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CME MOC

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COVID-19 and flu:
Dual threat, dual opportunity

Convalescent plasma in COVID-19:
Promising, not proven

COVID-19 plus other infections

COVID-19 Curbside
Consults: www.ccjm.org

The Clinical Picture: Spur-cell anemia

Pneumococcal vaccine:
Which shot when?

Do antirheumatic drugs
affect vaccines?

Contrast media
and acute kidney injury

Using and interpreting
electrodiagnostic tests

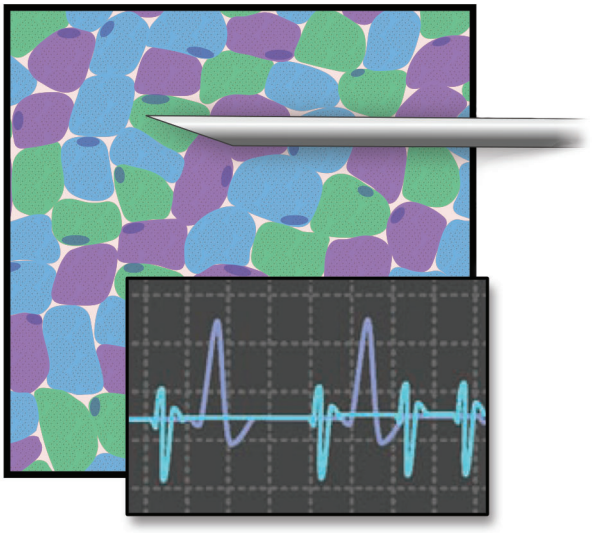

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Table of Contents

CONTINUED ON PAGE 644

CONTINUED FROM PAGE 642

Upcoming Features

- Precision care for non-small-cell lung cancer
- When premature babies grow up
- Echocardiography and endocarditis
- Testosterone for women
- Guidelines on reversing direct oral anticoagulants

WE CAN'T HUG YOU BUT WE CAN SALUTE YOU

The public may have pandemic fatigue. But COVID isn't resting and neither can you. That's why we created **#UniteInGratitude**, a national campaign to thank and honor all healthcare workers with a flag of your own, made from the colors and fabrics you wear to the fight every day. We're selling this Gratitude Flag (and other gear) to unite the public in ongoing support for healthcare workers, with proceeds going to the CDC Foundation's Coronavirus Emergency Response Fund. Visit **UniteInGratitude.com** to learn more. And thank you for everything you do...*we salute you*.

#UniteInGratitude

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2020

NOVEMBER

MULTIDISCIPLINARY COLORECTAL ONCOLOGY COURSE: A CASE-BASED APPROACH
November 6
LIVE STREAM

CLEVELAND CLINIC CASE REVIEWS IN CARDIOLOGY
November 7–8
LIVE STREAM

DECEMBER

LIVER UPDATE
December 4
LIVE STREAM

MASTERING THE TREATMENT OF MYELOID MALIGNANCIES IN THE ERA OF PERSONALIZED MEDICINE: VIRTUAL SYMPOSIUM
December 4
LIVE STREAM

A CASE-BASED APPROACH TO MASTERING THE MITRAL VALVE: IMAGING, INNOVATION, INTERVENTION
December 4–5
LIVE STREAM

DR. ROIZEN'S PREVENTIVE MEDICINE LONGEVITY CONFERENCE
December 5–6
LIVE STREAM

2021

JANUARY

SHAPING THE MANAGEMENT OF PARKINSON DISEASE: DEBATING THE MOST CONTROVERSIAL ISSUES AND DISCUSSING THE LATEST BREAKTHROUGHS
January 23–24
Lake Tahoe, NV

FEBRUARY

VALVE DISEASE, STRUCTURAL INTERVENTIONS, AND DIASTOLOGY/ IMAGING SUMMIT
February 5–7
Cleveland, OH

MARCH

MANAGEMENT OF CHECKPOINT INHIBITOR-RELATED TOXICITY
March 4–5
Cleveland, OH

INTERNATIONAL *PTEN* SYMPOSIUM: FROM PATIENT-CENTERED RESEARCH TO CLINICAL CARE
March 15
Cleveland, OH

PAIN MANAGEMENT SYMPOSIUM
March 27–31
Orlando, FL

APRIL

MANAGEMENT OF ADVANCED AND RECURRENT OVARIAN CANCER
April 16–17
Cleveland, OH

JUNE

WASOG/AASOG 2021: MULTIDISCIPLINARY MEETING FOR SARCOIDOSIS AND ILD
June 21–24
Hollywood, FL

JULY

UPDATES IN MELANOMA AND HIGH-RISK SKIN CANCER MANAGEMENT
July 15–16
Cleveland, OH

CLEVELAND SPINE REVIEW: HANDS-ON 2021
July 28–August 2
Cleveland, OH

SEPTEMBER

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
September 9–10
Cleveland, OH

COMPREHENSIVE LIFELONG EXPEDITIOUS CARE OF AORTIC DISEASE
September 17–18
Cleveland, OH

GENETICS EDUCATION SYMPOSIUM – GENETICS AND GENOMICS: APPLICATIONS FOR THE PREVENTION, DETECTION, AND TREATMENT OF CANCER
September 30
Cleveland, OH

Double the reasons for giving the flu vaccine in 2020

Regular readers of the *Journal* can anticipate an annual fall article related to the flu vaccine or, at the least, be unsurprised by its publication. This year I asked Dr. Sherif Mossad, one of our infectious disease consultants with special expertise in respiratory viruses, to specifically address the potential relationship between the annual influenza vaccine and the ongoing COVID-19 pandemic. On page 651 of this issue, you will find his thoughtful response.

I always learn from Sherif. In his article he notes a fascinating (prepublication) observation from Brazil[1]: patients who had received their 2020 influenza vaccination and who contracted SARS-CoV-2 fared better in several ways than those infected with the SARS-CoV-2 virus who had not been vaccinated. They were less likely to develop severe respiratory disease or die—a striking observation with obvious implications for all of us as we get ready for flu season.

The immunobiology underlying this observation, which hopefully is true, is not clear to me. This was an observational, not a prospective, randomized study. Hence there is the significant potential for bias due to potential specific reasons for giving the influenza vaccine to some but not all patients. The authors went to great lengths to limit this potential bias in their analysis. More than 90,000 patients were studied; final survival outcome data were available for 67,000, and recorded vaccination status data for more than 36,000 (about 40%). Outcome benefit was most pronounced in patients over age 60. Most intriguing is the observation that patients who received the influenza vaccine while symptomatic from COVID-19 still received significant benefit in terms of pulmonary and survival outcome (odds ratio for mortality 0.73, 95% confidence interval 0.58–0.91). This rapid effect argues against the boosting of an antibody that cross-reacts between the two viruses (adaptive immunity) being the mechanism, and rather favors a boosting of the innate immune response (less-specific pathogen recognition or perhaps stimulation of interferon generation). This is consistent with cross-agent protection from some other vaccines reported in the past.

I have already added this discussion to my dialogue with patients who are hesitant to get the flu vaccine this year. "This year in particular," I say, "is *not* the year to avoid getting vaccinated." I emphasize the similarity in symptoms between early influenza and COVID-19, which could lead to enormous angst and implications regarding quarantine from family, work, and school. Receiving the flu vaccine should lessen the likelihood of this happening. I think it has helped my case in promoting vaccination.

In a second vaccine-related paper in this issue of the *Journal*, Day et al (page 695) discuss the increasingly common question of which vaccines can and should be given to patients receiving immunosuppressive therapy. As use of "biologics" has proliferated in the successful treatment of more diseases, internists and other primary care providers in the office often face this question. New information indicates that patients receiving the Janus kinase inhibitors are more prone to experience outbreaks of herpes zoster, raising the imperative for considering administration of Shingrix, a

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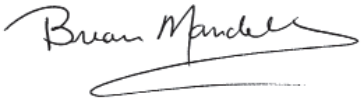
recombinant adjuvanted "dead" zoster vaccine, to these patients before or concurrent with starting one of these medications. Additionally, there are recent studies suggesting that the efficacy of the normal-strength influenza vaccine given to patients receiving methotrexate can be increased by withholding the methotrexate for 2 weeks after vaccination (or by using the higher-dose vaccine intended for patients over age 65). This is information relevant to both subspecialists and primary care providers.

I believe that vaccinations contribute to improving the public health. And while we all hopefully await the arrival of an appropriately evaluated, safe, and effective vaccine against COVID-19 endorsed by the National Institute of Allergy and Infectious Diseases, we need to do the best we can to limit the impact of other vaccination-preventable infectious diseases, as well as the spread of the current pandemic.

And thank you, Dr. Anthony Fauci.



Brian F. Mandell, MD, PhD
Editor in Chief

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Spur-cell anemia

A man with liver disease presents with dizziness and fatigue

A 59-YEAR-OLD MAN presented to the emergency department with dizziness and fatigue. He had a history of alcoholic liver disease with cirrhosis, diagnosed 1 month prior, with small esophageal varices and a Model for End-Stage Liver Disease–Sodium score of 33 (indicating a high predicted mortality risk, 66% at 90 days). There was no hematemesis or melena.

Physical examination revealed scleral icterus, mild abdominal distention, and bilateral pitting edema, with scattered bruising.

Laboratory testing revealed the following:

- Acute anemia, with a hemoglobin level of 6.3 g/dL, down from 10.6 g/dL 2 weeks earlier (reference range 13.0–17.0)
- Macrocytosis, with a mean corpuscular volume of 109 fL, up from 92 fL (80–100)
- Red blood cell distribution width 22% (11%–16%)
- Reticulocyte count 9% (0.4%–2.0%), absolute count 194 × 10^9/L (18–100)
- Lactate dehydrogenase 412 U/L (140–280).

Stable thrombocytopenia and hyperbilirubinemia were also noted. Tests for human immunodeficiency virus and hepatitis were negative.

Computed tomography showed only diffuse edema and mild ascites, without hemorrhage or fluid collections.

The patient received a transfusion of 2 units of packed red blood cells, after which his hemoglobin level was even lower—5.9 g/dL. An additional 4 units were transfused over the next 48 hours, but his peak hemoglobin level was still only 6.5 g/dL.

Further testing showed rising bilirubin, an undetectable haptoglobin, elevated lactate dehydrogenase, and a negative direct Coombs test.

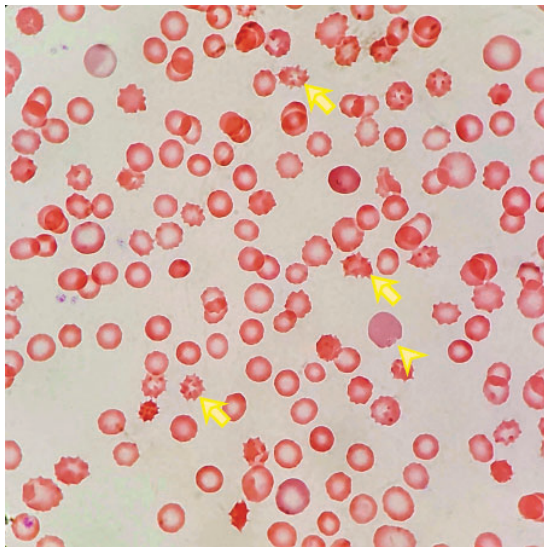

Figure 1. A peripheral blood smear showed numerous irregularly shaped erythrocytes with spinous projections ("spur cells") and increased reticulocytes.

The peripheral blood smear (**Figure 1**) showed numerous irregularly shaped erythrocytes with spinous projections (ie, acanthocytes, or "spur cells") and increased reticulocytes, confirming the diagnosis of spur-cell anemia.

HEMOLYTIC ANEMIA IN HEPATIC FAILURE

Hemolysis in hepatic failure is often overlooked as a cause of anemia. These patients often have decreased haptoglobin, elevated lactate dehydrogenase, and hyperbilirubinemia at baseline.

When Coombs-negative hemolysis is suspected in liver failure, the peripheral blood smear should be reviewed for morphologic abnormalities. Abnormal lipid and protein metabolism results in erythrocyte membrane defects—commonly, macrocytosis and target

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cells. These erythrocytes lose their plasticity and are deformed as they travel through the spleen, resulting in the formation of spur cells and increased clearance in the reticuloendothelial system. Zieve syndrome is a triad of jaundice, hypertriglyceridemia, and hemolysis.[1]

MANAGEMENT IS MAINLY SUPPORTIVE

Spur-cell anemia is associated with a poor prognosis, and liver transplant is the only definitive management.[2] Supportive management includes transfusion for symptomatic anemia, discontinuation of bone marrow-suppressive medications and alcohol, and appropriate treatment for the primary cause of liver disease. Medical management with prednisolone or pentoxifylline is based only on limited case reports, and further research is needed.[3,4]

Recurrence of spur-cell anemia after transplant can herald graft failure.[5]

Our patient's care

Our patient was not a candidate for transplant because of his ongoing alcohol use. He was enrolled in palliative care and died 1 month later.

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COMMENTARY

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COVID-19 and flu: Dual threat, dual opportunity

This fall, the Northern Hemisphere faces the dual threat of the annual influenza epidemic and the pandemic of coronavirus disease 2019 (COVID-19), which arrived here in March 2020 and never went away. But all is not bleak. Although the COVID-19 pandemic continues and has had a negative impact on preventive, routine, and acute medical care, the silver lining is that measures to combat the COVID-19 pandemic can help minimize the impact of seasonal influenza, and vice versa.

COVID-19 has justifiably occupied most of our attention in the last 10 months, but we need to keep our eyes on the ball of the upcoming flu season.

COVID-19: THE ONGOING THREAT

At the time of this writing, 1 million of the 33 million people with COVID-19 have died.[1]

The situation was similar in the 1918 influenza pandemic. Then, like now, no effective vaccine or medication was available to prevent or treat the pandemic disease. And despite significant advances in hygiene and supportive medical care achieved in the 100 years between these pandemics, the mortality rate during the early phase of the COVID-19 pandemic in New York City was comparable to that in the 1918 influenza pandemic.[2]

Youth at risk

During the early months of the COVID-19 pandemic, the incidence, disease severity, and mortality rates were highest among older adults. However, during June, July, and August 2020, the pattern shifted so that the incidence was highest in persons ages 20 to 29,[3] and increases in incidence in this age group preceded increases in incidence in those age 60 and older by 4 to 15 days.

In the years 1999 to 2014, global surveillance data from 29 countries showed that young adults ages 18 to 39 accounted for 30% of influenza cases.[4] Influenza vaccination coverage in the United States in adults ages 18 to 49 for the 2018–19 influenza season was 35%, the lowest among all age groups.[5] Even though disease severity of both COVID-19 and influenza may be less in healthy young adults than other age groups, it is becoming clear that the fight against both diseases may not be won without decreasing the incidence of both infections in that age group.

Concurrent infection is common

From March 3 to March 25 of this year, 20% of specimens testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were positive for 1 or more additional pathogens, including influenza.[6] Numerous reports have since documented simultaneous SARS-CoV-2 and influenza co-infection.[7]

Measures to combat COVID-19 can help minimize the impact of seasonal influenza, and vice versa

COMPARING THE COVID-19 AND THE 2009 INFLUENZA PANDEMICS

The COVID-19 pandemic, the 2009 influenza A (H1N1) pandemic (the most recent flu pandemic), and seasonal influenza have several things in common that we need to recognize.

Table 1 summarizes similarities and differences between COVID-19 and 2009 influenza A (H1N1).[8] Both have similar modes of transmission, but COVID-19 is much more contagious. Patients with COVID-19 are

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TABLE 1

The coronavirus disease 2019 and influenza 2009 pandemics compared

	Coronavirus disease 2019 pandemic	Influenza 2009 pandemic
Causative virus	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Influenza A (H1N1)
Mode of transmission	Respiratory droplets most common, but contact with surfaces contaminated with viral particles and airborne routes are possible	
Prevalence	0.11%	25%
Number of secondary transmissions from 1 infected person	2.5	1.7
Incubation period (days)	2–14	2
Interval from symptom onset to maximum infectivity (days)	0	2
Duration of infectivity after onset of illness (days)	8–10	5–7
Typical course of illness	Gradual onset, then sudden escalation in severity, then recovery within 2 weeks in those with mild or moderate illness, and 3–6 weeks in those with severe illness	Sudden onset of acute illness, which lasts 2–5 days, followed by milder symptoms that can last for several weeks
Typical clinical presentation	Fever, headache, myalgia, malaise, and dry cough; less commonly, vomiting and diarrhea	
Unique manifestations	Sudden loss of smell or taste	None
Asymptomatic or presymptomatic	30%–40%	20%
Illness requiring hospitalization	20%	5%–10%
Illness requiring intensive care	1/16,000	1/104,000
Complications	Respiratory failure, myocarditis, encephalitis, myositis, multi-organ failure, and secondary bacterial pneumonia	
Case fatality rate	0.5%–1%	0.02%–0.05%
Antiviral therapy	Intravenous remdesivir (investigational)	Oral oseltamivir, inhaled zanamivir, intravenous peramivir, and oral baloxavir
Dexamethasone therapy	Only if hypoxic	Not recommended
Convalescent plasma therapy	Investigational, only for severe cases	
Preventive measures other than vaccine	Social distancing, hand hygiene, face masks, isolation and contact tracing of confirmed cases, and quarantine of those exposed	
Preventive vaccine	In development; now 6 months into the pandemic	Was developed and approved within 5 months
Pandemic duration	Ongoing; 8 months so far	15 months

most contagious on the day of onset of symptoms, while those with 2009 pandemic influenza were most contagious during the first 2 days after the onset of illness. Asymptomatic or presymptomatic infections are up to twice as common with COVID-19 compared with influenza. Onset of illness with COVID-19 is usually gradual, while that of influenza is typically acute. Loss of sense of smell and taste are features of COVID-19, not influenza. Although the prevalence of influenza A (H1N1) during the 2009 pandemic was much higher than that of COVID-19 in the current pandemic, the latter is associated with up to 4

times higher rates of hospitalization, 5 times higher rates of need for admission to an intensive care unit, and up to 10 times higher case-fatality, all possibly due to readily available, effective antiviral therapy for influenza.

THE PANDEMIC'S NEGATIVE IMPACT ON OTHER MEDICAL CARE

A major negative impact of social distancing measures to curb the COVID-19 pandemic is their indirect effect on preventive health care. Shortly after the pandemic was declared, rates of routine childhood immunizations in Michigan fell by about 20%.[9] Yet Abbas et al[10] estimated that 84 deaths in African children would be prevented by sustaining routine childhood immunizations for every 1 excess COVID-19 death attributed to SARS-CoV-2 infections acquired during these routine vaccination clinic visits. The risk-benefit ratio extended to children's siblings, parents or adult caretakers, and older adults. This and other studies have led to a "call to action" to avoid the catastrophic negative impact the COVID-19 pandemic would have on vaccine-preventable diseases, including influenza.[11]

People are also avoiding routine and even urgent care. An estimated 40.9% of adults in the United States delayed or avoided routine medical care due to the COVID-19 pandemic.[12] In the 10 weeks after declaration of a national emergency in the United States in response to the COVID-19 pandemic, emergency department visits for heart attack decreased by 23% and visits for stroke decreased by 20%.[13] Primary percutaneous coronary interventions for ST-segment elevation myocardial infarction decreased by 38% after March 1, 2020.[14]

MEASURES TO CONTAIN COVID-19 HELP CONTROL SEASONAL INFLUENZA

Several teams around the world are at work on COVID-19 vaccines. Unfortunately, 31.6% of adults surveyed indicated they were not sure they would accept such a vaccine, and 10.8% said they did not intend to be vaccinated.[15] Not surprisingly, not having received the influenza vaccine the year before was one of the factors associated with vaccine hesitancy.

When a COVID-19 vaccine is approved, transparency and scientific integrity will be necessary to gain public trust and, hopefully, convince the hesitators and refusers.[16] We may need to choose our battles wisely by focusing on the slim majority (57.6%[15]) who intend to be vaccinated, and by implementing measures well-established in annual influenza vaccination to close the intention-to-behavior gap,[17] such as providing the vaccine free of charge at the workplace or school.

As an unexpected upside of the COVID-19 pandemic, the public health, nonpharmaceutical interventions for it such as social distancing, hand hygiene, face masks, isolation and contact tracing of confirmed cases, and quarantine of those exposed have resulted in collateral benefit on influenza activity. In the United States, within 2 weeks of the COVID-19 pandemic being declared on March 11, 2020, the percent of samples testing positive for influenza decreased sharply, from more than 20% before to 2.3%.[18] In addition, interseasonal influenza circulation has remained at a historically low level of 0.2%, compared with 1% to 2% in recent interseasonal periods. Moreover, data from several countries in the southern hemisphere[18,19] and others such as Taiwan,[20] Korea,[21] Hong Kong,[22] and Singapore[23] indicate influenza activity in 2020 is at historically low levels.

Despite the negative psychological impact social distancing measures may have, recent surveys suggested that more Americans have embraced healthy lifestyles amid the COVID-19 pandemic.[24,25]

A survey in June 2020 showed that an estimated 40.9% of adults had delayed or avoided routine medical care due to the COVID-19 pandemic

MEASURES TO CONTROL SEASONAL INFLUENZA HELP FIGHT COVID-19

Cross-reactivity of immune responses to influenza virus and coronavirus infections[26] offers some insight into the potential beneficial effect of influenza vaccination on the COVID-19 pandemic. Similarity in structures and evolution of these viruses[27] may explain this cross-reactivity of immunity. Another explanation is a "bystander immunity" induced by influenza vaccine against other viral infections.[28,29]

Preliminary data from more than 90,000 COVID-19 cases in Brazil showed that those who received influenza vaccine during the

2020 influenza vaccination campaign, even after the onset of symptoms of COVID-19, were 8% less likely to require treatment in an intensive care unit, 18% less likely to require invasive respiratory support, and 17% less likely to die.[30] The authors of this publication, which has not been peer-reviewed, cite adaptation in innate immunity as the most plausible mechanism for these beneficial effects.

Other intuitive beneficial effects of influenza vaccination during the COVID-19 pandemic include conserving resources, such as personal protective equipment, and more importantly healthcare providers. Healthcare systems were strained during the first several weeks of the pandemic,[31] and all efforts to maintain this capacity should be implemented.

Variability in influenza vaccine efficacy[32] has fueled continued suboptimal confidence in vaccination and therefore suboptimal vaccination rates.[33] Bartsch et al[32] estimate that if we could produce a vaccine that was reliably 70% effective, it could avert up to 54 million influenza cases, saving up to $6.5 billion in direct medical costs and up to $64.7 billion in productivity losses.[32]

In an earlier article,[34] I addressed how to respond to influenza vaccine doubters. In addition, for those who believe there is an association between maternal vaccination during pregnancy and autism spectrum disorder in offspring, a recent article has refuted any such association.[35]

While patients with suspected or confirmed COVID-19 should postpone influenza immunization until they recover,[36] everyone else 6 months of age and older who has no history of severe allergic reaction to any component if the vaccine, or to a previous dose of any influenza vaccine, should be immunized, preferably early in the flu season.[37]

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Does my healthy 65-year-old patient still need the 13-valent pneumococcal conjugate vaccine (PCV13)?

A: The short answer is no. In the summer of 2019, the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) removed its 2014 recommendation that all healthy adults 65 or older should receive the PCV13 vaccine followed in 1 year by the PPSV23 (23-valent pneumococcal polysaccharide) vaccine.[1] However, PCV13 can still be given after engaging in shared clinical decision-making with the patient. The ACIP continues to recommend that all patients in this population receive the PPSV23 vaccine.[1,2]

The short answer is no—but it is not that simple

WHY CHANGE THE RECOMMENDATION?

In its 2014 recommendation for pneumococcal vaccination in all adults 65 and older, the ACIP noted that certain high-risk groups should be vaccinated earlier or receive additional doses.[1] Pallotta and Rehm outlined these recommendations and discussed the rationale for vaccinating against *Streptococcus pneumoniae* to prevent invasive pneumococcal disease.[3]

So why did the ACIP modify its recommendation? The primary reason is that the incidence of PCV13-type pneumococcal disease in adults had gone down to historic lows (**Figure 1**). A key to this reduction was that children started to be vaccinated in 2000, at first with PCV7 and then with PCV13, which replaced PCV7 in 2010.[1,2] This incidence leveled out from 2014 to 2018 despite the ACIP recommendation and data showing that about half the Medicare beneficiaries older than 65 received the vaccine.[4] The decreased incidence of disease also has decreased the cost-effectiveness of vaccination. The cost of giving PCV13 and then PPSV23, compared with PPSV23 alone, is now estimated to be $200,000 to $560,000 per quality-adjusted life year,[1] whereas in 2014, it was only $65,000.[5]

In light of these facts, the ACIP voted to remove the recommendation requiring older patients to receive the PCV13 vaccine.

SHARED CLINICAL DECISION-MAKING

But it is not that simple. In an attempt to balance "the minimal population-level impact of routine [vaccination] with the potential for individual-level protection,"[1] the ACIP added the principle of shared clinical decision-making to its recommendation.[1,2,4]

The ACIP committee recognized that some immunocompetent patients at higher risk of invasive pneumococcal disease (or their physicians) may believe that PCV13 would still be worthwhile. This population includes patients with certain medical conditions (eg, alcohol or tobacco abuse; chronic heart, liver, or lung disease; diabetes) and patients living in nursing homes or other long-term care facilities.[1,4] By adding the concept of shared clinical decision-making, the ACIP committee ensured that "PCV13 would remain available to patients who want this added protection."[1]

A practical downside of this recommendation is that busy primary care practitioners

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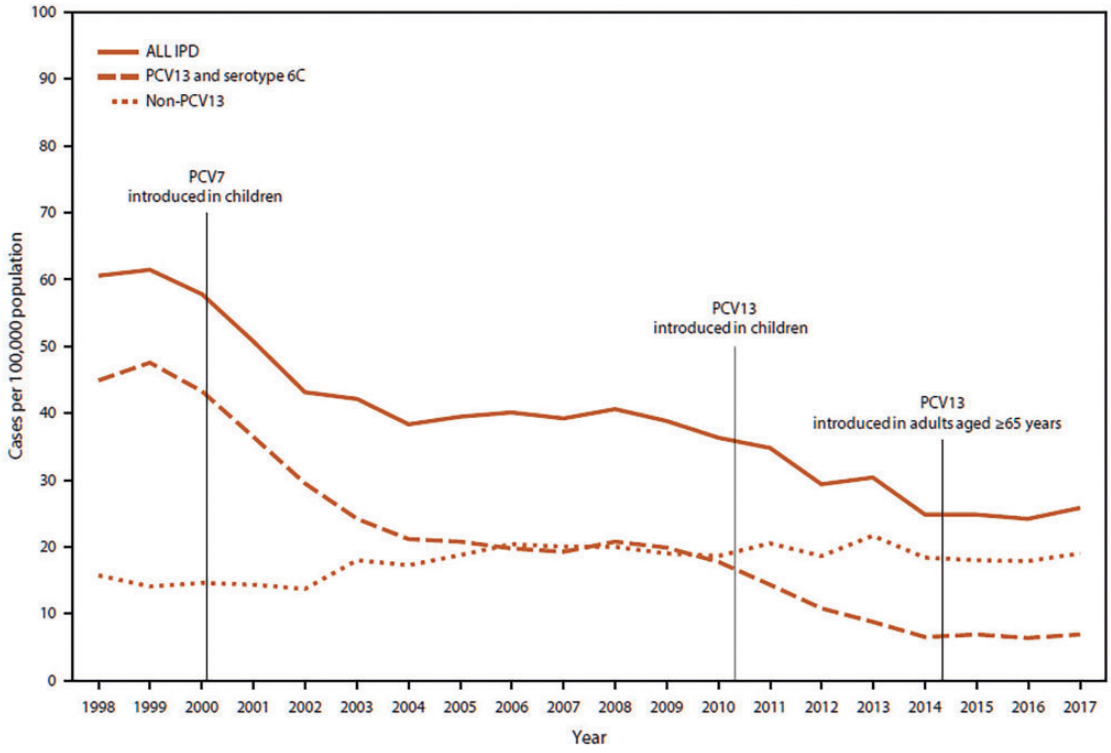

FIGURE 1. Incidence of invasive pneumococcal disease among US adults 65 and older by pneumococcal serotype, 1998–2017.

Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019; 68(46):1069–1075. doi:10.15585/mmwr.mm6846a5

may lack the time to effectively and efficiently review the potential benefit or lack of benefit of PCV13 for the individual. Also, universal recommendations (eg, vaccinate *all* patients over age 65) are generally easier to remember or implement than conditional recommendations (eg, vaccinate *some* patients over age 65). Strategies known to improve vaccination compliance rates include interventions such as electronic medical record reminders and direct patient outreach.

SUMMARY

The 2019 ACIP recommendations are to vaccinate all patients age 65 and older with PPSV23, but PCV13 can be used in shared clinical decision-making. The ACIP continues to endorse use of both PCV13 and PPSV23 in patients older than 19 (including those 65 and older) with immunocompromising conditions, cerebrospinal fluid leak, or cochlear implants.[1] These recommendations are summarized in **Table 1**.[2]

Some patients at higher risk (and their physicians) may believe that PCV13 is still worthwhile

TABLE 1

Summary of current recommendations for pneumococcal vaccination

Patient population	Dosing
≥ **65 years old**	1 dose of PPSV23 If PPSV23 was given before age 65, give another dose at least 5 years after previous dose
≥ **65 years old,** immunocompetent, with chronic heart disease, chronic lung disease, chronic liver disease, diabetes mellitus, alcoholism, or cigarette smoking	Shared clinical decision-making: can give PCV13 followed by PPSV23 at least 1 year later
19 through 64 years old, with chronic heart (excluding hypertension), lung, or liver disease, diabetes, alcoholism, or cigarette smoking	1 dose of PPSV23
19 through 64 years old, with cerebrospinal fluid leak or cochlear implants	1 dose of PCV13 followed by 1 dose of PPSV23 at least 8 weeks later At age 65 or older, give another dose of PPSV23 at least 5 years after PPSV23 (only 1 dose of PPSV23 recommended for ages 65 or older)
19 years or older, with congenital or acquired immunodeficiency (including B- and T-lymphocyte deficiency, complement deficiencies, phagocytic disorders, HIV infection), chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression (eg, drug or radiation therapy), solid organ transplant, multiple myeloma, or anatomical or functional asplenia, including sickle cell disease and other hemoglobinopathies	1 dose of PCV13 followed by 1 dose of PPSV23 at least 8 weeks later, then another PPSV23 dose at least 5 years after previous PPSV23 At age 65 or older, give 1 dose of PPSV23 at least 5 years after most recent PPSV23 dose (only 1 dose of PPSV23 is recommended for ages 65 or older)

PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

Based on information in reference 1.

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Recognition and management of respiratory co-infection and secondary bacterial pneumonia in patients with COVID-19

ABSTRACT

In COVID-19, respiratory infection with SARS-CoV-2 plus another virus (viral co-infection) or with SARS-CoV-2 plus a bacterial pathogen (combined viral and bacterial pneumonia) has been described. Secondary bacterial pneumonia can follow the initial phase of viral respiratory infection or occur during the recovery phase. No obvious pattern or guidelines exist for viral co-infection, combined viral and bacterial pneumonia, or secondary bacterial pneumonia in COVID-19. Based on existing clinical data and experience with similar viruses such as influenza and SARS-CoV, the management approach in COVID-19 should, ideally, take into consideration the overall presentation and the trajectory of illness.

KEY POINTS

All patients presenting with symptoms of respiratory infection should undergo testing for influenza with a polymerase chain reaction assay in addition to SARS-CoV-2 testing.

Guideline-driven empiric antibiotic use may be reasonable until secondary bacterial infection is ruled out.

The duration of antibacterial therapy is generally 5 to 7 days for community-acquired pneumonia and 7 days for hospital-acquired pneumonia and ventilator-associated pneumonia.

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Even as severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), spreads across the globe, the pathophysiology of the disease remains incompletely understood. Respiratory infection caused by more than one viral pathogen (viral co-infection) or by both viral and bacterial pathogens (combined viral and bacterial pneumonia) has been well described. Secondary bacterial pneumonia can follow the initial phase of viral respiratory infection or can occur during the recovery phase.[1] Data on SARS-CoV-2 are limited, but thus far, the overall incidence of viral co-infection has varied widely from 0% to 19% in different case series,[2–7] and combined viral and bacterial pneumonia rates appear to be low.[3,8–10] There is also a dearth of data on the predisposing factors and causative organisms.

Combined viral and bacterial pneumonia and secondary bacterial pneumonia by *Staphylococcus aureus* and other common community-acquired pneumonia pathogens have been best studied in seasonal[2] and pandemic[2,3] influenza and contribute significantly to morbidity and mortality. In the earlier pandemic of severe acute respiratory syndrome (SARS), secondary bacterial pneumonia occurred as ventilator-associated pneumonia in 25% of patients at a single center; methicillin-resistant *S aureus* (MRSA) was the causative organism in 47% of cases, although there was significant concern for cross-transmission.[7]

Because no obvious pattern or guidelines

exist for viral co-infection, combined viral and bacterial pneumonia, or secondary bacterial pneumonia in the context of SARS-CoV-2, the following commentary is based on existing clinical data and experience with similar viruses such as influenza and SARS-CoV. With what we know so far, the approach in the context of COVID-19 would, ideally, take into consideration the overall presentation as well as the trajectory of illness.

VIRAL CO-INFECTION

All patients presenting with symptoms of respiratory infection should be tested for influenza with a polymerase chain reaction (PCR) assay in addition to SARS-CoV-2. PCR assays can also be performed for other respiratory viruses if available.

Regardless of disease severity, all patients with influenza A or B viral co-infection should be treated with oseltamivir or an alternative agent.[11] Empiric treatment for influenza viral co-infection can be considered while waiting for test results if an obvious exposure or risk factor is present. If viral co-infection with another respiratory virus such as respiratory syncytial virus is identified, treatment options are limited and effective only in specific scenarios such as immunosuppression or hypogammaglobulinemia.[12,13] Infectious disease consultation is strongly recommended to determine the benefits of such treatment in light of the potential risk for exacerbating COVID-19–related organ failure and the potential adverse effects of the medication or medications.

Management should take into consideration the overall presentation and trajectory of illness

BACTERIAL PNEUMONIA

Recognizing combined viral and bacterial pneumonia or secondary bacterial pneumonia with COVID-19 requires a high index of suspicion. Some characteristics of bacterial infection may still be identifiable despite a significant overlap of viral and bacterial symptomatology (**Table 1**).[2–10,14–29] Neutrophilic leukocytosis is the hallmark of bacterial pneumonia, whereas COVID-19 patients typically present with a normal white blood cell count with lymphopenia.[5,8,14,15]

Procalcitonin is neither sensitive nor specific in differentiating the etiology of community-acquired pneumonia.[11] However, several series of COVID-19 cases have consistently reported normal (low) procalcitonin levels in isolated SARS-CoV-2 infection, leading to its widespread, albeit unvalidated, use to "rule out" combined viral and bacterial pneumonia, although the exact cutoff remains to be determined. This observation highlights the need to consider all variables in the context of the clinical scenario.

In patients with mild to moderate respiratory failure consistent with the presentation of COVID-19 and without obvious signs of bacterial infection, the likelihood of combined viral and bacterial pneumonia is low, and antibiotics can be safely held off. In this case, gradually worsening respiratory failure within the first week of presentation is more likely to be from progression of COVID-19 than from a new superimposed secondary bacterial pneumonia. This includes patients who are started on noninvasive forms of supplemental oxygen support and then ultimately require invasive mechanical ventilation.

In the absence of supporting evidence of bacterial pneumonia, antibiotics should not be initiated even if respiratory distress is progressing. However, if a patient develops new or acutely worsening respiratory failure, sepsis, or both after an initial phase of consistent improvement (considered to be days), then nosocomial acquisition of secondary bacterial infection is likely unless proven otherwise, ie, secondary bacterial pneumonia in the form of hospital-acquired pneumonia, infection at an extrapulmonary site, or both.

While COVID-19 by itself can cause acute respiratory decompensation, data regarding secondary bacterial pneumonia playing a role in such decompensation are limited. Therefore, guideline-driven empiric antibiotic use may be reasonable until this secondary infection is ruled out. Supportive evidence for secondary bacterial pneumonia includes one or more of the following: new or recrudescent fever; new onset or change in the character of sputum; new leukocytosis or new neutrophilia (or both); new relevant imaging findings; and new or increasing oxygen requirements. It is also important to consider all other sources of hospital-acquired infections in these patients, such as indwelling central venous catheters or

urinary tract catheters, and treat them accordingly.

For a critically ill patient admitted with severe respiratory failure, empiric treatment for all possible causes up front is essential. This is especially important because procalcitonin levels can be falsely elevated in patients with multiorgan failure,[30,31] and imaging studies may be limited in differentiating bilateral infiltrates of acute respiratory distress syndrome from obscured consolidation of bacterial infection.

Empiric therapy for community-acquired pneumonia should be based on the guidelines of the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), as well as on host risk factors and prior microbiologic data.[19] Respiratory samples (tracheal aspirate in mechanically ventilated patients is preferable to sputum) and blood cultures should be sent for all patients, ideally before antibiotics have been started. *Streptococcus pneumoniae* urine antigen should be tested in all patients presenting with severe community-acquired pneumonia. *Legionella pneumophila* urine antigen and *Mycoplasma pneumoniae* IgM and IgG antibodies can be sent based on clinical context and epidemiology.

In the absence of signs of bacterial pneumonia, a positive respiratory culture can represent colonization, especially in those with prior pneumonia with the same organism or altered airway anatomy. Laboratory markers, radiologic features (see **Table 1** and above), and quantitative and semiquantitative culture methods can help in making this distinction.[19]

Secondary bacterial pneumonia in a patient on invasive mechanical ventilation has a presentation similar to that of hospital-acquired pneumonia but warrants aggressive use of empiric broad-spectrum antibiotics with coverage for MRSA, *Pseudomonas aeruginosa*, and possibly other multidrug-resistant organisms in accordance with the guidelines.[19] It is also important to consider the side effects of antibiotics and institutional antibiograms.

Patients with ventilator-associated tracheobronchitis often lack the classic signs of secondary bacterial pneumonia, may have increased secretions and low-grade fevers, and can be difficult to wean from ventilatory support. The

TABLE 1

Key points for laboratory and imaging findings

Co-infection and secondary bacterial infection

Viral co-infection incidence varies in different case series (0%–19%)[2–7,29]

Combined bacterial and viral infection is rare in COVID-19 patients[3,8–10]

Secondary bacterial infection is not uncommon and leads to significant morbidity and mortality, especially in the elderly[4,9,16]

Procalcitonin

Detectable in 2 to 4 hours, peaks at 12 to 24 hours, and has a half-life of 25 to 30 hours

Levels are normal (< 0.5 µg/L) in COVID-19 patients with mild disease and may be elevated (≥ 0.5 µg/L) in patients with severe disease[10,14]

Elevated levels correlate with a nearly 5-fold higher risk of severe SARS-CoV-2 infection[17]

Elevated levels are not specific to bacterial infection because they can also be raised in patients with acute respiratory distress syndrome, end-stage renal disease, cardiogenic shock, and multiorgan failure[18]

A normal level makes bacterial infection less likely and can guide antibiotic discontinuation[19,20]

In bacterial infection, levels may be less affected by IL-6 inhibitors than is C-reactive protein (CRP)[21–23]

CRP, erythrocyte sedimentation rate (ESR)

CRP and ESR are nonspecific inflammatory markers. Both are generally elevated in COVID-19 and are therefore not helpful in differentiating it from bacterial infection

Tocilizumab rapidly reduces CRP and leukocytosis and may suppress fever[24–26]

Typical radiographic features of COVID-19

Chest radiography: bilateral, peripheral, lower-zone predominant air-space disease[27]

Computed tomography: bilateral, predominantly peripheral ground-glass opacities, crazy paving, and consolidation[28]; findings vary based on stage or phase of the disease

Typical radiographic features of bacterial pneumonia

Chest radiography: lobar or segmental air-space opacification ± air bronchograms

Computed tomography: segmental or lobar focal dense consolidation with or without ground-glass opacities

evidence to support antibacterial therapy for this clinical entity is limited and warrants a judicious case-based analysis.

The duration of antibacterial therapy is generally 5 to 7 days for community-acquired pneumonia[32] and 7 days for hospital-acquired pneumonia and ventilator-associated pneumonia[19] in the absence of complications. Consider shortening the duration if patients demonstrate signs of clinical stabilization, especially if adverse effects are seen. Checking the procalcitonin level at presentation will help in the de-escalation of antibiotics based on the trend of procalcitonin levels in 24 to 48 hours.[33] If a microbiological source is not identified within 48 hours of testing and the procalcitonin level is less than 0.5 µg/L or decreases by 80% or more from peak concentration, it is reasonable to discontinue all antibiotics.[19]

The use of interleukin 6 (IL-6) inhibitors such as tocilizumab for COVID-19–related cytokine activation syndrome presents a unique challenge because they suppress common signs of sepsis. The risk of serious bacterial infections has been consistently reported to be higher with tocilizumab use for rheumatologic diseases.[34–37] C-reactive protein and other acute-phase reactants including white blood cell count may be unreliable acute-phase reactants and may not rise in response to a secondary bacterial infection after tocilizumab use.[35,38,39] Exactly how long this effect lasts with 1 or 2 doses is unclear. Procalcitonin may be less affected by IL-6 inhibitors,[21–23] but the data to differentiate bacteria from viral pneumonia in this context are limited and should be further evaluated.

Lastly, invasive pulmonary aspergillosis has been described in critically ill patients with seasonal[40,41] and pandemic[42] influenza and is associated with high morbidity and mortality rates. Invasive pulmonary aspergillosis was also reported in patients with COVID-19–associated acute respiratory distress syndrome.[43] This complication should be considered in high-risk patients such as those with immune-compromising conditions, precedent or concomitant influenza viral co-infection, clinical deterioration despite appropriate antibiotics, and positive fungal markers such as galactomannan on culture. If invasive pulmonary aspergillosis is suspected, treatment with a broad antifungal such as voriconazole should be initiated promptly in consultation with infectious disease colleagues.

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Convalescent plasma for COVID-19: Promising, not proven

ABSTRACT

While promising, convalescent plasma remains experimental and is not proven effective for COVID-19. In addition, many questions remain regarding the accuracy and predictive value of antibody testing of donors and patients, optimal donor selection, optimal timing, and selection of patients most likely to benefit. Until these questions are answered, convalescent plasma should ideally be used in the context of well-designed clinical trials.

KEY POINTS

Transfusion of convalescent plasma may benefit patients with acute COVID-19 by a direct antiviral effect and possible nonspecific anti-inflammatory properties.

Convalescent plasma is likely most effective when given early in the course of the disease.

The ideal donor has high titers of neutralizing antibodies against SARS-CoV-2, although optimal testing for these antibodies is not yet established.

Convalescent plasma has been used for over a century, is likely safe, and observational data from the Expanded Access Program and limited cohort studies suggest it may be beneficial.

While convalescent plasma has received emergency use authorization from the US Food and Drug Administration, its effectiveness has yet to be established in well-controlled clinical trials, which are ongoing.

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COVID-19 convalescent plasma is plasma collected from donors who have recently recovered from acute COVID-19 infection. This plasma is likely to contain high levels of neutralizing antibodies against the SARS-CoV-2 virus, which, when transfused to patients with acute COVID-19 infection, can confer a degree of passive immunity.

Convalescent plasma has been used for over a century as treatment and postexposure prophylaxis for various infections. Case series from prior viral outbreaks suggest it can reduce viral load and cytokine levels and may improve clinical outcomes. Clinical trials to assess its effectiveness for the treatment of COVID-19 are ongoing.

MECHANISM OF ACTION AND POTENTIAL SIDE EFFECTS

The presumed mechanism of action of convalescent plasma is through direct binding and inactivation of the SARS-CoV-2 virus by anti-SARS-CoV-2 neutralizing antibodies. Antibody-dependent complement activation, cytotoxicity, and phagocytosis may also contribute to the therapeutic effect of neutralizing antibodies in convalescent plasma. In addition to improved viral clearance, neutralizing and nonneutralizing antibodies may also lessen disease severity and facilitate recovery by modulating the exaggerated immune response—the cytokine storm—associated with severe disease and multiorgan failure.[1–4]

Convalescent plasma differs from standard plasma only in that it contains anti-SARS-CoV-2 antibodies. The risk of transfusion-related adverse events is therefore likely identical to the risk associated with standard plasma, namely, transfusion-associated circu-

latory overload, transfusion-related acute lung injury, and allergic reactions.[5]

An increased risk of thrombotic events has previously been reported with treatment with hyperimmune immunoglobulin.[6] COVID-19 is a highly prothrombotic disease, and the impact of plasma transfusion on the coagulation system and the rate of thrombotic complications in COVID-19 is unknown.

Theoretical risks unique to anti-SARS-CoV-2 antibodies within convalescent plasma are antibody-dependent enhancement of infection and attenuated immune response with increased risk of future infection.

Antibody-dependent enhancement of infection is a phenomenon in which the presence of antibodies exacerbates the severity of the current infection. It has been well described for other viral infections such as dengue fever, and is usually due to prior infection with a virus of a different serotype. A proposed mechanism is that nonneutralizing antibodies bound to the virus surface facilitate viral entry into host cells by anchoring the virus to the host cell through host cell receptors to the Fc portion of the antibody.

Antibody-dependent enhancement of infection has been cited as a potential reason for regional differences in severity of illness of COVID-19, but evidence for it in coronavirus infection stems mostly from in vitro studies. It is unclear if this is truly contributing to the clinical manifestation of COVID-19 or if it is relevant to treatment with convalescent plasma with high titers of neutralizing antibodies. Unfortunately, currently available antibody tests lack accuracy to determine if the SARS-CoV-2 antibodies present in convalescent plasma are truly neutralizing in vivo.[5,7]

Convalescent plasma may also blunt the recipient immune response and lead to decreased formation of anti-SARS-CoV-2 antibodies, leaving patients at potentially increased risk for future infections.[5]

HISTORICAL PRECEDENCE

Convalescent plasma or "serum therapy" has a storied history dating back to 1901, when Emil Adolf von Behring was awarded the first Nobel Prize in medicine for its use in treating diphtheria. It was the only targeted therapy for acute infections until the advent of antibiotics in the 1940s and was used to treat various bacterial infections from pneumonia to meningitis and botulism, as well as viral infections such as mumps, measles, polio, and influenza.[1,2]

A meta-analysis of 8 studies involving 1,703 patients from the 1918–1920 H1N1 influenza outbreak concluded, despite many methodologic limitations, that patients treated with convalescent plasma may have experienced a clinically significant reduction in the risk of death.[8]

More recently, during the 2009–2010 influenza H1N1 pandemic, the use of convalescent plasma or hyperimmune globulin from convalescent plasma to treat critically ill patients was reported to be associated with improved viral clearance and decreased cytokine levels, particularly those of inflammatory cytokines. Subgroup analysis of patients treated within 5 days of disease onset showed higher survival rates with convalescent plasma-derived hyperimmune globulin than with placebo.[9,10]

Convalescent plasma was also used in the 2013 West African Ebola epidemic and in the 2 Ebola patients transferred to the United States (both of whom survived).[1,2]

In 1901, von Behring won the first Nobel Prize in medicine for work on convalescent plasma

Evidence supporting the use of convalescent plasma to treat coronavirus-associated disease comes from the outbreaks of SARS-CoV-1 in 2003 and Middle East respiratory syndrome (MERS) in 2012. The largest study[11] involved 80 critically ill patients treated with convalescent plasma during the SARS-CoV-1 outbreak in 2003 in Hong Kong. Compared with control patients (who were offered convalescent plasma but declined to give consent for experimental treatment), those who received it were reported to have higher rates of "good outcomes" if treated within 14 days of hospital admission. A good outcome was defined as being alive and discharged from the hospital by day 22.

A meta-analysis[12] of 32 studies in patients with SARS or severe influenza concluded, despite weak evidence, that convalescent plasma treatment led to statistically significant reduction in the pooled odds of mortality (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.14–0.45).

USE IN THE UNITED STATES

Given the extraordinary circumstances of this global pandemic and the lack of effective treatment, the US Food and Drug Administration (FDA) initially allowed the use of convalescent plasma as an investigational product through 3 pathways:

- Clinical trials
- The Expanded Access Program, active from April 1 through August 31, 2020
- A single-patient emergency investigational new drug application. This option allowed patients unable or ineligible to participate in clinical trials or the Expanded Access Program to receive convalescent plasma for "serious or immediately life-threatening" COVID-19 infections under Title 21, Code of Federal Regulations 312.310, from a licensed physician upon FDA authorization.[13] This option also ended August 31.

Plasma collection and donor selection

Convalescent plasma is collected by registered and licensed blood establishments that collect plasma, such as the American Red Cross. Once manufactured, it is distributed by blood centers for investigational use.

Convalescent plasma was used in the 1918–1920 flu, 2009–2010 flu, MERS, SARS, and Ebola epidemics

All donors must meet standard blood donation eligibility requirements and are tested for relevant transfusion-transmissible infections. The FDA[13] has set the following criteria for COVID-19 convalescent plasma donors:

Laboratory confirmation of SARS-CoV-2 infection, either by nasopharyngeal polymerase chain reaction (PCR) testing at the time of illness, or a positive serologic test for SARS-CoV-2 antibodies after recovery, if PCR was not performed at the time COVID-19 was clinically suspected.

Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary.

Male donors, or female donors who have never been pregnant or who have tested negative for human leukocyte antigen antibodies since their most recent pregnancy.

Testing for SARS-CoV-2 neutralizing antibodies has not been a requirement, but samples from each unit of convalescent plasma are stored for future testing once reliable antibody testing is available.

Based on studies of antibody kinetics showing immunoglobulin G seroconversion around day 10 and peak antibody titers around day 28, the optimal timing for convalescent plasma donation appears to be approximately 4 weeks after symptom onset. Older, male patients with more severe illness appear to develop higher antibody titers than those with minimal symptoms and may be more suitable donors.[14–16]

If antibody titers are available, the FDA suggests the viral neutralizing antibody titers should be at least 1:160, but titers of 1:80 are considered acceptable if an alternative matched unit is not available.

However, assays to determine viral neutralizing antibody titers are not widely available, in part because they are labor-intensive and require a biosafety level 3 laboratory if live virus is used. Viral neutralizing titers are therefore not known for the vast majority of plasma units, and a substantial portion of convalescent plasma donors may have titers below the FDA-recommended threshold.[14,17] Antibody titers determined by commercially available enzyme-linked immunosorbent assay may correlate with viral neutralizing antibody titers, but have poor specificity.[14]

Until reliable antibody testing is widely available, convalescent plasma is collected solely on the basis of the FDA criteria above, resulting in unpredictable and likely heterogeneous viral neutralizing antibody titers across all donations.

Clinical experience with convalescent plasma for COVID-19

To date, evidence on the effectiveness of convalescent plasma for the treatment of COVID-19 is limited to case series,[18–21] small cohort studies,[22,23] and data from the Expanded Access Program.[24] Randomized controlled trials are currently ongoing, and the currently available data from prospective trials are minimal.

Early case reports from China described patients who were alive at the time of publication with improved viral clearance, decreased cytokine levels, improved findings on chest imaging, and stable or improved oxygenation after treatment with convalescent plasma.[18–20] Similar outcomes were reported in early case series from the United States.[21]

Liu et al[22] reported stable or improved oxygenation in patients treated with convalescent plasma compared with matched controls, and a lower mortality rate with treatment for nonintubated patients (hazard ratio 0.23, 95% CI 0.05–0.98, *P* = .046), but not for intubated patients (hazard ratio 0.79, 95% CI 0.22–2.79, *P* = .716).

In contrast, Rogers et al[23] were unable to demonstrate a survival benefit for their cohort of 64 patients treated with convalescent plasma compared with a matched cohort of 177 patients treated with standard of care.

The first randomized controlled trial of convalescent plasma in COVID-19 was stopped early due to slow enrollment, as local infection rates declined thanks to strict lockdown measures in Wuhan, China.[25] The study was therefore underpowered to demonstrate statistically significant differences in either the primary end point (time to clinical improvement) or secondary end points (28-day mortality rate, time to hospital discharge, and rate of negative PCR testing at 72 hours). Although not statistically significant, the results appear to signal a more favorable outcome for patients treated with convalescent plasma.[25]

An analysis stratified by disease severity showed that patients who did not need mechanical ventilation and did not have multiorgan failure had a shorter time to clinical improvement if given convalescent plasma than with placebo. Clinically significant improvement at day 28 was also more likely to occur in the convalescent plasma group (91.3%) than in the control group (68.2%).[25]

Data from the Expanded Access Program

While clinical trials are still ongoing (on September 28, 2020, clinicaltrials.gov listed 93 clinical trials that were recruiting patients for the use of convalescent plasma to prevent or treat COVID-19), nearly all patients who received convalescent plasma in the United States did so through the US Convalescent Plasma Expanded Access Program, created in collaboration between the FDA and Mayo Clinic.[24]

This registry study was designed to facilitate rapid application of convalescent plasma in clinical practice and monitor its safety. It allowed physicians treating hospitalized COVID-19 patients to register and request convalescent plasma for individual qualifying patients. The physician registering a patient was required to complete all necessary documentation including consent, patient history, posttransfusion follow-up data, and adverse event reporting in a centralized electronic database administered by Mayo Clinic.[24]

From April through August of this year, 14,532 physicians at 2,759 sites registered 105,785 patients, 84,639 of whom received convalescent plasma through this program by August 31.[24]

Safety. In the first 20,000 patients who received convalescent plasma through the Expanded Access Program, the rate of serious adverse events within 4 hours of transfusion was less than 1%.[26] Sixty-three of these events (0.3% of all transfusions) were deaths, 13 of which were judged as related to convalescent plasma (12 possibly, 1 probably, and 0 definitely). Seventy-eight nonmortality events were reported, with 36 reports of transfusion-associated circulatory overload, 21 reports of transfusion-related acute lung injury, and 21 reports of severe allergic transfusion reaction.[26]

Within 7 days of completion of the transfusion, 1,247 other serious adverse events were reported,[26] including 113 thromboembolic or thrombotic events, 457 sustained hypotensive events requiring intravenous vasopressor support, and 677 cardiac events. The authors note that 75 of the thrombotic or thromboembolic complications and 597 of the 643 cardiac events were judged by the treating physician to be unrelated to the plasma transfusion.[26]

The Expanded Access Program ended August 31, 2020

In contrast, the incidence of transfusion-related reactions reported in a recent matched cohort study of 64 patients[23] and the randomized controlled trial in 102 patients[25] was significantly higher, at 2.8% and 2.1%, respectively. This highlights the challenges in assessing transfusion-related complications in critically ill patients and differentiating them from progression of disease.

Effectiveness. The first effectiveness analysis[27] of 35,322 patients treated with convalescent plasma through the Expanded Access Program between April 4 and July 4 reported an overall mortality rate of 10.5% by day 7 and 24.9% by day 30.

Subgroup analysis comparing patients treated with plasma early after diagnosis (within 3 days or less) vs late, and patients treated

with plasma containing high vs low levels of anti-SARS-CoV-2 antibody, signal a possible benefit of early administration of plasma with high antibody titers.

In patients treated with convalescent plasma within 3 days of the diagnosis of COVID-19, the 7-day mortality rate was 8.7% (95% CI 8.3%–9.2%) compared with 11.9% (11.4%–12.2%) in those who received it 4 or more days after diagnosis ($P < .001$). A similar trend was observed in 30-day mortality (21.6% vs 26.7%, $P < .0001$).[27]

Estimates of the antibody titers of the convalescent plasma transfused were available for 3,082 patients. Titers were estimated using the Ortho-Clinical Diagnostics VITROS Anti-SARS-CoV-2 immunoglobulin G (IgG) chemiluminescent immunoassay, a qualitative assay based on the sample signal-to-cut-off (S–Co) ratio, with values less than 1.0 and 1.0 or higher corresponding to negative and positive results. The authors used S–Co values to estimate relative levels of anti-SARS-CoV-2 antibodies by setting thresholds for "low" and "high" level sera based on approximately the 20th and 80th percentiles of the distribution for the S–Co ratios, respectively.[27]

IgG seroconversion occurs around day 10, and titers peak around day 28

Patients who received high-IgG plasma had a lower 7-day mortality rate (8.9% [6.8%–11.7%]) than those receiving medium- (11.6% [10.3%–13.1%]) or low-IgG plasma (13.7% [11.1%–16.8%]). The pooled relative risk of mortality among patients who received high-antibody-level plasma units, compared with low-antibody plasma units, was 0.65 [0.47–0.92] at 7 days and 0.77 [0.63–0.94] at 30 days.[27]

This difference in relative risk of mortality at 7 days led to the now infamously retracted statement of FDA commissioner Stephen Hahn that convalescent plasma led to a 35% improvement in survival.[28]

The authors of the study are more cautious in their interpretation and conclude[27] that these observed "relationships between mortality and both the time to plasma transfusion and antibody levels provide a signature that is consistent with efficacy."

Limitations of the data. While these results are promising, the ability to draw definitive conclusions on efficacy is limited by the lack of a control group and heterogeneity throughout the study period.

Mortality rates for patients hospitalized for COVID-19 declined significantly over the reporting period, with overall 7-day mortality rates decreasing from 15.5% in April to 6.6% in June. This correlates with a significant decrease in severity of illness, with 49.9% of patients requiring mechanical ventilation in April compared with only 16.4% in June.[27]

Similarly, concomitant use of therapies that have since been proven effective or ineffective changed dramatically. For example, the number of patients in this study treated with hydroxychloroquine, which is now generally regarded as useless, declined from 62.3% in April to 1.8% in June, while the use of remdesevir, which seems to be effective, increased from 4.7% to 46.3%.[27]

Over the same time, the proportion of patients receiving low-antibody-titer plasma decreased from 26.0% to 11.9%, while the proportion of patients receiving transfusions within 3 days increased from 24.7% to 50.3%.[25] The benefit in terms of lower mortality observed for early vs late plasma transfusion and transfusion with high- vs low-antibody-titer plasma may therefore simply reflect the correlation with an overall decrease in severity of illness. Again, without a well-defined control group, the data from the Expanded Access Program will not be able to answer the question of efficacy definitively.

Recent studies awaiting peer review

After the efficacy analysis of the Expanded Access Program was published, results of 3 more randomized controlled trials have been published on preprint servers. Although these publications are yet to be peer-reviewed and have some methodologic weaknesses, they raise serious doubts about the effectiveness of convalescent plasma.

Balcells et al[29] report no difference in outcomes in a single-center open-label study of immediate treatment with convalescent plasma vs delayed treatment only in case of disease progression. The early plasma group received their first plasma unit at enrollment. The deferred plasma group received convalescent plasma only if their respiratory status worsened (defined as a Pao_2/Fio_2 ratio < 200) or if the patient remained hospitalized after 7 days of enrollment with persistent symptoms.

Fifty-eight patients were randomized, 28 in the early treatment group, and 30 in the deferred treatment group, with 13 of the 30 patients in the deferred group eventually receiving plasma due to progression of symptoms.[29]

There was no difference in the primary composite end point of progression to mechanical ventilation, hospitalization greater than 14 days, or in-hospital mortality, which occurred in 9 (32%) of the 28 patients in the early treatment group vs 10 (33%) of the 30 patients in the deferred treatment group (OR 0.95, 95% CI 0.32–2.84).[29]

Patients who received plasma early had overall higher rates of death, which occurred in 5 (18%) of 28 vs 2 (7%) of 30 patients, OR 3.04, 95% CI 0.54–17.2) and need for mechanical ventilation: 5 (18%) of 28 vs 2 (6.7%) of 30 patients, OR 3.04, 95% CI 0.54–17.2, although the differences were not statistically significant.[29]

The Convalescent Plasma for COVID (ConCOVID) study,[30] a multicenter open-label randomized clinical trial in the Netherlands, was halted early after 53 of 66 patients tested were found to have high titers of SARS-CoV-2 neutralizing antibodies at the time of enrollment, before they received convalescent plasma. Analysis of the available outcomes data of the total of 86 enrolled patients showed no difference in disease severity, hospital length of stay or mortality rates between patients who received plasma and the control group.

The PLACID trial,[31] an open-label, multicenter randomized controlled trial comparing convalescent plasma to standard of care, enrolled 464 patients with moderate severity of illness (Pao_2/Fio_2 ratio 200–300, or respiratory rate > 24 per minute and $Spo_2 \leq$ 93% on room air) in 39 centers across India. Although it demonstrated a statistically significant greater absolute decrease in Fio_2 needed by day 7 (11% vs 9.5%) and greater rate of viral clearance as demonstrated by negative SARS-CoV-2 PCR testing (67.9% vs 54.6%), the study showed no difference in the primary composite outcome of progression to severe disease (defined as a Pao_2/Fio_2 ratio < 100) or death by day 28, which occurred in 44 (18.7%) of 235 in the treatment group vs 41 (17.9%) of 229 in the standard care group, OR 1.09, 95% CI 0.67–1.77. Interestingly, the study reported 3 deaths that were considered to be possibly directly related to convalescent plasma transfusion (1.3% of the active treatment group).

EVIDENCE IS SUGGESTIVE, BUT WEAK

Taken together, the evidence available today suggests treatment with convalescent plasma may improve viral clearance, decrease inflammation, and improve oxygenation, which may translate into a lower mortality rate for select patients. This treatment appears to be of greatest benefit if plasma with high titers of neutralizing antibodies is given early in the course of the disease in patients without advanced organ failure, such as respiratory failure requiring mechanical ventilation.

The evidence supporting convalescent plasma, however is weak, and serious questions remain about optimal timing, patient selection, dosing, and antibody testing of donors and patients. True safety and efficacy have yet to be confirmed in ongoing well-controlled prospective trials

Both the Infectious Diseases Society of America[32] and the National Institutes of Health Treatment Guideline Panel[33] therefore concluded there is currently not enough evidence to recommend convalescent plasma as the standard of care and recommend its use in prospective, well-controlled, randomized trials.

To date, evidence is limited for the effectiveness of convalescent plasma for COVID-19

Despite these limitations and concerns, the FDA determined that on the basis of these data the "known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product" and has granted emergency use authorization.[34] This finding authorizes the distribution and administration of COVID-19 convalescent plasma for the treatment of confirmed or suspected COVID-19. It requires that a fact sheet providing information of dosing and potential side effects be made available to patients treated with convalescent plasma and that healthcare providers maintain records, conduct a thorough investigation, and report adverse reactions and fatalities related to convalescent plasma transfusion, as required under Title 21, Code of Federal Regulations 606.170.

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REVIEW

CME MOC

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Using and interpreting electrodiagnostic tests

ABSTRACT

Electrodiagnostic testing, consisting of nerve conduction studies and needle electrode examination, serves as an extension of a neurologic examination for evaluating a variety of focal and generalized neuromuscular conditions. By providing important clues on location, chronicity, severity, and pathophysiology, it can help to establish a diagnosis, evaluate the need for surgery, and assess patients who do not improve as expected after surgery.

KEY POINTS

Electrodiagnostic testing helps to precisely locate disease processes affecting the peripheral nervous system (including peripheral nerves, neuromuscular junctions, and muscles) and has limited use in the evaluation of central nervous system disorders.

Electrodiagnostic studies can help establish if a patient is likely to have a muscle disease, a disorder of neuromuscular junction transmission, axon loss, or a demyelinating disease.

Electrodiagnostic testing should be done by physicians who have appropriate training in it, as there are potential pitfalls in performing and interpreting the studies.

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ELECTRODIAGNOSTIC TESTING (traditionally but less accurately called electromyography) consists of 2 distinct but related procedures typically performed together to interrogate the peripheral nervous system: nerve conduction studies and needle electrode examination.

This article reviews common indications for these tests, their limitations, and how to interpret the results, focusing on how they may best contribute to patient evaluation.

NERVE CONDUCTION STUDIES

Nerve conduction studies involve stimulating motor, sensory, or mixed nerves through the skin with a small pulse of electrical current (**Figure 1**). Recording electrodes, placed on the skin over nerves and muscles innervated by the stimulated nerve trunk, capture electrical responses generated by the stimulation. Multiple nerves may be stimulated in each affected limb or region, as determined by patient symptoms.

Sensory nerve conduction studies record the response along nerve fibers to electrical stimulation of the nerve trunk at some distance from the recording electrodes, whereas motor nerve conduction studies record the response of a muscle to electrical stimulation of a nerve trunk that innervates that muscle.

Values measured include amplitude and morphology of response and velocity or latency of conduction along the stimulated path. "Late" responses, including the F wave and H reflex, measure the integrity of proximal portions of a nerve and corresponding nerve roots.

The following disease processes are generally associated with characteristic electrodiagnostic findings, illustrated in **Figure 2**:

Nerve conduction studies: Principles

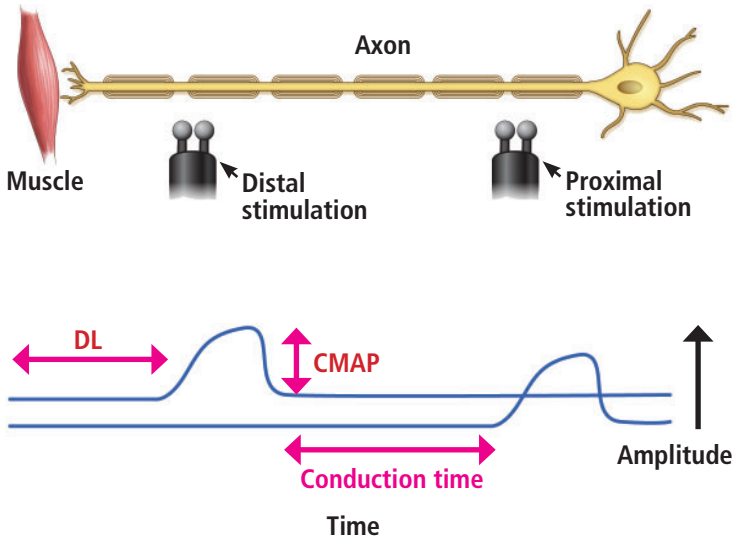


Figure 1.

A motor nerve, composed of numerous axons (represented by a single neuron), is stimulated through the skin with a pulse of current administered through a stimulator, with enough current to depolarize all of the nerve's axons. Recording electrodes on the surface of the skin overlying the innervated muscle (not pictured) produce a tracing of electric potential over time, which represents the depolarization of all activated muscle cells.

This deflection from the electric baseline is called the compound muscle action potential (CMAP). The time between stimulation at a distal site and the initial deflection of the CMAP is called the distal latency (DL), which is determined by the size and myelination of the motor nerve, as well as transmission across the neuromuscular junction and within the muscle itself. Motor nerves are often stimulated proximally as well, which allows for calculation of a conduction time and associated conduction velocity across a segment of the nerve. This parameter does not include the neuromuscular junction or intramuscular transmission, and represents purely nerve conduction within a nerve segment.

Electrodiagnostic testing consists of nerve conduction studies and needle electrode examination

Demyelinating diseases cause slow conduction velocities, prolonged distal latencies, conduction blocks, dispersion of the motor response waveform, and prolonged late responses.

Axon loss ("axonal pathology") does not significantly exhibit these features, but causes reduced amplitude of responses.

Acquired focal or segmental demyelination characteristically exhibits conduction block, ie, a significant reduction in motor response amplitude at proximal compared with distal stimulation sites.

Defects of neuromuscular junction transmission (eg, myasthenia gravis, Lambert-Eaton myasthenic syndrome) exhibit changes in motor response amplitudes during a volley of stimuli when tested with repetitive nerve stimulation.

NEEDLE ELECTRODE EXAMINATION

Needle electrode examination (**Figure 3**) involves inserting a needle into a muscle to record spontaneous and volitional electrical activity generated within muscle fibers during rest and active muscle contraction.

The test is typically performed on multiple muscles: between 6 (for a single-limb study) and 15 muscles (for a multiple-limb study). An electrode inserted in the muscle belly records electrical activity in the muscle at rest and during voluntary contraction to assess the integrity of the nerve-muscle connection and the presence of muscle disease.

At rest. Abnormal spontaneous activity in the form of fibrillation or positive sharp wave potentials signifies loss of muscle innervation, necrosis, or inflammation (**Table 1**).

During voluntary muscle activation. The needle electrode records the size, morphology, and firing pattern of a motor unit action potential (ie, an electrical discharge composed of the individual muscle fiber action potentials generated by activation of a single motor neuron in the spinal cord). The pattern of firing in relation to increasing effort is called the recruitment pattern (**Table 2**).

INTERPRETING RESULTS

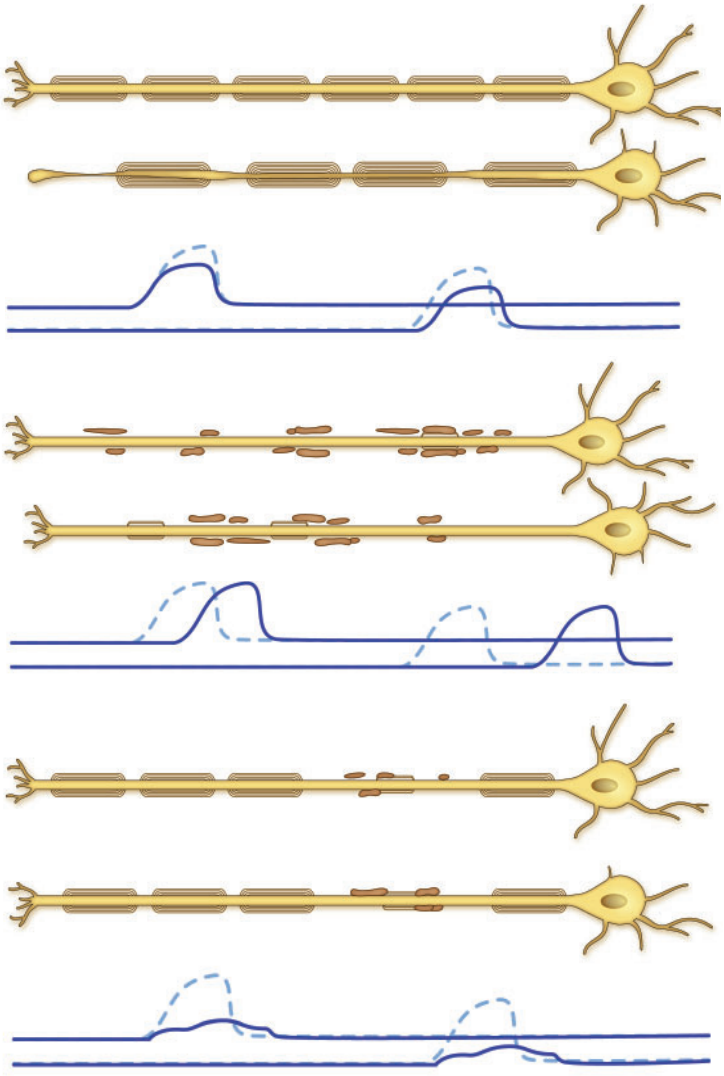
Nerve conduction studies and needle electrode examination can help address the following questions:

Where is the lesion? Is it in the nerve root, plexus, peripheral nerve, neuromuscular junction, or muscle?

What is the pathophysiologic nature of the disorder? If neuropathy, is it due to demyelination or to axon loss? If myopathy, is it due to inflammation and necrosis?

What is the chronicity of the problem?

Nerve conduction studies: Abnormal patterns



Axon loss. When axons are lost, there are fewer excitable axons, and therefore fewer muscle cells are excited, resulting in a lower compound muscle action potential (CMAP) regardless of stimulation site. This can occur in peripheral neuropathy or motor neuron disease. The dashed tracings represent normal, solid tracings are abnormal.

Diffuse demyelination. For diffusely disrupted myelin, distal latency is prolonged, and the conduction velocity is slow, but the CMAP retains normal amplitude because all of the axons are still available to depolarize the same number of muscle cells. This may be seen in hereditary demyelinating neuropathies, such as Charcot-Marie-Tooth disease.

Focal demyelination. For focal demyelination over a portion of nerve, focal slowing occurs only over the affected segments. In addition, the conduction in some neurons is too slow to cross the area of focal demyelination. This is called conduction block, and results in a more than 50% reduction of CMAP amplitude when stimulating proximal to the lesion. Because focal demyelination typically affects different neurons to varying degrees, the action potentials arrive at the muscle at more variable times, leading to a "spreading" of the CMAP, known as temporal dispersion. This pattern can be seen in some types of compressive nerve injury (eg, ulnar neuropathy at the elbow) and diffuse acquired demyelinating polyneuropathies (eg, Guillain-Barré syndrome).

Figure 2.

Is it acute, subacute, chronic, or chronic with ongoing denervation?

What is the electrical severity of the problem?

Electrodiagnostic testing can also reveal specific clues to etiology, such as myotonia in a patient with suspected myopathy.

LIMITATIONS OF ELECTRODIAGNOSIS

Electrodiagnosis has limitations.

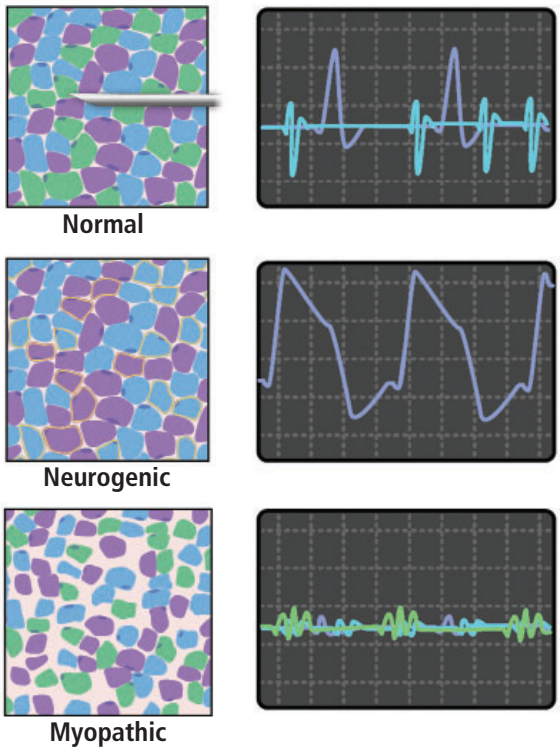
It does not evaluate small fibers

Nerve conduction studies assess the integrity of only large-diameter axons. Small-diameter fibers that predominantly comprise the autonomic, temperature-sensing, and pain-sensing portions of the peripheral nervous system generate electrical fields too small to be recorded with routine laboratory techniques. Hence, patients with small-fiber sensory neuropathy and those with radiculopathy only manifested by pain (affecting only sensory root fibers and not motor root fibers) will likely have normal results.

It gives clues, but not a specific diagnosis

Electrodiagnostic testing helps locate problems and objectively measures a portion of the peripheral nervous and neuromuscular sys-

Needle electrode examination in normal and diseased muscle



Normal. The recording needle is shown inserted into muscle perpendicular to the long axis of the muscle fibers. The electrode captures activity within a small range surrounding the needle tip. Normal tissue contains a mixture of different motor units (single units denoted by color). When a patient activates the muscle through voluntary control, force is generated by the orderly recruitment of additional motor units and an increase in the firing rate of motor units. The firing motor units are visualized to the right as tracings (color coding not present on actual reading). Each motor unit has a distinct morphology.

In neurogenic conditions, motor units are lost (represented by loss of the green motor unit), but if nearby motor units are intact, they can reinnervate the muscle fibers that have lost innervation (represented by increase of blue and purple-coded muscle fibers). During electrical activation, fewer motor units are available to generate the same level of force, so the remaining units must fire at a higher frequency ("reduced recruitment"). The size of the motor unit is increased because more muscle fibers now belong to each motor unit due to reinnervation.

In myopathic conditions, muscle fibers become smaller, although the motor units remain intact. In order to generate the same level of force, more motor units need to be activated ("early recruitment"). Motor units appear small due to electrical potentials generated from the smaller muscle fibers.

Figure 3.

tems. It does not usually identify the specific underlying cause of a condition and is best viewed as an extension of the physical examination. However, it often plays an important role in defining the differential diagnosis and directing further laboratory and imaging tests.

It is less useful for elderly patients

Nerve conduction studies are less reliable in advanced age. For example, sensory responses are not obtainable in the lower limbs of many healthy adults over age 75, making electrodiagnostic testing less useful for diagnosing polyneuropathy.[1]

It does not reveal much about the central nervous system

Electrodiagnostic testing does not adequately assess the central nervous system. It may demonstrate nonspecific abnormalities in central nervous system disorders, but findings cannot be used to definitively locate or diagnose a central nervous system lesion. Electrodiagnostic testing may be technically limited by central disorders of motor unit control.

It may require mild sedation

Although most patients tolerate electrodiagnostic testing well, those with especially low pain tolerance or lacking understanding of the testing (eg, children) may require premedication.

Some heart devices rule it out

In general, electrodiagnostic testing is safe. However, nerve conductions studies should not be performed near catheters and electrodes that directly reach the heart (eg, pacemakers with external leads, catheters measuring intracardiac pressures), although having an internalized pacemaker or defibrillator is not a contraindication.[2]

Risks of infection, bleeding

Needle electrode examination carries a small risk of infection and bleeding. Laboratories differ in their approach for patients on anticoagulation therapy. In general, even with anticoagulation, the risk of clinically significant bleeding is low, and risk associated with discontinuing anticoagulation therapy should be balanced against this risk.[3] For patients undergoing electrodiagnosis who stay on anticoagulation, the

TABLE 1

Commonly observed or notable abnormal spontaneous activity

Term	Description	Clinical significance
Fibrillation potentials and positive sharp waves	Spontaneous muscle fiber potentials recorded during rest; morphology and firing regularity determine categorization as fibrillation potentials or positive sharp waves	Muscle fibers are remaining without innervation, generally a sign of recent or ongoing denervation in neurogenic conditions In myopathic conditions, they may indicate inflammatory or necrotizing myopathies
Fasciculation potentials	Spontaneous, irregularly firing motor unit discharges	May be seen occasionally in chronic neurogenic conditions of any kind, but are seen more diffusely in disorders of the anterior horn cell and motor neuron disease
Myotonic discharges	Single muscle fiber firing repetitively in a waxing and waning pattern at high frequency	When diffuse and prominent, indicates a myotonic disorder Can also rarely be seen in any chronic neurogenic or myopathic condition
Complex repetitive discharges	Time-locked repetitive firing of a group of muscle fibers, with sudden start and stop of bursts	Very chronic neurogenic or myopathic conditions
Neuromyotonic discharges	Single motor unit firing repetitively at a very high frequency	Typically, disorders of voltage-gated potassium channels
Myokymic discharges	Single motor unit firing in regularly recurring bursts	Most commonly associated with chronic demyelination and radiation plexopathy

needle electrode examination may be tailored to exclude particularly vulnerable sites.

Examination of certain muscles (especially the diaphragm, rhomboid major, and serratus anterior) entails a higher risk of pneumothorax.

SPECIFIC INDICATIONS

In general, electrodiagnostic testing adds value to the diagnostic workup of many common symptoms and conditions by suggesting previously unsuspected diagnoses and further diagnostic tests or treatments.[4,5]

FOCAL SENSORY AND MOTOR SYMPTOMS

Patients with many conditions presenting with focal sensory and motor symptoms can benefit from electrodiagnostic testing.

Acute traumatic nerve injury

Peripheral nerves may be injured by blunt or penetrating trauma, stretch injury, and secondary ischemia (eg, from compartment syndrome). Electrodiagnosis can assess nerve continuity, injury severity, and prognosis, which may be especially helpful if peripheral nerve surgery is being considered.

Nerve conduction studies may be useful during the acute phase of an injury (within the first 24–72 hours) if nerve trunk stimulation can be performed above and below the lesion site to assess for conduction block or discontinuity. A repeat study at least 10 days after the injury is usually necessary to assess for maximal deterioration of sensory and motor responses, at which time wallerian degeneration should be complete, and a response from distal stimulation will be absent with complete axonal injuries.[6]

However, needle electrode evaluation is not usually useful until 3 weeks after an injury, when active denervation features may become apparent, so if a single study is requested, it should be done 3 weeks after the onset of neurologic deficits.

Electrodiagnosis often helps define the differential diagnosis and directs further evaluation

TABLE 2

Glossary of common electrodiagnostic terms

Term	Description	Clinical pearls
Chronic denervation	Remote axon loss identified by long-duration, high-amplitude motor units firing with a reduced recruitment pattern	Generally denotes a process that started at least several months before the examination
Active or ongoing denervation	A muscle exhibiting positive sharp waves or fibrillation potentials, reflecting a subacute (or more long-standing but uncompensated) neurogenic or axon-loss process	Does not always imply a truly active process. Fibrillation potentials and positive sharp waves are observed whenever a muscle fiber is awaiting reinnervation. These findings generally appear by about 3 weeks after the onset of injury and resolve within a few months, but may persist for longer in distal muscles and when reinnervation mechanisms are not fully successful or complete
Intraspinal canal lesion or process	Electrodiagnostic testing characterized by neurogenic or axon-loss changes in muscles of 1 or more specific myotomes (eg, a spinal root or segment derivative) without sensory findings	The lesion is proximal to the dorsal root ganglion. Most of these lesions are compressive radiculopathies; but infrequently; other lesions such as motor neuron disease produce similar findings
Neurogenic	Electrodiagnostic features resulting from lesions of the anterior horn cell, nerve root, plexus, or nerve	Neurogenic findings are further refined by distribution and the presence or absence of sensory findings
Myopathic	Electrodiagnostic features of muscle disease, including low amplitude, short duration, and polyphasic motor units	Electrodiagnostic testing may be less sensitive in many myopathies than in neurogenic conditions
Irritable myopathy	When myopathic features are accompanied by diffuse fibrillation potentials, positive sharp waves, or both	Suggestive of inflammatory or necrotizing etiologies, but not pathognomonic
Motor unit instability	The same motor unit on needle electrode examination varies in morphology from one firing to the next	Indicates dysfunction at the neuromuscular junction, but it can be seen in neurogenic conditions during early reinnervation, when neuromuscular junctions are immature
Reduced activation	Suboptimal voluntary activation of a muscle resulting from central nervous system causes	Can result from pain, cognitive dysfunction, poor effort, or upper motor neuron pathology, and indicates that the data may be of lower yield
Conduction block	Motor response in a nerve conduction study has > 50% reduced response when stimulating at a more proximal location	Indicates focal demyelination When occurring at noncompression sites or in multiple nerves, can suggest acquired demyelinating polyneuropathies

Carpal tunnel syndrome

Carpal tunnel syndrome is one of the most common peripheral nerve disorders and can cause significant pain and dysfunction.[7–9] When typical symptoms and signs are present, the diagnosis may be straightforward. However, in other cases, the sensory distribution of pain and paresthesias lie outside of the classic median nerve distribution, and in addition, other conditions can mimic it.

Electrodiagnosis is most applicable for evaluating suspected carpal tunnel syndrome

when the diagnosis is uncertain, when initial conservative therapy has been unsuccessful, or when surgery is being considered. Specifically, electrodiagnostic testing can help with the following:

Establishing a diagnosis. Diagnostic accuracy is high, especially when using specialized nerve conduction techniques (eg, palmar mixed nerve studies), with sensitivities of about 85% and specificities around 97%.[9] Standard electrodiagnosis may also exclude other neuromuscular diagnoses, such as cervical radiculopathy, other upper limb mononeuropathies, and brachial plexopathy.

Evaluating need for surgery. Electrodiagnostic testing may help determine indications for surgical release of a trapped median nerve. Lesions that are electrically moderate may be associated with a better prognosis, presumably because normal studies predict a disorder other than carpal tunnel syndrome, and severe findings suggest irreversible axon loss.[10]

Postoperative assessment. Electrodiagnostic testing is sometimes used after surgery if the outcomes are suboptimal. Electrodiagnostic findings typically improve after surgery, but abnormalities occasionally persist even after symptoms improve.

Neuromuscular ultrasonography. Interest has been growing for evaluating carpal tunnel syndrome with neuromuscular ultrasonography, as it has demonstrated favorable diagnostic accuracy.[11] However, it provides information that is complementary to electrodiagnostic testing results and is not useful for assessing severity. Neuromuscular ultrasonography should be considered for patients who prefer not to undergo electrodiagnostic testing or may not tolerate it. It may also be used to assess other structural causes of carpal tunnel syndrome in unusual presentations, or to aid in surgical planning or postoperative evaluation.

Ulnar neuropathy at the elbow

Ulnar neuropathy at the elbow is only slightly less common than carpal tunnel syndrome.[12] Typical symptoms are numbness or pain in the hand, with or without weakness and atrophy of ulnar-innervated muscles. The differential diagnosis often includes C8 radiculopathy, lower trunk brachial plexus lesions, musculoskeletal conditions, and ulnar nerve lesions located elsewhere (eg, at the wrist).

Electrodiagnostic testing can be useful for diagnosing ulnar neuropathy at the elbow, and guidelines have been published on electrodiagnostic techniques and criteria.[13] However, several challenges are unique to this condition. The anatomy of the nerve, variation in lesion site in the region of the elbow, and sparing of the muscles of the forearm that are innervated by the ulnar nerve, even with clear lesions at the elbow, can make electrical localization difficult, especially if the lesion primarily involves axon loss.

Diagnostic criteria may also have substantially different accuracies depending on the pretest probability of an ulnar neuropathy at the elbow.[14] If an ulnar neuropathy is nonlocalizable by nerve conduction studies, alternative diagnostic techniques (eg, neuromuscular ultrasonography) should be considered to aid in localization,[15] especially for a moderate or severe lesion that is being considered for surgery.

Electrodiagnosis may also help with prognostic guidance. Conduction block at the elbow indicates that focal demyelination may be contributing substantially to symptoms, which is associated with a more favorable recovery.[16]

Electrodiagnosis may especially be helpful if peripheral nerve surgery is being considered

Radiculopathy

Patients are commonly referred for electrodiagnostic testing to evaluate radiculopathies. Electrodiagnosis can typically identify the root level, chronicity, and electrical severity of a radiculopathy. Several conditions and settings merit special consideration, as follows:

Intraspinal compressive radiculopathies. These are usually located proximal to the dorsal root ganglion, so sensory nerve conduction studies are typically normal despite significant symptoms of pain and numbness. Motor nerve conduction studies often show only minimal axon loss because most lesions cause damage to a minority of nerve fibers. Needle electrode examination is often the most useful, as it reveals motor axon loss (neurogenic) changes in a myotomal pattern. Diagnosis typically requires examination of multiple muscles to isolate the affected level due to some interindividual variation and overlapping root innervation in many muscles.[17]

Demyelinating conditions. For predominantly demyelinating diseases, the only changes on electrodiagnostic testing are in the recruitment pattern of motor unit action potentials in affected muscles, which may be subtle.

Predominant sensory involvement. Radiculopathies that mainly affect sensory fibers do not result in significantly abnormal findings on electrodiagnostic testing.

Anatomic considerations. Certain radiculopathies may be difficult to isolate to a single level (eg, differentiating between C8 and T1, and C6 and C7 radiculopathies). In addition, electrodiagnostic testing does not truly localize a lesion to the nerve root in the intervertebral foramen, but rather proximal to the dorsal root ganglion. This means that electrodiagnosis cannot differentiate between a root and anterior horn cell lesion within the spinal cord.

The overall sensitivity and specificity of electrodiagnostic testing for radiculopathy is difficult to determine, with reported values varying widely.[18] This is partly due to lack of a gold standard and the various combinations of criteria that can be used for diagnosis. In general, electrodiagnosis can be used to determine if a radicular lesion (eg, one identified on magnetic resonance imaging) is severe enough to have caused motor axon loss and whether the lesion is acute, chronic and healed, or chronic and unhealed (ie, chronic with significant active and ongoing denervation).

Electrodiagnostic testing plays an important role in diagnosing amyotrophic lateral sclerosis

GENERALIZED SENSORY AND MOTOR SYMPTOMS

Other conditions that can be evaluated with electrodiagnosis are characterized by a more generalized presentation.

Polyneuropathy

Distal, symmetric axon-loss ("axonal") polyneuropathy is a common condition that may affect large-fiber or small-fiber nerves, or both.

Evidence is conflicting regarding the value of electrodiagnostic testing for assessing suspected polyneuropathy.[3,4,19–21] Some experts argue that it does not add substantial benefit, as it rarely yields a specific underlying cause, and results do not affect treatment.[22] However, electrodiagnostic testing can identify alternative or concomitant neuromuscular diagnoses, such as radiculopathy or mononeuropathies (eg, carpal tunnel syndrome). It can also distinguish demyelinating polyneuropathies (characterized by slowing of conduction velocities, prolonged distal latencies, conduction blocks, dispersion of the motor response waveform, and prolonged late responses) from axon-loss polyneuropathies, which do not significantly exhibit these features but will display reduced response amplitudes. This has important management ramifications, as demyelinating polyneuropathies and polyradiculoneuropathies are often associated with inflammatory conditions and respond to specific treatments.

Axon-loss polyneuropathy is considerably more common than demyelinating polyneuropathies. Diabetes mellitus confers high risk for axon-loss polyneuropathy[23] but is also associated with increased risk for other neuropathic disorders, including carpal tunnel syndrome, ulnar neuropathy, and diabetic radiculoplexus neuropathy (also known as diabetic amyotrophy).

Electrodiagnostic testing should be considered for polyneuropathy in the evaluation of patients with prominent weakness or gait abnormality, asymmetrical patterns, early upper extremity involvement, rapid progression, and diffuse loss of reflexes.

Limitations of electrodiagnosis for assessing polyneuropathy

Referring physicians should be aware of the following limitations of electrodiagnosis for assessing polyneuropathy:

It is less useful for small-fiber dysfunction. Patients whose history and examination indicate only small-fiber dysfunction are likely to have normal study results and may benefit more from alternative evaluations, such as skin biopsy for intraepidermal nerve fiber density measurement and the QSART (quantitative sudomotor axon reflex test) to assess for small-fiber neuropathy.

It is less useful for elderly patients with mild symptoms. Differentiating between normal age-related loss of sensory responses and features of polyneuropathy may be difficult.

Incidental findings may not be relevant. Especially in older patients, incidental electrodiagnostic findings (eg, an old radiculopathy,

carpal tunnel syndrome) may not help elucidate the cause of symptoms. Electrodiagnostic findings must always be evaluated in the context of a patient's target clinical features.

Demyelinating polyneuropathy

Electrodiagnostic testing plays an important role in diagnosing demyelinating polyneuropathies, which have substantially different management implications than axon-loss polyneuropathies. Electrodiagnostic testing can determine the likelihood that a demyelinating polyneuropathy is hereditary or acquired, the types of nerves affected, and the degree of concomitant axon loss. However, skill is required for acquiring and interpreting the electrodiagnostic data, because mild or focal demyelinating-type findings may actually be due to axon-loss polyneuropathy or compressive etiologies. The European Federation of Neurological Societies and the Peripheral Nerve Society have published guidelines for accurate electrodiagnosis, but misdiagnosis of chronic inflammatory demyelinating polyneuropathy commonly occurs and may lead to unnecessary and potentially harmful therapy.[24,25]

Generalized weakness

Weakness has diverse causes. A first approximation is often made clinically, differentiating upper from lower motor neuron-type weakness. Those with lower motor neuron-type weakness may have lesions at the level of the anterior horn cell, nerve root, plexus, peripheral nerve, neuromuscular junction, muscle, or some combination of these sites.

Electrodiagnostic testing can be a useful adjunct to a physical examination to help refine localization in the peripheral nervous system (including neuromuscular junction and muscle). In a prospective study of patients presenting with weakness, electrodiagnosis identified a single cause in approximately 80% of patients, with about 30% of diagnoses unsuspected before testing.[26]

Central disorders of motor control including upper motor neuron disorders may show a pattern of reduced voluntary activation on needle electrode examination. This finding, when pronounced, can suggest upper motor neuron localization. However, it is not specific and can also be seen in studies confounded by pain or lack of voluntary effort.

Motor neuron disease

Electrodiagnostic testing plays an important role in diagnosing motor neuron diseases, most commonly amyotrophic lateral sclerosis (ALS), a degenerative disorder of the upper and lower motor neurons. Diagnosis relies on clinical demonstration of progressive combined upper and lower motor neuron signs without alternative explanation, but electrodiagnosis can identify denervation that may not be apparent clinically.

Several sets of diagnostic criteria are available for ALS, the two most common being the the Awaji criteria and the revised El Escorial criteria.[27,28] The Awaji criteria have better sensitivity for diagnosing ALS, although possibly not for all patients.[29,30]

Motor neuron disease requires extensive electrodiagnostic evaluation. Nerve conduction studies should be performed to exclude polyneuropathy. Needle electrode examination includes study of the upper and lower extremities, thoracic paraspinal muscles, and often, cranial nerve-supplied muscles. A tiered approach may minimize the number of muscles requiring examination.[31]

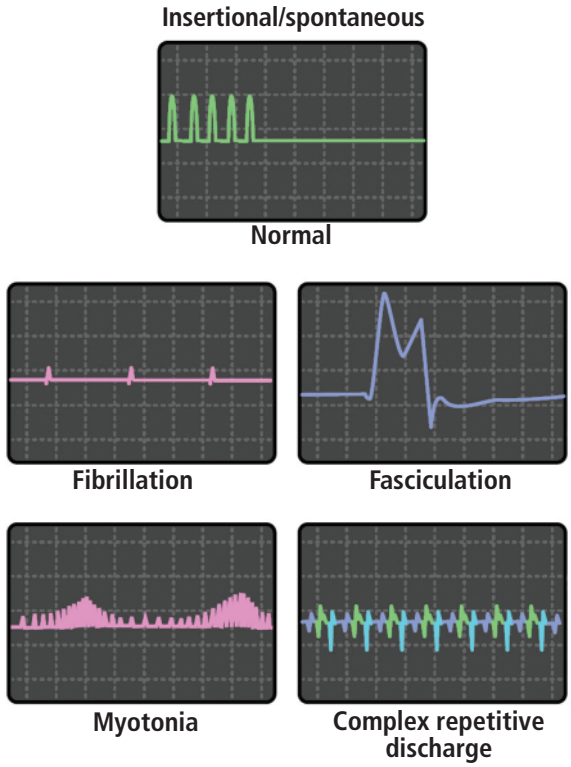
Key features suggesting a diagnosis of motor neuron disease are the following:

- Chronic and active motor axon loss in muscles from multiple myotomes and peripheral nerve distributions within each of at least 3 body regions
- Progressive clinical features of upper and lower motor neuron deficits
- Fasciculations on needle electrode examination and clinical inspection. Although they may be seen in other neurogenic conditions and in healthy people, when seen in association with weakness, atrophy, and chronic denervation features, they qualify by the Awaji criteria as a surrogate for active denervation in a muscle.

Electrodiagnostic testing is also useful in identifying ALS mimics, including multifocal motor neuropathy with conduction block, myopathies, neuromuscular junction disorders, structural radiculopathies, and severe neuropathies. Other motor neuron diseases include spinobulbar muscular atrophy (Kennedy disease) and spinal muscular atrophy.

Myopathies comprise a broad spectrum of generalized disorders that primarily affect skeletal muscles

Needle electrode examination: Spontaneous activity



Normal. Movement of the needle through uncontracted (relaxed) muscle causes irritation of muscle fiber membranes and a brief burst of muscle fiber depolarizations.

Abnormal. Most other spontaneous activity is abnormal. Activity is categorized by source of the discharge (ie, muscle fiber, motor unit, or muscle fiber circuit/nonmotor unit chain of fibers), the firing pattern (ie, regular, irregular, semiregular), and frequency. Most spontaneous activity is not specific to myopathic or neurogenic conditions, but may yield information about chronicity or underlying etiology. See **Table 1** for detailed descriptions of abnormal spontaneous activity.

Figure 4.

Electrodiagnosis can help narrow the differential diagnosis based on the distribution of muscle involvement

Myopathy

Myopathies comprise a broad spectrum of generalized disorders that primarily affect skeletal muscles. Nerve conduction studies are typically normal in most myopathies because sensory functions are unaffected and the muscles that are routinely tested are distal and less likely to be affected by a myopathy.

Needle electrode examination is more valuable, revealing myopathic motor units (short duration, low amplitude, polyphasic morphology).[32] However, myopathies that predominantly affect type II muscle fibers (notably, corticosteroid-induced myopathy) may have normal results on needle electrode examination, as these fibers are not typically evaluated.[6]

The absence of fibrillation potentials has a negative predictive value of about 80% to 90% for inflammation, necrosis, fiber splitting, or vacuolar changes on muscle biopsy. This information may be helpful in deciding which patients warrant a biopsy.[33]

Electrodiagnosis can help diagnose some myopathies and also perform the following valuable functions:

- Exclude neurogenic and neuromuscular junction etiologies that may mimic myopathies (eg, motor neuron disease, myasthenia gravis)
- Identify unusual myopathic needle electrode examination patterns (eg, myotonia)
- Narrow the differential diagnosis based on the distribution of muscle involvement (eg, inclusion body myositis).

In addition, needle electrode examination features may suggest (but not distinguish between) the following causes of myopathy in the appropriate clinical context:

- Necrosis (eg, anti-signal recognition particle and anti-hydroxy-3-methylglutaryl-CoA reductase autoantibody-related myopathies)
- Inflammation (eg, polymyositis and dermatomyositis).

"Irritative" features (ie, fibrillation or positive sharp wave potentials) in conjunction with motor unit potential configurational and recruitment changes consistent with myopa-

thy may occur in both types of myopathy. Differentiating between them depends primarily on histopathology (ie, necrotizing myopathy predominantly has features of myofiber degeneration without the inflammatory infiltrates typical of an inflammatory myopathy).

Myotonia is a unique electrical phenomenon (**Figure 4, Table 1**) resulting from quantitative or qualitative dysfunction of sodium and chloride channels in the muscle cell membrane. Although it may occur secondary to a wide variety of neuromuscular pathologies, prominent or diffuse myotonia is associated with a relatively small differential diagnosis (including myotonic dystrophies, inherited sodium and chloride channelopathies, and Pompe disease).

Needle electrode examination can also help identify an affected muscle for biopsy. However, the biopsied muscle is typically chosen from the contralateral side to avoid needle track artifacts.[34]

Myasthenia gravis

Electrodiagnosis can play an important role in evaluating patients with suspected disorders of neuromuscular junction transmission. The most common such disorder is autoimmune myasthenia gravis, which is diagnosed clinically but supported by ancillary testing. Electrodiagnosis is not always necessary if the history and autoantibody profile are consistent with the diagnosis, but it can be useful in cases in which antibody testing is negative and the diagnosis is unclear. It may also play a role in determining whether subjective weakness in a patient with myasthenia gravis is caused by uncontrolled disease or other causes.

In postsynaptic neuromuscular junction disorders such as myasthenia gravis, slow repetitive stimulation at 2 to 5 Hz produces a stereotyped, progressive decrease in the recorded motor response amplitude or area in weak muscles.

The overall accuracy of the test is dependent on the muscle studied, the reference values used, and type of myasthenia gravis (ie, generalized or oculobulbar, the latter of which does not significantly involve limb muscles). Sensitivities for repetitive nerve stimulation have been reported in the 40% to 50% range for generalized myasthenia gravis and in the 10% to 20% range for oculobulbar disease.[35–37] Sensitivity might also be reduced if the patient has not appropriately discontinued pyridostigmine before testing. Specificity in facial muscles is reported close to 100%. However, false-positives can occur from technical errors (which can be common in inexperienced hands) and disorders in which there is a secondary defect of neuromuscular junction transmission (eg, ALS).[38] A negative test result cannot be used to exclude the diagnosis.

Needle electrode examination may reveal motor unit instability in disorders of neuromuscular junction transmission. When routine electrodiagnostic testing is nondiagnostic or when symptoms are not generalized, a single-fiber electromyographic study may be diagnostic. This technique is 90% to 100% sensitive for myasthenia gravis, but not as specific[39]; however, it requires significant patient cooperation and is technically demanding and time-consuming.

BOTTOM LINE

By keeping in mind the capabilities and limitations of electrodiagnosis, referring providers can obtain the greatest value from testing and provide reasonable expectations for patients. Results are optimized with testing by physicians trained in electrodiagnosis and interpreting the results in the context of a thorough history and physical examination.

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REVIEW

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Contrast media in patients with kidney disease: An update

ABSTRACT

Concern for contrast-induced acute kidney injury (CI-AKI) or nephrogenic systemic fibrosis may lead to withholding important studies from patients with kidney disease. However, the actual risk or even the existence of these conditions has recently been called into question. The truth probably lies somewhere in the middle.

KEY POINTS

The risk of CI-AKI appears to be highest in patients with the lowest kidney function, but the overall risk is lower than initially thought.

In the absence of an equivalent alternate study, iodinated contrast studies that are thought to be crucial to the care of patients with kidney disease *should not* be withheld out of concern for CI-AKI.

Volume expansion with isotonic fluid appears to be the only intervention with a possible benefit in preventing CI-AKI. This is recommended in high-risk patients unless they are clinically volume-overloaded.

With the highly stable class II gadolinium-based contrast agents, the risk of nephrogenic systemic fibrosis appears to be extremely low and as such safe even for patients with advanced, predialysis kidney disease.

End-stage kidney disease patients on dialysis *do* require a hemodialysis treatment immediately after gadolinium administration.

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Contrast-induced acute kidney injury (CI-AKI) and nephrogenic systemic fibrosis (NSF) have been 2 of the most feared adverse effects of iodinated contrast media for computed tomography (CT) and gadolinium-based contrast media for magnetic resonance imaging (MRI), respectively. Newer and safer contrast agents and, perhaps, better patient selection and prophylactic measures have ameliorated those risks. Recently, some authors have suggested that NSF has been eradicated, while others question whether CI-AKI is an actual entity.

This review presents and evaluates the data around CI-AKI and NSF and critically highlights the most recent practice guidelines.

IODINATED CONTRAST AND 'RENALISM'

Iodinated contrast media are commonly used in modern medicine both intravenously with CT studies and arterially during angiographic procedures. Among the possible adverse effects is acute kidney injury, first reported in the 1950s in patients undergoing intravenous pyelography.[1] In the 1980s, larger series of cases of acute kidney injury following coronary angiography were reported, and the term *contrast-induced nephropathy* was coined.[2] With growing attention, it was said to be one of the most common causes of hospital-acquired acute kidney injury,[3] contributing significantly to incident chronic kidney disease, end-stage kidney disease, and death.[4]

Early publications defined contrast-induced nephropathy as an increase in creatinine of 0.5 mg/dL or more, or a 25% increase from baseline within 2 to 5 days of exposure.

In 2012, the Kidney Disease Improving Global Outcomes Working Group suggested

TABLE 1

Nomenclature and definitions of kidney injury related to iodinated contrast media

Contrast-induced nephropathy—Traditional term for worsening kidney function within 48 hours of iodinated contrast media. This term has largely been replaced by contrast-induced acute kidney injury.

Contrast-associated acute kidney injury—Any acute kidney injury occurring within 48 hours of iodinated contrast media. The term implies correlative diagnosis and does not suggest a causal relationship between the acute kidney injury and the iodinated contrast media.

Postcontrast acute kidney injury—Synonymous with contrast-associated acute kidney injury. This term appears in the radiology literature. Similar to contrast-associated acute kidney injury, it implies correlative diagnosis without suggesting a causal relationship between the acute kidney injury and the iodinated contrast media

Contrast-induced acute kidney injury—Replaced contrast-induced nephropathy as the accepted terminology when acute kidney injury is causally linked to iodinated contrast media. It is a subset of contrast-associated acute kidney injury.

the term *CI-AKI* and defined it as a 50% increase in creatinine from baseline within 7 days of exposure or a 0.3 mg/dL increase within 48 hours.[5] CI-AKI is now the accepted terminology to describe kidney injury precipitated by iodinated contrast media.

CI-AKI usually presents within 24 to 48 hours of exposure to iodinated contrast media

Presentation

CI-AKI usually presents within 24 to 48 hours of exposure to iodinated contrast media, with elevation in creatinine and, rarely, oliguria. The creatinine level peaks by 3 to 5 days and usually returns to baseline by 7 to 10 days. Sediment analysis shows granular casts and tubular epithelial cells, and the fractional excretion of sodium is usually low.

Risk factors include chronic kidney disease, diabetes, proteinuria, volume depletion, and concomitant exposure to other nephrotoxins. Procedure-related factors include higher-osmolality contrast media, higher volume given, multiple administrations of iodinated contrast media, and intra-arterial administration with first-pass effect.[2,6]

The diagnosis is clinical, and it is prudent to rule out other causes of acute kidney injury, in particular, atheroembolic kidney disease in patients undergoing angiography with iodinated contrast media.[7] While the true incidence of atheroembolic kidney disease compared with that of CI-AKI in this situation is not known, supporting evidence comes from reports demonstrating a correlation between the risk of acute kidney injury and atheroma burden,[8] and a lower risk with radial than with femoral angiographic procedures.[9] This disease has a very different clinical course but is commonly misdiagnosed as CI-AKI.

Pathophysiologic basis

The pathophysiologic basis for CI-AKI is still not completely understood, but direct and indirect mechanisms have been suggested.[10]

Iodinated contrast media are directly toxic to the tubular epithelial cells, leading to loss of polarity (loss of channel restriction to either luminal or basolateral membranes) and eventual apoptosis and necrosis. Elevated blood osmolality due to the contrast media, increased viscosity of the luminal fluid, and free radical formation have also been implicated in direct toxicity.[7,8]

Deranged hemodynamics underlie the indirect adverse effects of iodinated contrast media, with a brief initial vasodilatory state followed by pronounced and sustained vasoconstriction. Prolonged vasoconstriction, which appears to be mediated through alterations in endothelin, nitric oxide, adenosine, and prostaglandin levels, eventually leads to medullary ischemia. Tubuloglomerular feedback has also been postulated as an explanation for the drop in glomerular filtration rate observed in CI-AKI.

Is it all a myth?

Over the past decade, a number of large epidemiologic studies suggested that acute kidney injury following exposure to iodinated contrast media is not necessarily caused by the contrast media. Some reports even questioned whether it is a real disease.[11] This has sparked much debate and led to newer names for the phenomenon, including *postcontrast* acute kidney injury and contrast-*associated* acute kidney injury (**Table 1**). The rationale of these new definitions is to eliminate the causality associated with the term CI-AKI.

Whether one believes CI-AKI is real or a myth, this debate is not merely theoretical because conclusions drawn have significant implications for the care of our patients who have

chronic kidney disease. For example, Chertow et al[12] reported an inappropriately low rate of cardiac angiographic procedures in patients who have chronic kidney disease. Presumably, procedures were withheld out of concern for CI-AKI. They coined the term "renalism" to indicate the perhaps inappropriate attention to the kidneys while ignoring the bigger picture. Although it is not yet reported, one could presume the notion of avoidance may encompass all contrast-enhanced CT studies in the chronic kidney disease population.

Those who question the diagnosis of CI-AKI point to studies reporting similar rates of acute kidney injury in patients undergoing contrast-enhanced CT compared with those undergoing an unenhanced study. Davenport et al[13] used a 1:1 propensity matching algorithm and retrospectively reviewed over 17,000 patients who underwent contrast-enhanced CT or unenhanced CT. In patients whose estimated glomerular filtration rate (eGFR) was less than 30 mL/min/1.73 m^2, the rate of acute kidney injury was significantly higher in those exposed to contrast (36.4% vs 19.4%, odds ratio 2.96, 95% confidence interval 1.22–7.17). In those with eGFRs of 30 to 59 mL/min/1.73 m^2 rates were numerically higher with contrast than without contrast, but the difference did not reach statistical significance, and rates were the same with or without contrast in those with eGFRs of 60 or higher.

McDonald et al[14] and, more recently, Hinson et al[15] performed similar large epidemiologic propensity-controlled studies showing no difference in rates of acute kidney injury between contrast recipients and those who underwent unenhanced CT. Notably, both studies demonstrated no difference regardless of the definition of acute kidney injury or eGFR stratification. However, patients with eGFRs less than 45 mL/min/1.73 m^2 were significantly underrepresented in these studies, accounting for only 5% to 10% of participants, with some studies completely excluding patients whose creatinine was above 4 mg/dL.[15]

Does that mean that CI-AKI does not exist? We believe that would be an erroneous conclusion. Despite the complex algorithms used in the propensity matching, a selection bias remains as to who undergoes contrast CT and who does not. Clinicians' perceptions of risks and consequently their decisions to give or withhold contrast cannot be ascertained from retrospective analyses. In addition, prevention strategies, or lack thereof, are not accounted for in these large database-driven studies. Moreover, as stated previously, patients with severely decreased eGFR, who are at highest risk of CI-AKI, were underrepresented in the propensity score studies.

However, the risks of CI-AKI are probably overstated. Initial descriptive studies were mostly uncontrolled, and rates of acute kidney injury were based mostly on ICD codes with little adjudication as to the cause. This would ultimately inflate the rates of acute kidney injury attributed to the iodinated contrast media.[16,17] In addition, changing practices, such as prophylaxis, minimizing exposure, and the development of less toxic, lower-osmolar iodinated contrast media have probably played an important role in reducing the rates of CI-AKI.

Nevertheless, CI-AKI remains real. A recent meta-analysis with more than 1,500 patients undergoing peripheral angiography found a higher incidence of acute kidney injury with iodinated contrast media than with carbon dioxide contrast (11% vs 4%, respectively.[18] In addition, our group recently published a propensity-matched study evaluating rates of acute kidney injury in patients with stage 3 or 4 chronic kidney disease undergoing coronary angiography, contrast-enhanced CT, or nonenhanced CT.[19] Postcontrast acute kidney injury was noted in 27%, 24%, and 24% of patients, respectively. All cases of acute kidney injury were then adjudicated by 2 nephrologists through chart review to ascertain the cause. They found that the incidence of CI-AKI was 16.5% in the coronary angiography group and 12.5% in the contrast-enhanced CT group.

Therefore, despite the lack of conclusive data, CI-AKI remains very much a real entity, although the incidence is lower than originally thought.

CI-AKI remains very much a real entity, although the incidence is lower than originally thought

The evidence, or lack of evidence, for preventive strategies

The evidence regarding strategies to prevent CI-AKI is far from satisfying. Hiremath and

Velez[16] described it as "a proliferation of small, underpowered trials, often with interventions that were poorly thought out" and said that "subsequent meta-analyses have spawned meta-confusion." With that in mind, we will try to critically evaluate some of the proposed prophylactic interventions.

Volume expansion

Solomon et al[20] first reported volume expansion with 0.45% saline to be effective in preventing CI-AKI. Mueller et al,[21] analyzing 1,620 patients, reported a lower incidence of acute kidney injury with periprocedural use of isotonic saline than with 0.45% saline.

Although hydration has become the accepted standard, the recent AMACING trial challenged its role in preventing CI-AKI. Nijssen et al[22] randomized 660 patients undergoing contrast-enhanced procedures to undergo volume expansion with 0.9% normal saline or no volume expansion. The latter was found to be noninferior to saline, but the overall rates were low. Notably, patients with an eGFR less than 30 mL/min/1.73 m^2 were excluded from the study.

More recently, Timal et al[23] performed a randomized multicenter trial in 523 patients with stage 3 chronic kidney disease undergoing contrast-enhanced CT. Randomization to no hydration was noninferior to prehydration with bicarbonate in terms of postcontrast acute kidney injury, with event rates of 2.7% vs 1.5% respectively (relative risk 1.7, 95% CI 0.5–5.9). Noninferiority was also shown on subgroup analyses based on age, eGFR (30–44 vs 45–60 mL/min/1.73 m^2) alone or in combination with risk factors including diabetes. However, the event rate in this trial was lower than in previous trials, and therefore, caution should be used with interpreting the results.

Being able to produce as little as 250 mL of urine per day was associated with 36% lower relative risk of death in patients on peritoneal dialysis

The type of fluid used for volume expansion has also been a topic of debate, with bicarbonate-based hydration protocols proposed. The premise is that urinary alkalinization would ameliorate the direct toxicity of iodinated contrast media by decreasing oxygen free-radical generation.[10]

Multiple small trials and subsequent meta-analyses provided highly divergent results until the Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial put this discussion to rest.[24] This large 2-by-2 factorial study randomly assigned 5,177 patients undergoing nonemergency angiography to receive isotonic sodium bicarbonate vs isotonic saline as well as oral acetylcysteine vs placebo. The trial was stopped early due to futility, with acute kidney injury rates of 9.5% in the bicarbonate group and 8.3% in the saline group (P = .13). Therefore, there is no additional benefit to bicarbonate-based hydration compared with isotonic saline.

Pharmacotherapy

Acetylcysteine. The acetylcysteine story mirrors that of bicarbonate: a multitude of small studies followed by a series of meta-analyses yielding conflicting results. However, 2 studies over the past few years should settle this discussion for good: the Coronary and Peripheral Vascular Angiography (ACT) trial,[25] with 2,308 patients undergoing an intravascular angiographic procedure randomized to acetylcysteine vs placebo, and the previously mentioned PRESERVE trial.[24] Both trials showed no difference in rates of acute kidney injury between the acetylcysteine and placebo groups.

Statins have been postulated to reduce the risk of CI-AKI because of their pleiotropic anti-inflammatory and antioxidant effects, which help stabilize plaque. There have been many conflicting studies, with recent meta-analyses suggesting a possible benefit in patients undergoing coronary angiography.[10] Whether this benefit is due to prevention of CI-AKI or atheroembolic kidney disease is not clear. Most patients who undergo coronary angiography ultimately receive high-dose statin therapy anyway, making this a moot point.

Other interventions, including vitamin C, high-flow oxygen, and ischemic preconditioning are promising but the evidence remains lacking.

In summary, volume expansion with isotonic saline appears to be the only intervention with a possible benefit in preventing CI-AKI. This is probably important in patients deemed to be at intermediate to high risk (**Table 2**). Acetylcysteine has no role as a prophylactic measure, and bicarbonate-based fluids do not appear to offer an added benefit beyond volume expansion. Other preventive measures

TABLE 2

Iodinated contrast media in patients with kidney disease: Key points from the ACR-NKF consensus statement

Consensus statement	Authors' comments
The risk of contrast-*induced* acute kidney injury is substantially less than the risk of contrast-*associated* acute kidney injury, but the actual risk remains uncertain. However, necessary contrast-enhanced CT without an alternative should not be withheld.	We believe this statement should be extrapolated to patients in whom coronary angiographic procedures are deemed necessary.
Patients at risk for contrast-induced acute kidney injury include those with recent acute kidney injury or those with eGFR < 30 mL/min/1.73 m^2 (including nonanuric dialysis patients).	Age, diabetes, hypertension, and proteinuria are absent from the risk classification. We believe patients with an eGFR < 45 mL/min/1.73 m^2, particularly those with the above noted risk factors, should also be considered at increased risk.
Prophylaxis with intravenous isotonic saline is indicated for patients with eGFR < 30 mL/min/1.73 m^2 not undergoing dialysis and in patients with acute kidney injury.	We believe that prophylaxis is also warranted in nonanuric patients on hemodialysis or peritoneal dialysis to preserve residual kidney function. Careful attention to volume status is required to avoid hypervolemia.
Prophylaxis should be individualized for high-risk patients with eGFR between 30 and 44 mL/min/1.73 m^2.	We support prophylaxis in this population, particularly in the presence of traditional risk factors (diabetes, hypertension, proteinuria).
Prophylaxis is not indicated for patients with stable eGFR ≥ 45 mL/min/1.73 m^2.	We concur that the risk of contrast-induced acute kidney injury in this population is low.

ACR = American College of Radiology; CT = computed tomography; eGFR = estimated glomerular filtration rate; NKF = National Kidney Foundation

Based on information in Davenport et al, reference 28.

include using low- or iso-osmolar contrast media with the lowest necessary total dose.

We also advocate withholding nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers in high-risk patients, acknowledging that the data in that regard are insufficient.

Figure 1 shows our approach when patients with chronic kidney disease require iodinated contrast media.

Note that we generally include nonanuric patients undergoing hemodialysis or peritoneal dialysis in our high-risk category, and unless they are clinically hypervolemic, we recommend prophylaxis to preserve residual kidney function. A reanalysis of the Canada-USA (CANUSA) peritoneal dialysis study[26] elegantly demonstrated that being able to produce as little as 250 mL of urine per day was associated with a 36% lower relative risk of death in peritoneal dialysis patients.

Although the data are less robust, this observation likely applies to hemodialysis patients as well, thus underscoring our recommendation for prophylaxis.[27] We emphasize that the goal of hydration in this nonanuric dialysis population is not to make them hypervolemic, and as such, hydration should be forgone in overtly volume-overloaded patients.

The ideal hydration protocol for prevention remains uncertain, and various volume-expansion algorithms have been suggested using fixed or weight-adjusted regimens. Our practice is to give 1 to 1.5 mL per kg per hour starting 1 hour before and continuing for 6 hours after exposure to iodinated contrast media.

Volume expansion with isotonic saline appears to be the only intervention with a possible benefit in preventing CI-AKI

Updated recommendations

In response to the changing evidence, the American College of Radiology and the National Kidney Foundation released a joint consensus statement this year[28] on the use of intravenous iodinated contrast media in patients with kidney disease. Key points are presented in **Table 2**.

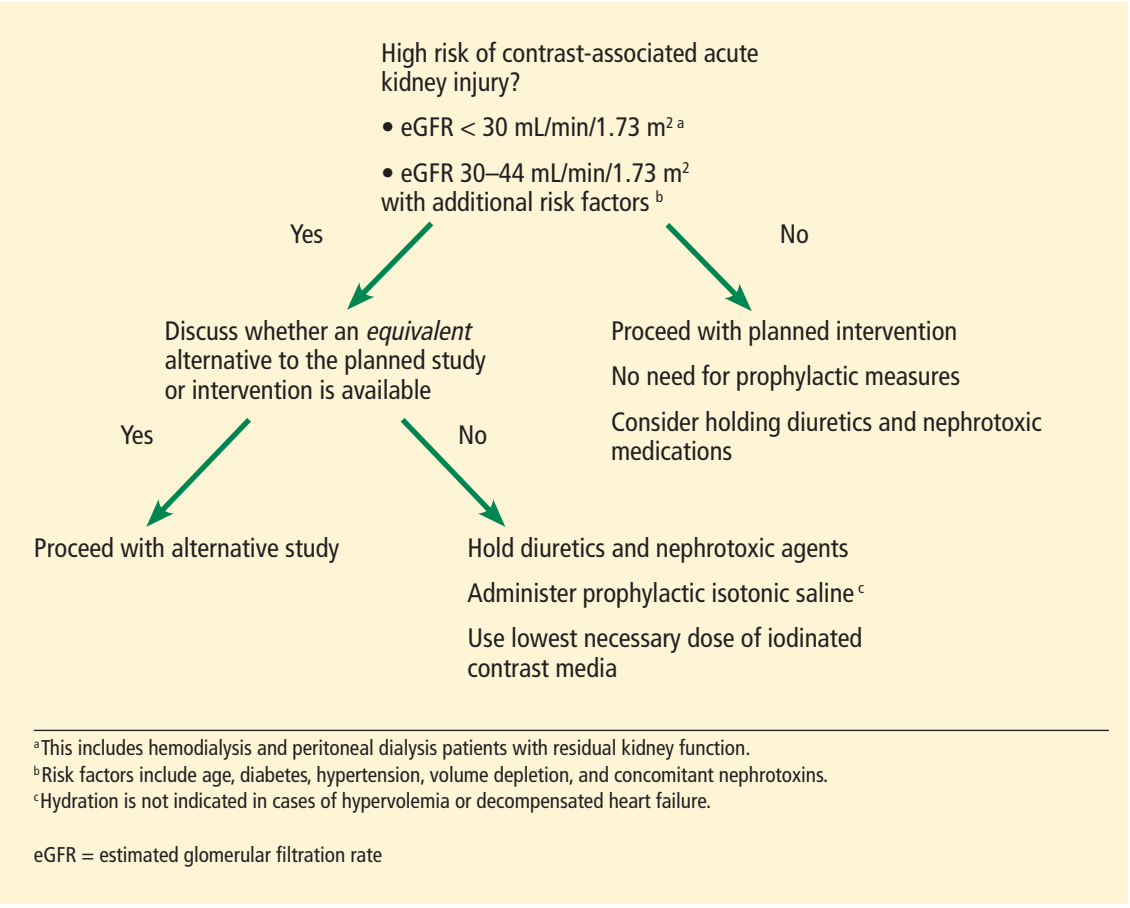

Figure 1. Our approach to chronic kidney disease patients requiring iodinated contrast media.

Authorities and radiology societies were quick to react to the crisis of gadolinium-induced NSF

Future directions

Despite decades of research on iodinated contrast and kidney injury, many questions are yet to be answered. What is the exact mechanism of CI-AKI? What is its true incidence with intravenous vs arterial administration? What significance, if any, does CI-AKI carry?

In our aforementioned study,[19] cases adjudicated to be CI-AKI carried no mortality risk, with an overall survival rate similar to that in patients who did not have acute kidney injury. Adjudication is key. We need clear definitions that capture CI-AKI clearly and distinctly from all the potential noise associated with other causes of postcontrast acute kidney injury.

The concept of "renalism" has not only led to fewer angiographic procedures being performed in the chronic kidney disease population,[13] it probably also underlies the reason why patients with advanced chronic kidney disease were underrepresented in the observational cohorts described above. Studies need to target this high-risk cohort to better delineate the risks and better establish the utility, or futility, of the currently practiced prophylactic measures. Additional work is clearly needed.

GADOLINIUM-INDUCED NEPHROGENIC SYSTEMIC FIBROSIS

NSF is a debilitating and often-fatal fibrosing disease characterized by skin thickening and organ fibrosis.[29] It was first reported in 15 dialysis patients in San Diego in the year 2000.[30] However, the relationship between NSF and the use of gadolinium as contrast during MRI remained obscure for a long time, finally being suggested 6 years later in Europe.[31]

The postulated mechanism was the deposition of toxic free gadolinium molecules in the tissues[32] with subsequent increases in circulating fibrocytes,[33] an increase in the expression

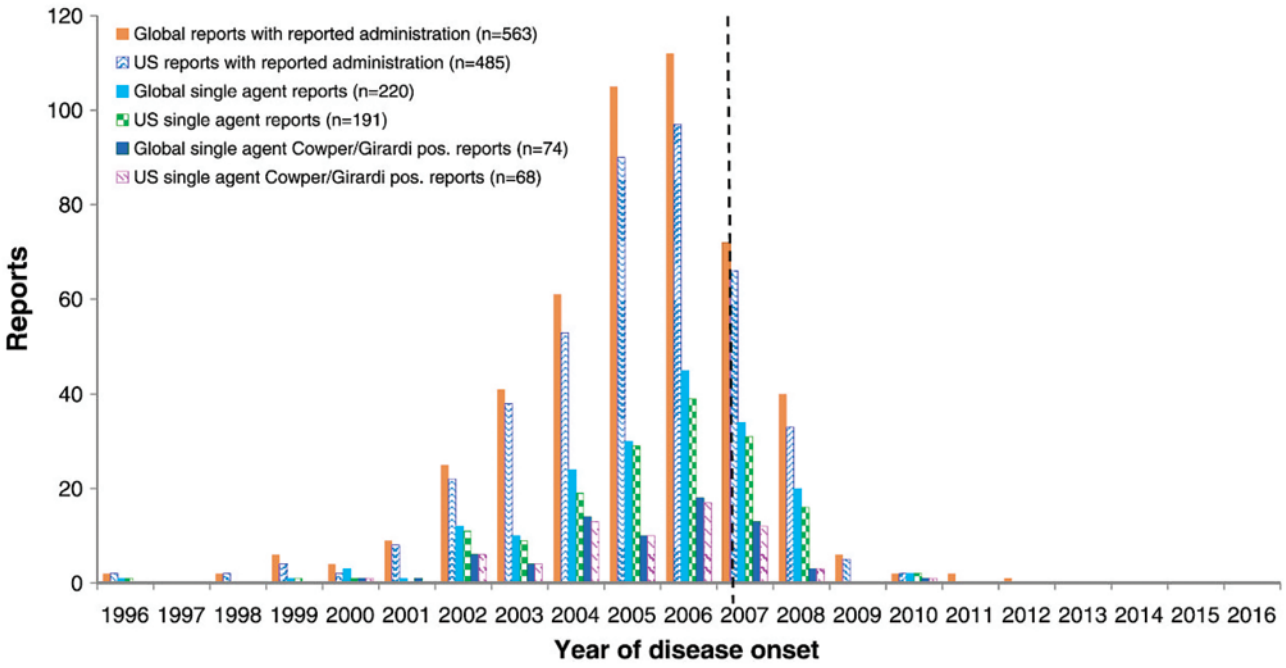

Figure 2. Number of cases of nephrogenic systemic fibrosis associated with gadopentetate dimeglumine in the United States and around with world, by year of disease onset. Vertical dotted line indicates the introduction of the boxed warning by the US Food and Drug Administration in May 2007.

Endrikat J, Dohanish S, Schleyer N, Schwenke S, Agarwal S, Balzer T. 10 Years of nephrogenic systemic fibrosis: a comprehensive analysis of nephrogenic systemic fibrosis reports received by a pharmaceutical company from 2006 to 2016. Invest Radiol 2018; 53(9):541–550. https://journals.lww.com/investigativeradiology/fulltext/2018/09000/10_years_of_nephrogenic_systemic_fibrosis__a.5.aspx

of transforming growth factor beta 1,[34] and release of proinflammatory and profibrotic cytokines.[35] Eventually, gadolinium was detected by electron microscopy on a skin biopsy specimen, specifically in areas of calcium phosphate deposition in blood vessels.[36]

By 2009, the disease was well established, and the US Food and Drug Administration (FDA) had received over 500 reports, most of them from the United States[37] and Denmark.[38]

In response to this crisis, the authorities and radiology societies were quick to react. In 2007, both the FDA[39] and the European Medicine Agency[40] issued warnings highlighting the risk of NSF associated with the use of gadolinium-based contrast agents. The American College of Radiology,[41] European Society of Urogenital Radiology,[42] and other radiology societies published guidelines and recommendations on how to use gadolinium-based contrast agents, particularly in patients with kidney disease.

Gadolinium agents that have a linear molecular shape pose a higher risk, and their use was contraindicated in patients with acute and severe chronic kidney disease with eGFRs less than 30 mL/min/1.73 m^2, as well as in patients on dialysis. Additionally, evidence that gadolinium-based contrast agents are removed with dialysis[43] prompted clinicians to change their clinical practice by offering dialysis to patients with advanced kidney dysfunction who were exposed to these agents.

Gadolinium agents that have a linear molecular shape pose a higher risk

As a result of those measures, the number of cases of NSF was drastically reduced. The last reported case in the United States dates back to 2010, and the last report in the world was in 2012 (**Figure 2**).[44]

Classification of gadolinium-based contrast agents

Gadolinium-based contrast agents have been used since the 1980s and were initially thought to have an excellent safety profile.[45] This led to their liberal and preferential use compared with iodine-based agents, particularly in patients with reduced kidney function.[46] However, their incriminating role in NSF highlighted their potential toxicity.

Gadolinium-based contrast agents share

TABLE 3

Gadolinium-based contrast agents and risk of nephrogenic systemic fibrosis

	Cyclic	Linear
Ionic	Gadoteric acid	Gadobenate dimeglumine
		Gadofosveset Gadoxetic acid
		Gadopentetate dimeglumine
Nonionic	Gadoteridol Gadobutrol	Gadodiamide Gadoversetamide

Red—group I agents: associated with the greatest number of cases of nephrogenic systemic fibrosis

Green—group II agents: associated with few cases

Yellow—group III agents: data are limited, but few unconfirmed cases have been reported

Several cases of NSF have been reported in patients who never were exposed to gadolinium

a common structure, with a central heavy metal ion (gadolinium) bound tightly by an organic ligand to form a stable complex, thus minimizing the potential natural toxicity of the free metal ion.[47] To avoid gadolinium toxicity, these agents should be highly stable so the gadolinium does not dissociate. Their stability is conferred by their chemical structure, namely whether they are linear or cyclic and whether they are charged (ionic) or electrically neutral (nonionic).[48] It is generally recognized that macrocyclic and ionic structures are more stable than linear and nonionic ones.[49] Thus, in highly stable agents, gadolinium dissociation is minimized and so is the risk of NSF.

On the basis of their NSF risk (and specifically on the numbers of unconfounded single-agent cases of NSF recorded for each agent), the 9 available gadolinium-based contrast agents are grouped into 3 groups (**Table 3**)[41]:

- Group I—agents associated with the greatest number of NSF cases.
- Group II—agents associated with few, if any, unconfounded cases of NSF.
- Group III—agents for which data are limited.

It is generally accepted that groups I and III should be avoided in patients with advanced chronic kidney disease.

Risk of NSF today

The guidelines set by the FDA and the radiology societies were undoubtedly effective in curbing the disease and eventually eliminating it. A recent review of 639 patients with biopsy-proven NSF from 173 articles estimated that the risk of NSF per million exposures had decreased from 2.07 before 2008 to 0.028 afterward.[50]

Most cases were associated with exposure to group I agents. However, those guidelines were applied to all gadolinium-based contrast agents without considering their stability or association with NSF. The downside of this approach was the denial of clinically indicated contrast-enhanced MRI in patients with severe kidney disease, with a subsequent potential real (though unmeasured) harm resulting from misdiagnosis or diagnostic delay.[51]

In recent years, evidence has been accumulating as to the safety of group II agents. A recent systematic review and meta-analysis evaluated the pooled risks of NSF in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent.[52] The authors analyzed 16 studies with 4,931 patients who received group II agents. The pooled risk of NSF was 0% (upper bound of 95% CI 0.07%). Thus, they estimated the per-patient risk of NSF from receiving group II gadolinium-based contrast agents in stage 4 or 5 chronic kidney disease to be less than 0.07%.

This risk is much smaller than that of contrast-induced nephropathy in patients with advanced chronic kidney disease who receive iodinated contrast,[53] and thus argues for a better safety profile of contrast-enhanced MRI using group II agents. In fact, the risk appears to be comparable to that of developing a severe allergic reaction to contrast agents, which is estimated at 0.04% for low-osmolality iodinated contrast agents[54] and 0.002% to 0.006% for group II agents.[55]

Updated recommendations

On the basis of accumulating evidence,[56–60] the recent guidelines of the American College of Radiology,[41] the European Society of Urogenital Radiology,[61] and the Canadian As-

TABLE 4

Key points from the *ACR Manual on Contrast Media* regarding prevention of nephrogenic systemic fibrosis in patients at risk

Kidney function	Recommendation	Authors' comments
Chronic kidney disease stage 1 and 2	No increased risk of developing NSF. Any gadolinium-based agent can be given safely.	There are no cases reported in this category with any of the gadolinium-based agents.
Chronic kidney disease stage 3	The risk of developing NSF is exceedingly rare. No special precautions are necessary.	There have been no definite cases reported in patients with stage 3 chronic kidney disease.
Chronic kidney disease stage 4 and 5 not on chronic dialysis	Group I agents are contraindicated. If a gadolinium-enhanced MRI study is to be done, a group II agent should be used.	Given the risk of CI-AKI in this population, we believe that MRI using a group II agent would be preferable to CT with iodinated contrast.
End-stage kidney disease on hemodialysis	The ACR favors CT rather than MRI if the anticipated diagnostic yield is similar. Group I agents are contraindicated. Group II agents are preferred and gadolinium-enhanced MRI should be performed as closely before hemodialysis as is possible.	We urge caution in dialysis patients with residual kidney function, which is associated with a survival benefit. We lean toward MRI with group II agents. Our current practice is to perform a single dialysis session rather than 2 consecutive sessions.
End-stage kidney disease on peritoneal dialysis	The ACR favors CT when possible, but if MRI is desired, then the ACR recommends a group II agent. The ACR recognizes that peritoneal dialysis may provide less NSF risk reduction than hemodialysis.	We urge caution in dialysis patients with residual kidney function, which is associated with a survival benefit. We lean toward MRI with group II agents. The committee does not comment on the necessity of subjecting these patients to hemodialysis. We believe it is safer to perform a single session of hemodialysis, particularly for peritoneal dialysis patients with no residual kidney function.
Acute kidney injury	Group I agents should be avoided in patients with known or suspected acute kidney injury. Group II agents are preferred.	We favor a stratified approach: Acute kidney injury on dialysis: As in patients with end-stage kidney disease, we recommend a single session of dialysis following gadolinium exposure. Nonoliguric acute kidney injury not on dialysis: Similar to advanced chronic kidney disease, if a gadolinium-enhanced MRI study is needed, a group II agent should be used. Oliguric acute kidney injury not on dialysis: We favor avoiding administration of gadolinium if possible. Otherwise, our practice is to perform a single hemodialysis session.

ACR = American College of Radiology; CI-AKI = contrast-induced acute kidney injury; CT = computed tomography; MRI = magnetic resonance imaging; NSF = nephrogenic systemic fibrosis

Based on information in reference 41.

sociation of Radiologists[48] all permit the use of group II gadolinium-based contrast agents in patients with advanced kidney disease. The American College of Radiology[41] defines patients at risk of NSF as those:

- With advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2 not on dialysis)
- On dialysis (any form)
- With acute kidney injury.

In these patients, group I and III gadolinium-based contrast agents are contraindicated, with the caveat that there is insufficient real-life data to determine the risk of NSF from administration of group III agents. In patients at risk, if a gadolinium-enhanced MRI study is to be performed, a group II agent should be used. The lowest dose required to obtain the needed clinical information should be used, and it should generally not exceed the recommended single dose.

A summary of those recommendations with our comments and opinions is provided in **Table 4**.[41]

Gadolinium—the end of the story?

Although NSF has been basically eradicated since the guidelines were implemented, several cases of NSF have been reported in patients who never were exposed to gadolinium. In a review of biopsy-proven cases of NSF reported in 98 articles, 27 (8%) of 325 patients had no clear exposure to these agents,[62] and in the review of 639 biopsy-proven cases discussed above, 14 (2%) did not.[50] This suggests that gadolinium-based contrast agents are a major trigger for NSF, but they may not be the only one. Time will tell if indeed other triggers have yet to be discovered.

Additionally, in recent years, there have been data suggesting that gadolinium can deposit in the brain after repeated exposure to gadolinium-based contrast agents, even in patients with healthy kidneys.[63] This finding was confirmed histologically[64] and has led to the birth of a new term to describe it: *gadolinium deposition disease*.[65] The significance of this brain deposition remains unknown, and to date, no adverse health effects have been uncovered. However, the FDA published a safety alert in 2015 indicating the active investigation of the risk and clinical significance of these gadolinium deposits. The recent position statement of the American College of Radiology also recognizes this phenomenon and states, "Until we fully understand the mechanisms involved and their clinical consequences, the safety and tissue deposition potential of all [gadolinium-based contrast agents] must be carefully evaluated."[66]

It thus appears that we haven't heard the last of gadolinium-based contrast agent-related disease. Additional research will be needed to understand the potential consequences of the use of these agents.

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CME MOC

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The effect of disease-modifying antirheumatic drugs on vaccine immunogenicity in adults

ABSTRACT

Patients with immunocompromising conditions are at higher risk of vaccine-preventable infections. Further, those receiving immunosuppressive disease-modifying antirheumatic drugs (DMARDs) can have variable responses to vaccines depending on which vaccine and which DMARD they are receiving.

KEY POINTS

Influenza vaccine should be given yearly to all patients on DMARDs, with modification to either the timing of DMARD or vaccine administration for patients receiving methotrexate or rituximab.

Pneumococcal vaccination should be given to all patients on DMARDs beginning at age 19 with pneumococcal 13-valent conjugate vaccine (PCV13) and then the 23-valent pneumococcal polysaccharide vaccine (PPSV23). Methotrexate, abatacept, tofacitinib, and rituximab reduce pneumococcal vaccine immunogenicity.

The live herpes zoster vaccine is contraindicated in those with severe immunosuppression (eg, those on biologics or Janus kinase inhibitors) but may be given to those on conventional synthetic DMARDs.

Limited data exist on the effects of DMARDs on human papillomavirus vaccine.

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Patients can become immunocompromised from primary or secondary causes. Primary causes are typically inherited, whereas secondary causes may be iatrogenic (ie, medication-related) or due to the underlying disease process. Infections represent a serious risk to patients who are immunocompromised, and the US Centers for Disease Control and Prevention (CDC) has developed specific vaccination recommendations for these individuals beginning at age 19.[1]

Live vaccines are contraindicated in the severely immunocompromised, which, in patients receiving immunosuppressive drugs, is defined as those receiving any of the following:

- Prednisone in a dosage of 2 mg/kg or more, or more than 20 mg/day
- Methotrexate in a dosage of more than 0.4 mg/kg/week
- Azathioprine more than 3 mg/kg/day
- 6-Mercaptopurine more than 1.5 mg/kg/day
- Any biologic agent.[2]

In this review, we discuss the use of various vaccines in immunocompromised patients, with a focus on iatrogenic immunosuppression for patients with systemic rheumatic or other immune-mediated inflammatory diseases.

IMMUNE-MEDIATED INFLAMMATORY DISEASES AND INFECTION

Patients with immune-mediated inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and Crohn disease are at increased risk of infections, often due to the immunosuppressive medications they need (**Table 1**).

TABLE 1

Selected disease-modifying antirheumatic drugs

Antimetabolite
Methotrexate

Tumor necrosis factor inhibitors
Adalimumab
Certolizumab
Etanercept
Golimumab
Infliximab

Anti-CD80/CD86
Abatacept

Janus kinase inhibitors
Baricitinib
Tofacitinib
Upadacitinib

Anti-CD20
Rituximab

Interleukin (IL-) 6 inhibitors
Sarilumab
Siltuximab
Tocilizumab

IL-17 inhibitors
Brodalumab
Ixekizumab
Secukinumab

IL-12/23 inhibitors
Ustekinumab

Vaccines should be offered when appropriate to reduce risk

A large, retrospective US study[3] evaluated the incidence of hospitalization for infections in patients with rheumatoid arthritis who had no exposure to a biologic agent in the year preceding the study compared with those who switched among various biologic agents in the year preceding the study. The mean rate of hospitalization for infections was 4.6 per 100 person-years in biologic-naive patients, compared with 7.0 for biologic-experienced patients switching to a new therapy. This suggests that those with more refractory disease (using switching of biologic drugs as a proxy for more treatment-refractory disease) were at greater risk of infection. Pneumonia and soft-tissue infections were the most common types of infections.

Risk stratification for patients at high risk is important in both counseling patients and addressing modifiable risk factors for infection (eg, vaccination, tobacco use, glucocorticoid use). Infection risk calculators, such as the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) Risk Score,[4] or similar approaches developed for use in large administrative databases,[5] have been developed to estimate the yearly probability of a serious infection. The risk of most if not all types of infections is increased in patients with immune-mediated inflammatory diseases, and certain therapies for these disease further increase the risk. For example, the incidence of herpes zoster is higher in immune-mediated inflammatory diseases than in the general population and is further increased with Janus kinase inhibitors.[6]

More broadly, a systematic literature review of articles published from October 2009 to August 2018 was performed to determine the incidence and prevalence of vaccine-preventable illnesses in patients with autoimmune inflammatory rheumatic diseases.[7] Of the 3,876 articles initially retrieved, 63 met the inclusion criteria that allowed for analysis of incidence and prevalence rates of influenza, pneumococcal disease, hepatitis B, herpes zoster, and human papillomavirus (HPV) infection. The rates of influenza, *Pneumococcus*, herpes zoster, and HPV infections were higher than those in the general population.

Due to the significant risk of infection in patients with autoimmune inflammatory rheumatic diseases, vaccines should be offered when appropriate to reduce the risk.[1,8]

INFLUENZA VACCINATION

All adults, regardless of immunocompromised status, should receive a single dose of the annual influenza vaccine each year. Immunocompromised patients should receive either the recombinant influenza vaccine or the inactivated influenza vaccine[1]; the live attenuated influenza vaccine is contraindicated in this population. An egg allergy is not an absolute contraindication, as cell-culture based vaccines are available.[9]

Which influenza vaccine to use?

The standard inactivated influenza vaccine is trivalent, containing 2 influenza A strains and 1 influenza B strain. A quadrivalent vaccine,

TABLE 2

Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity

DMARDs	Influenza vaccine	PPSV23	PCV7/13	Live zoster vaccine	Recombinant zoster vaccine	Hepatitis B vaccine	Human papillomavirus vaccine
Methotrexate	Decrease[14,15]	Decrease[14,24]	Decrease[28]	No effect[17,34]	Not studied	Not studied	No effect[40,41]
TNF inhibitors	No effect[14]	No effect[14,24]	No effect[28,29]	Study pending, contraindicated[35]	Study pending	Decrease[37–39]	No effect[40,41]
Abatacept	No effect[16]	No effect[16]	Decrease[30]	Study pending, contraindicated	Study pending	Not studied	Not studied
Janus kinase inhibitors	No effect[17]	Decrease[17]	No effect[31,32]	Not studied, contraindicated	Study pending	Not studied	Not studied
Rituximab	Decrease[14,18,19]	Decrease[19,25]	Decrease[30,33]	Not studied, contraindicated	No effect[36]	Not studied	Not studied
IL-6 inhibitors	No effect[20]	No effect[20]	No effect[30]	Not studied, contraindicated	Not studied	Not studied	Not studied
IL-17 inhibitors	No effect[21–23]	No effect[26]	Not studied	Not studied, contraindicated	Not studied	Not studied	Not studied
IL-12/23 inhibitors	Not studied	No effect[27]	Not studied	Not studied, contraindicated	Not studied	Decrease[38]	Not studied

DMARDs = disease-modifying antirheumatic drugs; IL = interleukin; PCV7/13 = 7- or 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; TNF = tumor necrosis factor

also available, contains the standard strains with an additional influenza B (Yamagata) strain. A high-dose trivalent vaccine can be considered in individuals over age 65, as it confers a higher percentage of protective titers than the standard-dose vaccine and has been shown to have greater clinical effectiveness in preventing influenza infection.[10]

The recommendation to use the high-dose vaccine in at-risk individuals was further supported by a 2019 trial from Hong Kong that enrolled community-dwelling adults ages 65 to 82.[11] Sera were collected before and after vaccination with the 2017–2018 standard-dose quadrivalent, the trivalent with MF59 adjuvant, the high-dose trivalent, or the recombinant hemagglutinin quadrivalent vaccine. The MF59-adjuvanted trivalent, high-dose trivalent, and recombinant-hemagglutinin quadrivalent vaccines are considered enhanced vaccines, as either the increased dosage or use of an adjuvant causes a more robust immunogenic response. The mean rise in titer to egg-propagated H1N1 and H3N2 and microneutralized H3N2 was significantly higher in all enhanced-vaccine groups than in the group that received the standard-dose quadrivalent vaccine.

Enhanced vaccination in patients with immune-mediated inflammatory diseases was evaluated in a randomized controlled trial in patients with rheumatoid arthritis.[12] The high-dose trivalent vaccine was compared with the standard-dose quadrivalent vaccine in 279 seropositive patients on conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs (tumor necrosis factor [TNF] inhibitors, anti-interleukin-6 [anti-IL-6]), or Janus kinase inhibitors. Even though this group of individuals was not selected for being age 65 or older (the mean age was 61.0 ± 12.9 years), the high-dose trivalent vaccine significantly improved immunogenicity compared with the standard-

dose vaccine. While clinical outcomes (eg, incidence of influenza infection) were not assessed, this laboratory finding likely indicates that high-dose vaccination is preferable for all rheumatoid arthritis patients, irrespective of age.

The choice of influenza vaccine may also depend on local virulence patterns, as the Yamagata strain, which is not covered by the high-dose trivalent vaccine, may be the primary strain, or at least a relatively common strain. Although not as common on a national scale in recent years, the Yamagata strain varies in prevalence from year to year and has accounted for a significant portion of influenza B in the recent past. A high-dose quadrivalent influenza vaccine that includes coverage for the Yamagata strain will be available for the 2020–2021 influenza season.[13]

Effect of DMARDs on influenza vaccine effectiveness

Most DMARDs do not have a major effect on influenza vaccine seroprotection (**Table 2**).[14–41] However, rituximab significantly reduces it.[14,18,19] Rituximab is typically given every 6 months, and vaccination should be given about 2 weeks before the next rituximab dose.[18]

A high-dose quadrivalent flu vaccine that covers the Yamagata strain will be available for the 2020–2021 season

Methotrexate also decreases seroprotection from the influenza vaccine, but to a lesser degree than rituximab.[14,15] Holding methotrexate dosing for 2 weeks after influenza vaccination can improve vaccine seroprotection, as was demonstrated in a randomized controlled trial conducted among rheumatoid arthritis patients in Korea.[15] The diminution of beneficial effect of vaccination was related to methotrexate dose, and patients receiving 15 mg or more per week had a more reduced response than those on lower methotrexate doses. Patients on even lower but commonly used methotrexate doses had a minimal effect of methotrexate on vaccine immunogenicity.

TNF inhibitors,[14] abatacept,[16] tofacitinib,[17] tocilizumab,[20] and secukinumab[21–23] have not been shown to substantially reduce the proportion of patients who achieve adequate seroprotection.

While most studies have evaluated only the laboratory outcome of immunogenicity as a surrogate for clinical effectiveness, some observational studies have examined clinical outcomes such as the incidence of infection.[42] A retrospective observational study[42] of 30,788 patients with immune-mediated inflammatory diseases compared those who received and did not receive vaccination. In propensity score-adjusted analysis, vaccination reduced the risks of:

- Influenza-like illness (adjusted hazard ratio [aHR] 0.70, 95% confidence interval [CI] 0.54–0.92)
- Hospitalization for pneumonia (aHR 0.61, 95% CI 0.50–0.75)
- Hospitalization for chronic obstructive pulmonary disease exacerbation (aHR 0.67, 95% CI 0.46–0.99)
- Death due to pneumonia (aHR 0.48, 95% CI 0.33–0.71).

PNEUMOCOCCAL VACCINATION

For immunocompromised patients such as those with immune-mediated inflammatory diseases, pneumococcal vaccination is recommended starting at age 19.[1] Immunocompromised individuals should first receive a single dose of PCV13. A dose of PPSV23 follows, at least 8 weeks later. A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23. After a second dose of PPSV23, no further booster vaccinations are recommended. Additionally, individuals who received PPSV23 before age 65 for any indication should receive another dose at least 5 years later. For those who received PPSV23 before PCV13, PCV13 should be given at least 1 year after PPSV23.

Effect of DMARDs on pneumococcal vaccine effectiveness

Similar to influenza vaccination, most DMARDs have limited effects on pneumococcal vaccine immunogenicity (**Table 2**). Methotrexate and rituximab, however, decrease the humoral response to pneumococcal vaccine.[14,19,24,25,28–30,33,36]

A systematic review and meta-analysis was performed to determine the effects of methotrexate, TNF inhibitors, and rituximab on the immunogenicity of the influenza and pneumococcal vaccines in patients with rheumatoid arthritis.[14] Twelve studies were included in the analysis, but only 2 of them specifically

tested methotrexate's effect on pneumococcal vaccine effectiveness.[24,28] Methotrexate significantly reduced the vaccine response against pneumococcal serotypes 6B and 23F, with a pooled odds ratio (OR) of 0.33 (95% CI 0.20–0.54) for 6B and 0.58 (0.36–0.94) for 23F. These serotypes were chosen because they were commonly seen in invasive pneumococcal disease both worldwide and in Sweden, where the study was performed.

Similarly, only 2 of the studies evaluated the effect of rituximab.[19,33] Serotype 6B immunogenicity was significantly reduced with rituximab (OR 0.25, 95% CI 0.11–0.58), and there was a trend toward a similar reduction for serotype 23F (OR 0.21, 95% CI 0.04–1.05). Later studies have also shown a significant reduction in both 6B and 23F serotype immunogenicity with rituximab compared with controls.[30] The addition of methotrexate to rituximab further reduced immunogenicity.

Similar to the recommendation for the timing of influenza vaccination in patients treated with rituximab, pneumococcal vaccination should be given as close to the start of a subsequent rituximab dosing cycle as possible (eg, approximately 2 weeks before the next rituximab cycle).

Tofacitinib also decreases the humoral response to PPSV23,[17] yet both tofacitinib and baricitinib showed that a high percentage of patients who received PCV13 while on these treatments were able to mount a satisfactory immune response, although there was no control group in those studies.[31,32] TNF inhibitors have not been shown to have a significant effect on humoral response in PPSV23[14,24] or PCV7[28] in the absence of concomitant methotrexate. Tocilizumab did not reduce response to PPSV23[20] or PCV7.[30] Ixekizumab[26] and ustekinumab[27] did not significantly reduce immunogenicity to PPSV23 in healthy controls or in patients with moderate-to-severe psoriasis respectively, but PCV13 has not been studied for patients receiving these classes of biologics.

HERPES ZOSTER VACCINATION

Herpes zoster vaccination in the general population is recommended starting at age 50 with a 2-dose series of recombinant zoster vaccine.[1] Many primary care practices have stopped using the live zoster vaccine (Zostavax), as recombinant zoster vaccine (Shingrix) is more effective,[43] and the live zoster vaccine was discontinued in the United States in July 2020.[44]

The guideline published by the American College of Rheumatology in 2015 recommended live zoster vaccination for all patients with rheumatoid arthritis who are at least age 50.[8] Recommendations to use recombinant zoster vaccine among rheumatology patients have not yet been formulated or issued, and we currently have few data on its efficacy, safety (eg, risk of disease flare), and systemic reactogenicity in these populations.

Recombinant zoster vaccine is not a live vaccine. However, its clinical trials excluded people who were considered severely immunocompromised and also those with rheumatoid arthritis, systemic lupus erythematosus, and similar diseases receiving typical immunomodulatory therapies (eg, conventional synthetic DMARDs, biologics, and Janus kinase inhibitors). There is at least the potential concern for flare of underlying autoimmune conditions with recombinant zoster vaccine due to the potent immune response stimulated by the adjuvant.[45] Recombinant zoster vaccine is currently being studied in patients with immune-mediated inflammatory diseases and a variety of other immunocompromised patient populations.[1]

Methotrexate and rituximab decrease the humoral response to pneumococcal vaccine

Although recombinant zoster vaccine is not yet recommended for patients with immune-mediated inflammatory diseases, a retrospective review of 300 patients with rheumatic disease who received it showed only a 3% incidence of rheumatoid arthritis flare within 12 weeks of vaccination and no cases of herpes zoster reactivation.[46] Key limitations of this study included retrospective flare ascertainment, as recorded by documentation in rheumatologists' medical records, rather than prospective and systematic capture of flare and severe reactogenicity according to validated prespecified case definitions.

Despite US recommendations that favor recombinant over live zoster vaccine for healthy older patients, there are a number of countries worldwide in which it is not available, and the live vaccine remains the only option for herpes zoster vaccination. How-

ever, since it is a live vaccine, there are potential concerns about transmitting infection to patients with severe immunosuppression. The CDC[47] says its use is acceptable for patients treated with:

- Methotrexate ≤ 0.4 mg/kg/week
- Azathioprine ≤ 3.0 mg/kg/day
- 6-Mercaptopurine ≤ 1.5 mg/kg/day
- Prednisone < 20 mg/day or equivalent
- Intra-articular, intrabursal, or peritendinous corticosteroid injections.

For patients with rheumatoid arthritis who are at least 50 years old, the live zoster vaccine, if used, should be given before starting DMARDs or biologics whenever possible,[8] as incidence rates of herpes zoster have been shown to be increased and occur at an earlier age in patients with rheumatic and inflammatory diseases when compared to healthy individuals.[6] For example, the risk of herpes zoster in rheumatoid arthritis patients in their 40s is approximately equal to or higher than that in healthy older persons in their 60s.

Use of live zoster vaccine has also been shown to be safe and immunogenic when given 2 to 3 weeks before starting tofacitinib in patients with rheumatoid arthritis, but its long-term efficacy was unclear and did not seem to lower the risk of herpes zoster in follow-up of this small cohort.[34]

Recombinant zoster vaccine is more effective than the live vaccine, but new recommendations for rheumatology patients are yet to be issued

Due to the disease burden of herpes zoster in this population and uncertainties regarding the safety of live zoster vaccine in patients receiving biologic therapies, a randomized, blinded, placebo-controlled trial of live zoster vaccine in patients age 50 and older treated with TNF inhibitors for any on-label or off-label indication was performed to evaluate for safety and immunogenicity.[35] The study randomized 617 participants, and there were no cases of disseminated or local varicella infection in the 6-week period following live zoster vaccination, the at-risk period of concern. The immunologic effectiveness of live zoster vaccine in this trial is still being evaluated.

HEPATITIS B VACCINATION

In those who were not vaccinated as children, hepatitis B vaccination is not recommended routinely in the United States for adult rheumatic disease patients, but only in those for whom special situations or circumstances increase the risk for transmission.[1] These circumstances include:

- Hepatitis C virus co-infection
- Other chronic liver disease
- Human immunodeficiency virus infection
- High-risk sexual behavior
- Injection drug use
- Other high risk for percutaneous or mucosal exposure
- Incarceration
- Travel to countries with high or intermediate endemic hepatitis B.

Practitioners other than rheumatologists may give different recommendations for hepatitis B vaccination. For example, gastroenterologists routinely recommend it for patients with inflammatory bowel disease regardless of age.[48]

Three hepatitis B vaccines are currently available:

- Heplisav-B, given in a 2-dose series
- Engerix-B or Recombivax HB, given in a 3-dose series
- Twinrix, a combination hepatitis A and B vaccine given in a 3-dose series.

Effect of DMARDS on hepatitis B vaccine effectiveness

The effect of most DMARDs on hepatitis B vaccine immunogenicity has not been evaluated (**Table 2**); however, TNF inhibitors and ustekinumab have been shown to reduce it.[37,38,39] Response to the hepatitis B vaccine depends on T-cell activation, and the impairment of T-cell response caused by TNF inhibitors and ustekinumab (and presumably other IL-12/23 inhibitors) is thought to lead to the diminished response.[49] Several strategies may be needed to improve the immune response to hepatitis B vaccine, including repeated vaccine series, intradermal vaccine administration, development of new vaccine adjuvants, and high-dose vaccines.

A high-dose vaccine containing 40 µg/mL (the usual dose is 20 µg/mL) was studied in 109 patients with various rheumatologic and inflammatory diseases who were treated with TNF inhibitors or ustekinumab.[38] The development of a protective antibody titer was seen in 49.3% of patients who received the standard-dose vaccine and in 61.1% of those given

the high-dose vaccine. The difference was not statistically significant, however (P = .246).

Given the likelihood of nonresponse in these groups, it is important that the clinician evaluate for response with postvaccine hepatitis B surface antibody titers to determine if protection has been achieved, with adequate seroprotection typically defined as a titer of 10 mIU/mL or higher.[50]

HUMAN PAPILLOMAVIRUS VACCINATION

Vaccination against HPV is recommended for all adults through age 26, with initial vaccination routinely recommended in adolescents at age 11 or 12.[1,51] Using shared decision-making, HPV vaccination may also be offered to those ages 27 to 45. The age of initial HPV vaccination determines the number of vaccinations given in the series, with a total of 2 or 3 doses comprising a complete series.

Although 3 HPV vaccines are licensed for use, only the 9-valent HPV vaccine (Gardasil 9) is available in the United States; it covers HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Most HPV-associated cancers are caused by HPV types 16 or 18. There is no recommendation to alter the vaccination schedule for HPV in immunocompromised conditions.

Women with immune-mediated inflammatory diseases and those receiving immunosuppressive medications are at higher risk of HPV infection leading to high-grade cervical dysplasia and cervical cancer. However, vaccination rates are low.[7,52] Given these concerns, it is important to be aware of barriers to care. Many patients with immune-mediated inflammatory diseases receive vaccinations from their rheumatologists, who may not routinely stock the HPV vaccine. Further, given the complexity of many immune-mediated inflammatory diseases, discussions about preventive care may be deferred. Efforts should be made by both rheumatologists and those in the primary care specialties to encourage vaccination.

Effects of DMARDs on HPV vaccine effectiveness

Few studies have examined the effects of DMARDs on the immunogenicity of the HPV vaccine (**Table 2**). A 2013 prospective, controlled observational study compared the immunogencity of a bivalent HPV vaccine in 68 girls with juvenile idiopathic arthritis compared with 55 healthy girls.[40] Use of methotrexate did not affect seroconversion. In addition, the rates of seroconversion were not significantly lower in the patients receiving TNF inhibitors; however, the number of patients was considered to be too low to draw strong conclusions.

The effect of TNF inhibitors on HPV vaccine effectiveness was also evaluated in a prospective cohort of 37 female patients ages 9 to 26 with inflammatory bowel disease compared with matched healthy controls from a database.[41] Patients treated with the TNF inhibitors adalimumab or infliximab comprised 51% of the cohort, and the remaining 49% were on other immunomodulators including azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus. Overall, there was no difference in rates of seropositivity between the inflammatory bowel disease patients and the healthy controls.

There are currently no studies evaluating the effects of abatacept, Janus kinase inhibitors, rituximab, anti-IL-6, anti-IL-17, or anti-IL-12/23 inhibitors on the immunogenicity of the HPV vaccine.

TNF inhibitors and ustekinumab reduce hepatitis B vaccine immunogenicity

TAKE-HOME POINTS

- Immunocompromised patients are at increased risk of infection due to their primary condition or secondarily due to treatment.
- Vaccination provides an important method of prevention, but use of live vaccines is not recommended in severely immunocompromised persons.
- Non-live vaccines can be used at any time, although preferably they should be given before use of DMARDs in order to minimize negative effects on immunogenicity where they exist.
- For current DMARD users, temporarily holding methotrexate for influenza vaccination could be considered, and most importantly for rituximab, vaccination should occur near the end of the treatment interval 1 month before the next planned dose. ■

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