D, Nabi-HB) and varicella zoster (VARIZIG). All contain high titers of neutralizing antibodies purified from recovered or vaccine-immunized plasma donors. Monoclonal antibody preparations have similarly proven effective for prevention of lower respiratory tract infection caused by respiratory syncytial virus (RSV) in susceptible pediatric patients (SYNAGIS [palivizumab]) and, very recently, for treatment to reduce mortality in patients with symptomatic Zaire ebolavirus infection (INMAZEB).

To produce each batch of COVID-Ig, thousands of CCP donations are individually screened to assure presence of significant IgG antibody titers against SARS-CoV-2, similar to screening of potential CCP donor units for transfusion. But following pooling and processing of CCP units into COVID-Ig, gram-for-gram the final hyperimmune IgG product contains several times more SARS-CoV-2 neutralizing antibodies than is found in the plasma units from most donors who have recovered from COVID-19.[5]

Why is this? In part, it is likely because anti-SARS-CoV-2 IgG titers generally identified by ELISA binding assays donor CCP units do not always fully correlate with viral neutralizing titers. In tests of CCP units from 26 recovered patient donors, for example, one research team reported just three of those donor units demonstrated effective blockade of SARS-CoV-2 spike protein RBD binding to ACE2 receptors.[6]

The variability in anti-SARS-CoV-2 antibody and neutralizing titers from one unit of donor CCP to the next raises a basic question about the clinical utility of donor CCP therapy, both in the setting of postexposure prophylaxis and early treatment of high-risk symptomatic COVID-19 patients. Now that COVID-Ig with consistently high viral neutralizing titers is available for clinical investigation, is it still valid or advisable to separately evaluate single-donor convalescent plasma whose SARS-CoV-2 neutralizing capacity and potential protective efficacy are known to vary widely from one individual unit "dose" to the next?

Consider, for example, a multicenter clinical trial currently randomizing 500 high-risk adults who have been exposed to COVID-19 to transfusion of a single 200 mL to 250 mL unit of CCP with SARS-CoV-2 antibody titers of ≥1:320, or curiously, a unit of conventional nonimmune donor plasma.[7] Now that plasma fractionators are processing thousands of units of high-titer CCP into clinical quantities of hyperimmune COVID-Ig with consistent high-titer, broad-spectrum neutralizing anti-SARS-CoV-2 antibody, would it not make sense to include COVID-Ig as a second active treatment arm?*** The same reasoning could equally apply to other large-scale

*** *A similar argument could be made for including a highly neutralizing investigational MAb preparation as a second active treatment arm. An example is Eli Lilly's LY-CoV555, currently being evaluated in the 2,400-subject placebo-controlled Phase III BLAZE-2 trial (NCT04497987) in nursing home residents and staff at facilities with a high risk of SARS-CoV-2 exposure.*

Table 1. Advantages of COVID-Ig vs. COVID-19 Convalescent Plasma for Postexposure Prophylaxis and Outpatient Treatment

COVID-19 Hyperimmune Globulin (COVID-Ig)	COVID-19 Convalescent Plasma (CCP)
Consistent anti-SARS-CoV-2 neutralizing antibody titers; pooling assures IgG antibodies directed against a broad spectrum of viral epitopes	Inconsistent anti-SARS-CoV-2 neutralizing antibody titers from one donor unit to the next; antibodies target fewer viral epitopes
Potential for subcutaneous or intramuscular infusion requiring minimal training, which can be performed in a clinic or nonclinic setting	Transfusion procedure must be performed by a nurse fully trained in blood transfusion therapy in a hospital or equivalent setting
No risk of transfusion reaction; serious systemic adverse reactions are rare	Small but significant risk of transfusion reaction (TRALI and allergic reactions)
No requirement for HLA matching or involvement of blood bank personnel	Hospital blood bank facility and personnel must be involved in the provision of the CCP unit
High IgG gram dosages may be administered IV or subcutaneously, permitting dose-ranging studies	Transfused volume limitations restrict CCP dosing to 1 to 2 units, or roughly 2 to 4 grams of IgG

clinical trials currently investigating whether a single unit of CCP can reduce hospitalizations or death in symptomatic adult outpatients with COVID-19.[8,9]

There are other more pragmatic questions about the use of CCP for prevention or early treatment of COVID-19. Is it safe, practical or even feasible to potentially perform many thousands of plasma transfusion procedures each day in individuals in the community who have been exposed to COVID-19, or are sick but still at home with mild to moderate COVID-19 symptoms? Table 1 identifies a number of potential advantages of a standardized COVID-Ig preparation over CCP in a real-world clinical setting.

CCP, COVID-Ig and MAbs in Hospitalized COVID-19 Patients

The much-anticipated NIAID-sponsored ITAC trial investigating high-dose (400 mg/kg body weight) COVID-Ig in hospitalized COVID-19 patients started subject enrollment in early October and is projected to be completed in July 2021. With support from Grifols, Octapharma and LFB, a number of other studies are also evaluating high-dose standard intravenous immune globulin (IVIG) in severely ill COVID-19 patients to test the hypothesis that the immunomodulatory properties of IVIG can limit the progression of acute respiratory distress syndrome (ARDS) and other major complications attributed to the inflammatory cytokine-mediated "cytokine storm" phenomenon seen in severely ill patients.[10,11]

Clinical testing of MAbs for treatment of hospitalized COVID-19 patients has not started out well. In late October, a Phase III randomized placebo-controlled clinical trial evaluating intravenous infusion of Eli Lilly's investigational anti-SARS-CoV-2 MAb (LY-CoV555) in hospitalized COVID-19 patients was halted early after a review of unblinded data showed little likelihood of therapeutic value. Shortly after the start of a separate inpatient trial of REGN-COV2, its two-antibody MAb cocktail, Regeneron, suspended further enrollment of hospitalized subjects requiring high-flow oxygen or mechanical ventilation pending further analysis. The company explained this decision was based on "a potential safety signal and an unfavorable risk-benefit profile" identified by the trial's Independent Data Monitoring Committee (IDMC). However, the IDMC recommended continuation of enrollment of other COVID-19 inpatients on low-flow oxygen or who do not require oxygen.

Thus far, investigations of CCP account for nearly all published findings involving SARS-CoV-2 antibody therapy for hospitalized COVID-19 patients. They include an uncontrolled 20,000-patient case series,[12] a number of matched-control studies[13] all reporting mortality odds ratios clearly favoring CCP, and several randomized controlled trials,[11] most notably a 464-subject trial that found no difference in mortality, regardless of the presence or absence of neutralizing antibodies in administered CCP.

The cumulative evidence to date points to two likely predictors of clinical benefit that should apply for any of the

three investigational antibody treatment modalities:

• Antibody administration as early as possible following initial development of symptoms or hospital admission. This finding is the basis for the ITAC/COVID-Ig trial's inclusion criterion that subjects must have had COVID-19 symptoms for 12 days or fewer; and

• Absence of or a very low measured patient serum anti-SARS-CoV-2 antibody titer at enrollment. It is reasonable if not self-evident that patients who have already seroconverted and are producing their own anti-SARS-CoV-2 antibody are less likely to benefit from infusion of exogenous antiviral antibodies.

In addition, published findings to date strongly indicate that in instances when CCP is transfused within the first three days of hospital admission, all-cause mortality is significantly lower in patients given CCP units with higher anti-SARS-CoV-2 antibody or neutralizing titers.[14,15]

Polyvalent Immune Globulin: An Added Advantage?

Particularly for people whose age, medical history or underlying comorbidities place them at higher risk for progression to severe disease, both COVID-Ig and spike protein-targeted MAbs appear highly promising for postexposure prophylaxis and early treatment of symptomatic COVID-19. But that said, a case can be made for added potential therapeutic benefit of COVIG-Ig as it comprises not one or two but literally thousands of unique antibodies targeting different viral epitopes. "This multiplicity of natural anti-SARS-CoV-2 antibodies can tie up the virus in ways that reduce the infection and make it more difficult to escape through mutation," said Laura Saward, PhD, Emergent BioSolutions' senior vice president, therapeutics.

Recognizing that this natural polyvalent antiviral activity could translate into improved clinical efficacy, South San Francisco-based GigaGen has applied proprietary technology to produce a "recombinant hyperimmune" containing a mixture of 12,500 anti-coronavirus antibodies isolated from CCP of numerous recovered donors.[16] Called "GIGA-2050," this COVID-19 antibody-based drug candidate is claimed to be 100 times more protective than high-titer CCP using live virus neutralization assays.

GigaGen recently announced it has initiated large-scale manufacturing of GIGA-2050, and it expects to begin clinical trials in early 2021. Remaining to be seen is whether this ground-breaking anti-COVID-19 recombinant hyperimmune can be manufactured economically, particularly in relation to extraordinarily efficient bioreactors that we also know as convalescent plasma donors.

In any case, dosing COVID-19 patients with significant gram quantities of human plasma-derived polyvalent COVID-Ig may bring yet one more potential therapeutic bonus to the table: potent anti-inflammatory activity mediated by thousands of immunomodulatory IgG antibodies that are always present in the circulation of healthy donors.

For people at risk for suffering the worst ravages of this disease, there are too many unknowns to confidently predict whether high-titer, human plasma-derived COVID-Ig will turn out to be more, less or similarly protective as the drug makers' concentrates of one or two highly neutralizing monoclonal antibodies. We will have to wait patiently for results of clinical trials. But one would be foolish to bet against what is essentially the successful human humoral immune response to COVID-19 in a bottle.

References

1. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systemic review and exploratory meta-analysis. *JID* 2015 Jan 1;211:80-90.
2. FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration's Fight Against Pandemic. Accessed Oct. 29, 2020 at www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment.
3. DoD funds industry trio to develop hyperimmune globulin product for COVID-19. Accessed Oct. 23, 2020 at federallabs.org/news/dod-funds-industry-trio-to-develop-hyperimmune-globulin-product-for-covid-19.
4. Silva TF, Tomiotto-Pellissier F, Sanfelice RA, et al. A 21st century evil: immunopathology and new therapies of COVID-19. *Front Immunol* 2020 Oct 27.
5. National Institutes of Health. NIH clinical trial testing hyperimmune intravenous immunoglobulin plus remdesivir to treat COVID-19 begins. Accessed Oct. 24, 2020 at www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-hyperimmune-intravenous-immunoglobulin-plus-remdesivir-treat-covid-19-begins.
6. Chen X, Li R, Pan Z, et al. Human monoclonal antibodies block the binding of SARS-CoV2 spike protein to angiotensin converting enzyme 2 receptor. *Cell Molec Immunol* 2020;17:647-9.
7. Johns Hopkins University (sponsor). Convalescent Plasma to Stem Coronavirus (CSSC-001). Accessed Oct. 27, 2020 at clinicaltrials.gov/ct2/show/NCT04323800?term=NCT04323800&draw=2&rank=1.
8. Johns Hopkins University (sponsor). Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004). Accessed Oct. 27, 2020 at clinicaltrials.gov/ct2/shoNCT04373460?term=NCT04373460&draw=2&rank=1.
9. Stanford University (sponsor). Convalescent Plasma in Outpatients with COVID-19 (C3PO). Accessed Oct. 27, 2020 at clinicaltrials.gov/ct2/show/NCT04355767?term=NCT04355767&draw=2&rank=1.
10. A Study to Evaluate the Safety and Efficacy of High Dose IVIG Plus Standard Medical Treatment (SMT) Versus SMT Alone in Participants in ICU with COVID-19. CliicalTrials.gov (NCT04480424). Accessed Oct. 29, 2020 at clinicaltrials.gov/ct2/show/NCT04480424?term=IVIG&cond=covid-19&draw=2&rank=3.
11. A Study of Standard of Care (SOC) Plus IVIG Compared to SOC Alone in the Treatment of COVID-19 Infection. ClinicalTrials.gov (NCT04411667). Accessed Oct. 29, 2020 at clinicaltrials.gov/ct2/show/NCT04411667?term=IVIG&cond=covid-19&draw=1&rank=4.
12. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proceed* 2020 Sep;95(9):1888-97.
13. Klassen SA, Senefeld JW, Johnson PW, et al. Evidence favoring the efficacy of convalescent plasma for COVID-19 therapy. *medRxiv* 2020 Oct 29.
14. Salazar E, Christensen PA, Graviss EA, et al. Treatment of COVID-19 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol* 2020 Nov;190(11):2290-2303.
15. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv* 2020 Aug 12.
16. GigaGen announced publication of research describing a new class of drugs, recombinant hyperimmunes, including its novel COVID-19 therapy, GIGA-2050. Accessed Oct. 30, 2020 at www.globenewswire.com/news-release/2020/08/10/2075748/0/en/GigaGen-Announces-Publication-of-Research-Describing-a-New-Class-of-Drugs-Recombinant-Hyperimmunes-Including-its-Novel-COVID-19-Therapy-GIGA-2050.html.

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

Philip Wagner, who contracted COVID-19 during a men's spiritual retreat, encourages people to take the disease seriously and recognize it can be spread by people who are asymptomatic.

COVID-19: *A Patient's Perspective*

By Trudie Mitschang

WHEN THE spiritual retreat he'd signed up for in March was rescheduled for early August, Philip Wagner was looking forward to a time of renewal and refreshment. The remote Texas ranch where the event was held hosted 16 men plus event staff, and although body temperatures were taken twice daily and facilities were disinfected, at least one asymptomatic COVID-19 carrier infected a number of the men who attended, including Wagner.

BSTQ: Did the event center provide safety guidelines for attendees?

Wagner: When it started, they said we could wear face masks if we wanted to, but everyone chose not to. I hesitated but didn't want to be the only one wearing a mask. I've since thought about how easy it was for me to give in in that situation. In reality, since we were all sharing the same air conditioning, it would not have mattered if I wore a mask or not.

BSTQ: What were the facilities like?

Wagner: We were in a large retreat center that had about eight rooms with three beds in each room, a meeting area and an eating area. We were close to each other and did not practice social distancing. Clearly, at least one person who probably did not realize it was asymptomatic but contagious.

BSTQ: When did you suspect you'd been infected?

Wagner: A week after I got back from the event, a few friends who attended told me they tested positive for the virus. A short time later, I suspected I had the virus when I began to feel pains and aches in my muscles similar to how I've felt when I had the flu. I also began to feel chills on my skin. I got tested, and the test was negative, but my symptoms continued to get worse. The nurses at the urgent care center suggested I retest, and the results came back positive.

BSTQ: What were your other symptoms?

Wagner: I had pain in my muscles, fatigue, dizziness, drowsiness, brain fog and chills. I had a dry cough for a few days, but it didn't last. I was sick for about 16 days when the symptoms shifted to my stomach and colon. The pain became so severe I checked into the hospital where I learned about 30 percent of COVID-19 patients have gastrointestinal, as well as respiratory, problems.

BSTQ: What treatment did you receive in the hospital?

Wagner: They gave me morphine several times during the two days I was there. They also gave me laxatives to help eliminate as many toxins from my colon as possible, and a medication to help relieve any gas-related pain.

BSTQ: Did you have risk factors for severe complications?

Wagner: I am 67 years old, and I have had immune deficiencies. For the last five years, I seem to have caught anything that's going around. I had cancer, and after treatment, I've had so many sicknesses such as shingles, flu, colds, allergies and fatigue that eventually caused me to become semi-retired for health reasons. In 2020, I had not been sick for nearly seven months, my longest period of health since 2014. Then, I caught the virus.

BSTQ: Did anyone else in your family test positive?

Wagner: When I was first diagnosed, I quarantined myself in our bedroom. My wife would bring some food or drink to my door and knock. I would wait until she left the area and then open the door to get what she left for me. She and I wore masks if there was any need for me to leave the room or to stand at a distance to talk. Unfortunately, after a few days, she started getting symptoms and was sick for about a week but recovered quickly. She did not have respiratory issues, but she did lose her taste and smell for a while.

BSTQ: What was the psychological toll of being quarantined?

Wagner: During the sickness, I felt hopeless and isolated. Every day felt like the previous day for almost 30 days. I wondered if I would ever feel better again. The nights were the worst because the feeling of isolation increased. The social restrictions of the pandemic already were having an impact on all of us, so getting sick after a few months of isolation multiplied that sense of aloneness for me.

BSTQ: How is your health today?

Wagner: I still have low energy, and I struggle with concentration, attention span, information processing and short-term memory.

BSTQ: What if any advice would you give to others?

Wagner: I would encourage people to take COVID-19 seriously. It was definitely a type of illness I've never experienced before in my life. I highly recommend people wear masks, wash hands more than normal and practice social distancing. The important thing to remember is people can be contagious but asymptomatic. ❖

COVID-19: *A Physician's Perspective*

Dr. Dasgupta, who treats patients who have contracted COVID-19, the virus he and his family also recovered from, believes patient care is improving as more data is obtained and patient stories are shared.

RAJ DASGUPTA, MD, is an assistant professor of clinical medicine at the Keck School of Medicine at the University of Southern California. His mission in life is to educate patients, students and aspiring doctors and to inspire better patient care. Since the onset of the pandemic, Dr. Dasgupta has been actively treating patients as a pulmonary critical care physician. Then in July 2020, he went from being a physician to a patient when he and his family contracted COVID-19.

BSTQ: Tell us about the work you've been doing to support patients through the pandemic.

Dr. Dasgupta: From the moment this pandemic started, we've been trying to find the best way to help patients, and this virus has been throwing us curveballs. I think we've learned some of the traditional things that worked in the past for similar disorders don't apply to COVID. So, maybe we have to think outside the box. At the same time, we're still trying to practice evidence-based medicine. What does the data show? What does the science show? But it's hard when we haven't experienced a pandemic in a long time. Patients are experiencing horrible symptoms right in front of us, and sometimes we're pushed into a corner to make a decision to start medications with limited evidence available to us. I think this whole experience for many physicians has been very humbling.

BSTQ: When did you and your family contract the virus, and what were your symptoms?

Dr. Dasgupta: It was July 2020. I felt some fatigue, more than usual. I had a little brain fog, making it hard to concentrate. I had some mild headaches. But all those symptoms went away quickly. I'm eternally grateful my kids, wife and I had a very mild course, because it could have been much worse.

BSTQ: What is giving you hope right now?

Dr. Dasgupta: I love the three preventive strategies we've been talking about over and over again: good hand hygiene, social distancing and wearing a mask. I also have faith that, as pulmonary critical care doctors, we are learning. As more data comes in and we share our experiences, patient care is improving. We do also have some weapons that I have faith in, whether it's steroids, remdesivir or convalescent plasma.

BSTQ: What about a vaccine?

Dr. Dasgupta: What I'm hoping for is the vaccine will be at least 50 percent effective, safe and can be administered in a timely fashion.

BSTQ: Based on your experiences, what would you want other patients to know?

Dr. Dasgupta: I would say enjoy every moment with your family, because things can change very quickly. I would say if you're waiting for fevers, cough and shortness of breath, you're going to miss an opportunity to get evaluated early. And if you ever find out you're positive, my advice is to take a deep breath. I think trying to stay calm initially is important.

BSTQ: In your opinion, what is our best weapon against this virus?

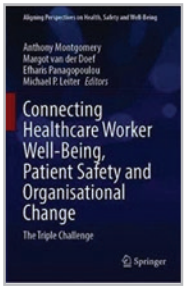
Dr. Dasgupta: Whether you've been infected with the virus or not, whether you think that you're at high risk or low risk, I truly want to emphasize that our best weapon right now is prevention. And when we talk about wearing a mask, not only is it about safety, it's about respect. I wear a mask to be safe and to be a role model, and because I want to respect other people. ❖

Whether you've been infected with the virus or not, whether you think that you're at high risk or low risk, I truly want to emphasize that our best weapon right now is prevention.

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

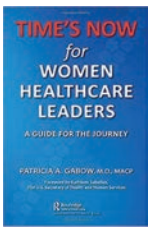
Connecting Healthcare Worker Well-Being, Patient Safety and Organisational Change: The Triple Challenge (Aligning Perspectives on Health, Safety and Well-Being)

Editors: Anthony Montgomery, Margot van der Doef, Efharis Panagopoulou and Michael P. Leiter



There is a growing realization within the healthcare industry that worker well-being, patient outcomes and organizational change are symbiotically linked. Burnout and stress in healthcare workers and toxic organizational cultures can lead to a cycle of patient neglect, medical errors, suboptimal care and further stress. This book outlines the ways in which worker well-being, patient outcomes and organizational change can be aligned to contribute to a healthy workplace and, therefore, better medical care. It includes an array of authors from different disciplines, including primary care, clinical medicine, psychology, sociology, management, clinical governance, health policy and health services research. And, it integrates different voices and reaches meaningful conclusions to address the challenges facing the healthcare workforce.

www.amazon.com/Connecting-Healthcare-Well-Being-Patient-Organisational/dp/3030609979



TIME'S NOW for Women Healthcare Leaders: A Guide for the Journey

Author: Patricia M. Gabow, MD, MACP

Women comprise more than 80 percent of healthcare frontline employees, but they often hit the proverbial glass ceiling. Only 30 percent of healthcare C-suite executives and less than 15 percent of CEOs are women. Moreover, while 51 percent of medical students are women, only 16 percent of department chairs and deans are women. With women facing barriers to achieving their potential, limiting their ability to add their unique talents and skills to the tables of leadership, Dr. Gabow provides extensive detail on these barriers and approaches to their solutions. This is a practical how-to book written to help women in healthcare envision their ability to contribute and inspire them to lead. The author sees this as not only helping women, but also facilitating solving healthcare's myriad problems, improving health and benefiting society.

www.amazon.com/TIMES-NOW-Women-Healthcare-Leaders/dp/1138365580

How Technology Is Shaping the Future of Health Care

Author: STAT

This ebook includes all of STAT's coverage of the 2020 STAT Health Tech Summit, which brought together researchers, policy experts and top executives working at the intersection of health and technology, including leaders from Google Health, Teladoc, Livongo, 23andMe and Fitbit. It includes stories that highlight the rapidly evolving health tech landscape, including a look at how Lyft's growing health business is trying to close gaps in healthcare access, and an examination of how artificial intelligence could reduce existing biases in healthcare — or exacerbate them.

www.statnews.com/technology-future-health-care/?utm_campaign=stat_plus_marketing&utm_medium=email&_hsmi=97413405&_hsenc=p2ANqtz-_UFyox9Jge5XiGiICsA6IAOQ7sByHdmL9dH-yWSIYJqysdivFDoceuWt8VicY2V2qSyAZWERgUndKanY93IsWE7ev6Gw&utm_content=97413405&utm_source=hs_email

The Moral Distress Syndrome Affecting Physicians: How Current Healthcare Is Putting Doctors and Patients at Risk

Author: Eldo E. Frezza, MD, MBA, FACS

The rise of suicide and burnout among physicians has brought a new disease to the healthcare provider, which previously was thought only affected soldiers: moral distress syndrome, second only to moral injury. This book introduces the concept of moral distress syndrome, which includes any or all of the following: depression, post-traumatic distress syndrome, risk of suicide, divorce, emotional detachment and the inability to build healthy relationships and empathy. This book is intended to raise awareness of the problems related to moral distress, and is designed around physicians talking to other physicians about their moral distresses in a safe space. It brings all the aspects of the moral distress syndrome in a format familiar to the physician: grand rounds with a magistral lecture, where the audience asks the question and directly participates in the subject.

www.amazon.com/Moral-Distress-Syndrome-Affecting-Physicians/dp/0367471531

Infection Rates in PI Patients Decline with Increasing IVIG Dosages and IgG Trough Level

A systematic review and meta-regression analysis of published clinical studies was conducted to evaluate the impact of increasing immunoglobulin G (IgG) trough levels on infection rates in patients with primary immunodeficiency disorders (PI) receiving intravenous immune globulin (IVIG) treatment.

From a search of all relevant articles published between 2001 and 2018, 28 clinical studies reporting on 1,218 patients were included. Across all studies, the mean IVIG dose ranged from 387 mg/kg to 560 mg/kg every three to four weeks, and mean IgG trough level ranged from 660 mg/dL to 1,280 mg/dL. A random-effect meta-regression slope analysis found the IgG trough level increases significantly by 73 mg/dL with every increase of 100 mg/kg in the dose of IVIG. Overall infection rates declined significantly by 13 percent with each increment of 100 mg/dL in the IgG trough level, up to 960 mg/dL ($p < 0.05$).

The study authors concluded that titrating the IgG trough level up to 960 mg/dL progressively reduces the infection rate in PI patients, but there is less incremental benefit above this trough level. "Further studies to validate this result are required before it can be used in clinical practice," they added.

Lee JL, Shah NM, Makmor-Bakry M, et al. A systemic review and meta-regression analysis on the impact of increasing IgG trough level on infection rates in primary immunodeficiency patients on intravenous IgG therapy. J Clin Immunol *2020 Jul;40(5):682-98.*

Low Serum Albumin Level Strongly Associated with Severe COVID-19

Given that hypoalbuminemia has been associated with critical illness and mortality across numerous clinical settings, and laboratory markers are needed for early recognition of worsening COVID-19 disease, University of Toledo investigators conducted a systematic review and meta-analysis to determine whether there may be an association between hypoalbuminemia and severe COVID-19.

An extensive literature search of PubMed/MEDLINE, Embase, Cochrane and Web of Science was conducted through April 30, 2020. Two independent reviewers performed screening and article data extraction; a total of 11 studies, totaling 910 patients with a mean age of 47.6 ± 8.2 years, were included. Severe COVID-19 was defined as respiratory distress (with either rate ≥30/minute, oxygen saturation ≤93 percent at rest and/or PaO2/FIO2 ≤300 mmHg), ICU admission and/or death. Hypoalbuminemia was reported based on reference laboratory parameters for each cited study.

The weighted mean serum albumin on admission was 3.50 g/dL (95% confidence interval [CI] 3.26-3.74 g/dL) and 4.05 g/dL (95% CI 3.82-4.27 g/dL) in the severe and nonsevere COVID-19 groups, respectively. This was statistically significant with a mean difference (MD) of -0.56 g/dL, 95% CI -0.69 to -0.42 g/dL, $p < 0.001$. The results were consistent on subgroup analysis of eight studies that defined severe COVID-19 based on

a respiratory distress definition (MD -0.58 g/dL, 95% CI -0.78 to -0.37 g/dL, $p < 0.001$). Four of these studies that specifically assessed hypoalbuminemia status in relation to severe COVID-19 found a very strong association, with an odds ratio of 12.6 (95% CI 7.5-21.1, $p < 0.001$).

The study authors acknowledged it is difficult to assess whether severe COVID-19 resulted in hypoalbuminemia, or the opposite. Whether hypoalbuminemia should be corrected or not "needs further evaluation in future studies," they added.

Aziz M, Fatima R, Lee-Smith W, et al. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care *2020 May 26;24(1):255-8.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2021, through March 30, 2021

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	ASCENIV	ADMA Biologics	90283/J1599	**	**
	BIVIGAM	ADMA Biologics	J1556	$140.98	$138.72
	FLEBOGAMMA	Grifols	J1572	$73.72	$72.54
	GAMMAGARD SD	Takeda	J1566	$133.94	$131.80
	GAMMAPLEX	BPL	J1557	$99.62	$98.02
	OCTAGAM	Octapharma	J1568	$83.26	$81.93
	PANZYGA	Pfizer	90283/J1599	**	**
	PRIVIGEN	CSL Behring	J1459	$84.85	$83.49
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$87.25	$85.85
	GAMMAKED	Kedrion	J1561	$87.35	$85.95
	GAMUNEX-C	Grifols	J1561	$87.35	$85.95
SCIG	CUTAQUIG	Octapharma/Pfizer	90284/J3590	**	**
	CUVITRU	Takeda	J1555	$139.44	$137.20
	HIZENTRA	CSL Behring	J1559	$110.94	$109.16
	HYQVIA	Takeda	J1575	$143.36	$141.06
	XEMBIFY	Grifols	J1558	$146.87	$144.51

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

Calculate your reimbursement online at www.FFFenterprises.com.

** ASP-based Medicare payment rate not yet available; payment rate assigned by your Medicare Administrative Contractor.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	2.5 g, 5 g
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	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
	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 g, 30 g
	PANZYGA Liquid, 10%	Pfizer	PI, ITP	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 SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	5 g, 10 g, 20 g
	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma/Pfizer	PI	1 g, 2 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 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
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease
PFS Prefilled syringes

2020-2021 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90688
AFLURIA PEDIATRIC (IIV4)	SEQIRUS	0.25 mL PFS 10-BX	6-35 months	90685
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 PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662

aIIV3 MF59-adjuvanted trivalent inactivated injectable
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.

FFF enterprises

VERIFIED

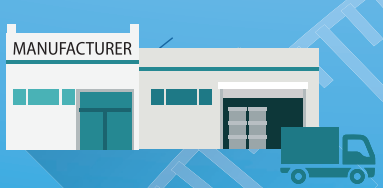
INVENTORY PROGRAM®

WHEN MINUTES MATTER

VIPc CABINET INSTALLATION

REAL-TIME 24/7 MONITORING & INVENTORY VISIBILITY

RFID TAG TECHNOLOGY



PRODUCT SAFETY

The VERIFIED

Spend less time managing inventory

Emergency Ordering 24/7

THE PRODUCTS YOU NEED

ARE ALREADY THERE

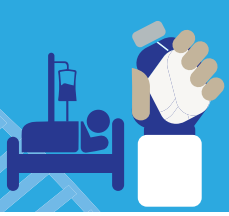
With FFF's Verified Inventory Program (VIPc)® Forward-Deployed Inventory (FDI) System, you have plenty of time to care for your patients.

- Eliminate carrying costs
- Real-time 24/7 monitoring
- Inventory PAR levels
- Increased visibility
- Accurate reporting
- Temperature alerting
- High-touch service
- Integrated split-billing

CONVENIENT WEB PORTAL & AUTOMATED ALERTS

CUSTOMIZED INVENTORY

NATIONWIDE COVERAGE



Advantage

and more time focusing on patient care.

(800) 843-7477 | FFFenterprises.com

BioSupply Trends Quarterly
44000 Winchester Road
Temecula, CA 92590-9760

PRSRT STD
US POSTAGE PAID
LEBANON JUNCION, KY
PERMIT NO. 714