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CME MOC

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Skin side effects of biologic drugs

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*A Tsunami of Death and Destruction*
Kristin Highland, MD, 2020

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# COVID-19 Curbside Consults at www.CCJM.org

*"They fancied themselves free, and no one will ever be free so long as there are pestilences."* —Albert Camus, *The Plague*

I am rereading Camus's *The Plague*, and I am reading it in digital format. There was a significant delay in ordering the actual book. I am apparently not the only person searching for perspectives on our current surreal and, within hospital walls, palpably terrifying situation.

My age puts me in a vulnerable demographic group, and I have not been redeployed to the front lines of COVID-19 care. I am seeing patients mostly from my office via video virtual and phone visits. I find it unsatisfying, clearly a compromise for many encounters, but appropriate for the moment. We are still providing medication infusions to patients who have autoimmune and inflammatory diseases, now with more pointed discussions and angst regarding the potential risks of these therapies. My electronic medical record and e-mail inboxes are bursting with questions from patients and friends regarding their treatments, emotional and physical concerns, and what to do when they have been exposed to someone with COVID-19 or are having some combination of anosmia, acute malaise, fever, rigors, or cough.

These are tough times. There are many shared adversities and fears. Social landscape decisions need to be made, and these decisions are made more difficult and contentious by the mixed messages we are getting from some of our national and regional leaders. The medical community seems to be of one mind on this, following and responding to local realities and the population statistics as they accumulate and are analyzed. We recognize the limitations of epidemiologic models as well as the need to plan for the worst. And I think that we in medicine grasp the concept that "flattening the curve" does not equate with disappearance of the virus. The Groundhog Day conversation in my house invariably includes the unanswerable questions of when we will actually be comfortable again to sit in a restaurant or get on a plane to fly somewhere to give a lecture.

What we in medicine can *really* uniquely relate to are the clinical implications of COVID-19 infection in individual critically ill patients—the true reality of this pandemic. This is a wicked disease. The spectrum of clinical illness is enormous. Many people are infected and remain relatively well, while others progress quickly to profound respiratory failure. And still others have high fevers and debilitating fatigue, with some experiencing a bimodal course with respiratory failure developing more than 5 days into their symptomatic illness. A portion of infected patients exhibit features of "cytokine storm" driven by interleukin 6 (IL-6) and IL-1, a sepsis-like syndrome with rapidly escalating and quite marked elevations in C-reactive protein and ferritin and fever, which has prompted use of anti-IL-6 and anti-IL-1 therapies in clinical trials and in off-trial "routine" care of ill COVID-19 patients admitted to the hospital.

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Clinical data are coming fast and furious. Markers of worse outcome are being proposed (eg, lymphopenia, D-dimer elevation, troponin T elevation) and will be validated or refuted as the clinical context of these tests becomes better defined. Recognizing that some (all?) patients have hypercoagulability is an important contribution to understanding the morbidity of COVID-19. The marked clinical heterogeneity is thus far not understood; the individual patient's genetics governing their immune response, viral receptor polymorphism, comorbidities including smoking, and the presence of cross-reacting anticoronal antibodies are among the candidate explanations.

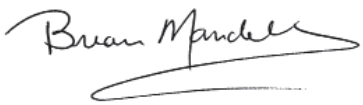
Medical centers are responding in unique ways, dictated by their own personnel and physical resources. But there is fantastic sharing of information and learned "best practices." Physicians and healthcare providers are communicating and sharing their learned lessons in every way imaginable, despite working unlimited shifts and having emotionally draining experiences.

With the goals of sharing our experiences with COVID-19 and analyzing rapidly appearing information from various outlets, we at *CCJM* have initiated a new online section, "COVID-19 Curbside Consults," a collection of short and, hopefully, point-of-care-useful pieces on the management of patients with COVID-19. These can be found at www.ccjm.org. We are focusing on specific clinical issues, asking seasoned specialists to comment in the context of their experience and expertise. We are also including descriptions of some healthcare system approaches that we have been instituting and modifying, including a description of our systemwide home monitoring program, the success of which I can personally vouch for, having used it for several patients and friends. We plan to update these regularly, and we have more pieces in the editorial queue that we will post soon.

The way that our colleagues, including (and with special shout-out to) our residents and fellows, have stepped up to confront this pandemic is beyond inspirational. And then, our providers on the front lines of patient care have additionally volunteered to write and share their experiences and analyses of the literature in between their emotionally and physically draining shifts in the hospital COVID-19 units with the hope of helping others provide care to the infected.

The day before I wrote this, a team of our physicians and nurses left after their inpatient rotations in our hospitals to fly to New York City to care for patients and provide some much-needed relief to healthcare providers there, clearly putting themselves in additional harm's way. Among them is at least 1 graduate and former chief resident from our internal medicine residency program. Having spent about 35 years involved with medical education, I don't recall ever feeling prouder of our trainees and my colleagues.

As Camus said, "What's true of all the evils in the world is true of the plague as well. It helps men to rise above themselves."



BRIAN F. MANDELL, MD, PhD
Editor in Chief

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# Can multiple ARDS patients be ventilated with a single ventilator?

FACED WITH A SURGE in demand for mechanical ventilators and fewer machines than patients who need them, hospitals are considering ventilating more than 1 patient with a single ventilator (multiplex ventilation). First reported as technically feasible in a test lung model,[1] the technique was anecdotally used in humans after the 2017 Las Vegas shooting.[2]

*More COVID-19 Curbside Consults: www.ccjm.org*

In response to the COVID-19 pandemic, several methods of providing mechanical ventilation to 2 to 9 patients have been posted on the Internet. Almost all of them involve diverting flow with off-the-shelf respiratory Y connectors applied at the inspiratory and expiratory ports of the ventilator (**Figure 1**). Valves, typically water valves, are repurposed for regulating gas flow (**Figure 2**). Some of these techniques employ 3-D printed devices that divide flow.

Mechanical ventilation is a life-support intervention. In acute respiratory distress syndrome (ARDS), it has several distinct goals, including maintaining low tidal volume ventilation, controlling positive end-expiratory pressure to improve oxygenation, removing enough carbon dioxide, and providing enough oxygen gas concentration to avoid hypoxemia.

To what extent can multiplex ventilation achieve these goals in individual patients with ARDS? What are the critical problems that need to be addressed for it to be practical and safe?

## MECHANISTIC ISSUES

From a mechanistic standpoint, 3 critical issues need to be addressed to minimize risk to

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**Figure 1.** Inspiratory and expiratory inputs to ventilator, with Y connectors.

**Figure 2.** Ventilator setup with volume monitor.

**With more patients than machines, multiplex ventilation is a reasonable last resort to prevent certain death**

patients on multiplex ventilation:

**Partitioning the volume delivered by the ventilator to each patient.** The volumes and pressures registered by the ventilator represent the aggregate volume and total pressure delivered to both patients. Without any intervention, partitioning of volumes between the patients would depend on the respiratory system mechanics of each patient. Therefore, the first issue is partitioning inspiratory flow from the ventilator individually between patients, ensuring safe volume delivery to each.

**Measuring tidal volume delivered to each patient.**

**Providing individualized positive end-expiratory pressure.**

These mechanistic issues are less relevant if the ventilator partners are evenly matched for respiratory mechanics, but if their disease courses take different directions, the best-case scenario in matching can turn into the worst.

## CLINICAL ISSUES

There are several important issues concerning clinical management in multiplex ventilation:

**Several mechanistic and clinical issues need to be addressed**

**Patients need to receive neuromuscular blockade.** If this is not done, the individual triggering efforts by patients could create significant patient-ventilator dyssynchrony, hyper- or hypoventilation, and potential exchange of gases between patients. However, neuromuscular blockade is associated with prolonged mechanical ventilation.

**Gradual withdrawal of support (weaning from mechanical ventilation) is impossible for an individual patient,** as it would affect the partner.

**There is no known way to provide different oxygen concentrations to the individual patients.** This means that the ventilator should be set at the minimum oxygen concentration that would achieve adequate saturation in the patient with worse oxygenation. This could potentially be too high for the patient next door.

Ventilator-related complications such as mucus plugging or pneumothorax in a single patient could go undetected due to lack of individual alarms. During this time, each patient could get lower tidal volumes if on volume-control ventilation, or 1 patient could get critically low tidal volumes in pressure-control ventilation.

Such pitfalls increase risk of harm to a patient who was being ventilated by his or her own machine and now has to share. Ideally, there would happen to be 2 patients who are intubated at the same time with 1 ventilator available, but chances are that alternative scenarios occur when one simply runs out of ventilators. Consequently, ethical concerns arise.

**Infection risk.** Although the risk of infection can be mitigated with appropriate filter placement in multiplex ventilation circuits, pairs of patients should be chosen so that both either have or do not have COVID-19.

Given these risks, several professional societies have issued a joint statement cautioning against the use of multiplex ventilation with currently available equipment.[3]

## A REASONABLE LAST RESORT

Multiplex ventilation is a reasonable last resort. There are no human data available to inform its practice, and therefore its routine use cannot be endorsed. However, COVID-19 has stretched resources to the limit and forced clinicians to consider multiplex ventilation to prevent certain death.

Clearly written protocols and trained staff are essential for implementation, with the goal of temporary support until individual ventilators are available. Two hospitals in New York City had to issue protocols for implementation of multiplex ventilation. One of these protocols has been cited by the US Public Health Service Commissioned Corps.[4]

Individual monitoring with the necessary alarm controls and ability to change ventilator parameters to suit individual needs are surmountable technical obstacles. The ventilator industry has to consider design features to enable safe multiplex ventilation for future pandemics.

## REFERENCES


1. **Neyman G, Irvin CB**. A single ventilator for multiple simulated patients to meet disaster surge. Acad Emerg Med 2006; 13(11):1246–1249. doi:10.1197/j.aem.2006.05.009
2. **Lake CK**. A day like no other. A case study of the Las Vegas mass shooting. Nevada Hospital Association. https://drive.google.com/file/d/1CxbLHiWJwL9ZRbWddbaPv15NN6YiNFEc/view. Accessed April 6, 2020
3. **The Society of Critical Care Medicine (SCCM), American Association for Respiratory Care, American Society of Anesthesiologists, Anesthesia Patient Safety Foundation, American Association of Critical Care Nurses, American College of Chest Physicians**. American joint statement on multiple patients per ventilator. March 26, 2020. https://www.aarc.org/wp-content/uploads/2020/03/032620-COVID-19-press-release.pdf. Accessed April 6, 2020
4. **U.S. Public Health Service Commissioned Corps.** Optimizing ventilator use during the COVID-19 pandemic. March 31, 2020. https://www.hhs.gov/sites/default/files/optimizing-ventilator-use-during-covid19-pandemic.pdf


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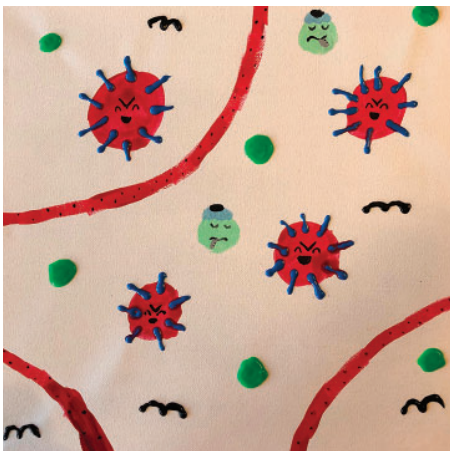
## COVID-19: Perspectives of 3 generations

***A Tsunami of Death and Destruction***
Kristin Highland, pulmonary and critical care physician and mother, age 51



***Viral Particles in the Blood Stream and Tissues. The Red Blood Cells Are Green and Glow in the Dark. The White Blood Cells That Fend Off Infection Are All Sick. Small Bats Are Flying Around***
Rosemary Highland, 5th-grade student and daughter, age 11

***The Virus Is Mutating, and There Are Various Stages of Inflammation***
Martha Highland, mother and grandmother, age 78

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

# Q: What mask should I wear to protect against transmissible acute respiratory infections?

**A:** Clinical trials have not shown any direct advantage to using an N95 respirator compared with a surgical mask for many acute respiratory infections. Until further evidence is available, current guidelines recommend wearing a surgical mask when caring for patients who have respiratory infections with droplet transmission and a respirator for those with airborne transmission, except for the emerging infection of COVID-19 in which guidelines regarding mask use are still evolving.

*See COVID-19 Curbside Consults: www.ccjm.org*

**Guidelines on personal protective equipment and COVID-19 are still evolving**

Healthcare workers are routinely exposed to respiratory infections that can be transmitted to other patients and develop into a cluster or outbreak of healthcare-acquired respiratory infections.[1] Healthcare personnel are both a vulnerable population and a potential vector for transmission, which was evident during the epidemics of severe acute respiratory syndrome (SARS) and influenza H1N1 ("swine flu").[2] The subject is even more timely with worldwide concern about protection against the recent pandemic of coronavirus disease 2019 (COVID-19).[3,4]

## ROUTES OF TRANSMISSION

Different classes of pathogens, including viruses, bacteria, fungi, parasites, and prions, can be transmitted by one or more routes, depending on the type of organism. There are 3 principal routes of transmission: contact, droplet, and airborne.

**Contact transmission** is further classified as either *direct contact*, in which infection spreads from an infected person to another without an intermediary object or person, and *indirect contact*, in which the agent is transmitted through an intermediate object or person on which pathogens have been deposited.[5,6]

**Droplet transmission** occurs when pathogens hitch a ride in droplets, usually traveling directly from the respiratory tract of the infectious person by coughs or sneezes over short distances (≤ 3 feet around the patient) to the mucous membranes of other individuals, or landing on surfaces of objects and then being transferred to the mucous membranes of other individuals by contaminated hands. This route of transmission is seen with infections such as *Bordetella pertussis*, influenza, and SARS-associated coronavirus.[7]

**Airborne transmission** involves smaller pathogen-bearing particles (or naked pathogens themselves), which can remain suspended in air longer and travel farther. The World Health Organization uses a 5-µm cutoff for infectious particle size to differentiate between airborne (≤ 5 µm) and droplet transmission (> 5 µm).[8,9] This type of transmission can be further classified:

*Obligate airborne transmission* means that disease occurs only though inhalation of small particles, such as with pulmonary tuberculosis.

*Preferential airborne transmission* means the disease has multiple routes of transmission but is predominantly transmitted by inhalation of aerosolized particles, such as in measles and varicella.

*Opportunistic airborne transmission* occurs when the agent usually causes infection by other routes, but under special circumstances can be

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transmitted by the airborne route, as highlighted in the Amoy Gardens experience in Hong Kong during the 2003 SARS epidemic.[5,6,10]

As for COVID-19, the US Centers for Disease Control and Prevention (CDC) states that transmission results from close contact with an infected person (within about 6 feet) through respiratory droplets produced when the infected person coughs or sneezes. It is also possible that infection happens by touching a contaminated surface or an object and then touching the mucous membranes of the nose, mouth, or eyes.[3]

## PERSONAL PROTECTIVE EQUIPMENT

Nonpharmacologic interventions, including personal protective equipment, are urged to decrease transmission of disease, especially if the disease has no vaccine or treatment. These include wearing surgical masks, respirators, gloves, and gowns. The CDC recommends that patients presenting with signs and symptoms of respiratory infections adhere to handwashing and cough etiquette, including covering the mouth when coughing and using disposable tissues. These measures have been shown in several clinical trials to be specifically effective and crucial in respiratory infection control, particularly when used with face masks.[5,11]

However, the evidence is still limited on the effectiveness of personal protective equipment in healthcare settings for preventing the spread of infections, as studies of their efficacy are inherently challenging to do, in part because of the need to recruit enough patients to have statistical power to evaluate efficacy for low-incidence outcomes. Another difficulty is that people don't always use their personal protective equipment; for example, rates of adherence to using eye protection in the setting of direct droplet transmission range between 10% and 84%.[12–14] This highlights the need for clinical trials assessing the overall efficacy of personal protective equipment and the best equipment to limit the exposure of healthcare workers to acute respiratory infection.[15]

N95 respirators are so named because they are certified to filter out 95% of airborne particles larger than 0.3 µm, but not oil. They have been found to be better than surgical masks in laboratory studies,[5] but this has not been translated into a clinical advantage, and clinical trials conclude that evidence remains insufficient to determine whether N95 respirators are superior to surgical masks in protecting healthcare personnel against transmissible acute respiratory infections in clinical settings.[13,16–21] In addition, N95 respirators have the disadvantages of being uncomfortable and possibly impractical for regular use, especially in low-resource settings, as they require fit-testing, regulation, and certification.[22]

These factors led to conflicting recommendations regarding the best mask to use to prevent the different respiratory infections. Therefore, guidelines for personal protective equipment and the type of masks recommended to be used to prevent exposure to respiratory viruses in healthcare settings were published by the CDC in 2007 for standard practice among physicians.[5]

## EVOLVING GUIDELINES ON COVID-19

Guidelines on the use of personal protective equipment in caring for patients with confirmed or suspected COVID-19 are still evolving.

The CDC[23] currently recommends placing all patients with confirmed or suspected COVID-19 in single rooms with doors closed. Healthcare workers who enter rooms of patients with suspected or confirmed COVID-19 should adhere to standard precautions, which include hand hygiene and wearing gloves, gowns, and eye protection.

**For COVID-19, an N95 is preferred, but a surgical mask is acceptable for routine care**

Both the N95 mask (or higher respirators) and surgical masks are acceptable for routine care of these patients; however, respirators are preferred. Respirators must be used when performing an aerosol-generating procedure.

Recommendations regarding donning and doffing of personal protective equipment have also been established to decrease spreading of the virus. It is preferred to discard the respiratory mask after exiting the patient's room with performing hand hygiene after discarding the mask. However, due to the current shortage of respiratory masks, it is now acceptable to reuse the same respiratory mask to assess different patients or for more than one encounter.

Further, updated guidelines were recently published regarding isolation precautions in the setting of diagnosed or suspected COVID-19,

including the aforementioned standard precautions, placing patients in a single-patient room with negative pressure, and using personal protective equipment that includes gloves, gowns, eye protection, and masks.[23] The CDC currently recommends using respirators that are at least as protective as a fit-tested N95.[3,5]

## EXISTING EVIDENCE

In 2009, after the emergence of the first influenza epidemic in years, recommendations stated that respirators are needed when caring for any patient infected with H1N1 pandemic strain. These recommendations came as a part of drastic measures taken to limit exposure to the infection until it was clear whether the H1N1 strain was transmitted by the usual routes, the same as seasonal influenza. Later, medical masks were recommended in most settings for all types of influenza, as it appeared they had the same routes of transmission.[24]

Guidelines for infection control from the CDC and World Health Organization include measures for reducing respiratory infection transmission in healthcare settings, with hand hygiene and cough etiquette as part of standard precautions being the key components. Personal protective equipment, including surgical masks, is recommended for routine care in patients infected with influenza, while an N95 respirator or a higher-level protection is recommended when performing aerosol-generating procedures (eg, intubation, bronchoscopy, suctioning) in those patients.[24,25]

**Research has not shown a direct advantage to using an N95 respirator compared with a surgical mask for many acute respiratory infections**

Furthermore, the CDC recommended N95 respirators as a part of personal protective equipment for severe infections such as smallpox and SARS, despite lack of data on the efficacy of these masks in real-world settings. Contact precautions including personal protective equipment (such as gowns and gloves), protection of equipment, environmental control, and patient placement and transport were also recommended by the CDC in certain infections and in immunocompromised patients and others at high risk.[5,24]

Many clinical trials since then have compared the efficacy of surgical masks with that of N95 respirators in preventing transmission of influenza in healthcare settings.[16,18]

Loeb and colleagues[16] reported that surgical masks were noninferior to N95 respirators in protecting against laboratory-confirmed influenza.[16] McIntyre et al[18] found no difference between surgical masks and N95 respirators against influenza during the 2008–2009 influenza season.

Radonovich et al[15] reported the results of the Respiratory Protection Effectiveness Clinical Trial, a randomized, multicenter pragmatic clinical trial comparing surgical masks vs respirators in the outpatient setting, that showed no significant difference between the effectiveness of N95 respirators and surgical masks in preventing laboratory-confirmed influenza among participants who are routinely exposed to respiratory illnesses in the workplace. In addition, there were no significant differences between N95 respirators and surgical masks in the rates of acute respiratory illness, laboratory-detected respiratory infections, laboratory-confirmed respiratory illness, and influenza-like illness among participants.[15]

Smith et al[14] conducted a meta-analysis reviewing clinical trials that compared N95 respirators and surgical masks for preventing transmissible acute respiratory infections. Their analysis included 6 clinical studies (3 randomized controlled trials, 1 cohort study, and 2 case-control trials) and 23 surrogate exposure studies. This study reported no significant difference in risk of respiratory infection transmission to patients from healthcare workers using N95 respirators vs surgical masks. The surrogate exposure studies showed N95 respirators to be superior to surgical masks under laboratory testing.[14,16,19]

## THE MESSAGE

Clinical trials have not shown a direct advantage to using an N95 respirator compared with a surgical mask for many acute respiratory infections. Thus, healthcare workers should adhere to the current CDC recommendations on standard precautions, including handwashing, cough etiquette, and wearing a surgical mask to prevent respiratory infections with droplet transmission—and an N95 for agents or scenarios where airborne transmission may occur. Healthcare providers are also encouraged to follow updated CDC recommendations regarding protection against emerging infections such as COVID-19.

## REFERENCES


1. **Goins WP, Talbot HK, Talbot TR**. Health care-acquired viral respiratory diseases. Infect Dis Clin North Am 2011; 25(1):227–244. doi:10.1016/j.idc.2010.11.010
2. **Trajman A, Menzies D**. Occupational respiratory infections. Curr Opin Pulm Med 2010; 16(3):226–234. doi:10.1097/MCP.0b013e328338639b
3. **Centers for Disease Control and Prevention**. Coronavirus Disease 2019 (COVID-19). Interim guidance for public health personnel evaluating persons under investigation (PUIs) and asymptomatic close contacts of confirmed cases at their home or non-home residential settings. https://www.cdc.gov/coronavirus/2019-ncov/php/guidance-evaluating-pui.html. Accessed April 3, 2020.
4. **Gates B**. Responding to Covid-19—a once-in-a-century pandemic? N Engl J Med 2020 Feb 28. doi:10.1056/NEJMp2003762. Epub ahead of print.
5. **Siegel JD, Rhinehart E, Jackson M, Chiarello L; Health Care Infection Control Practices Advisory Committee**. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 2007; 35(10 suppl 2):S65–S164. doi:10.1016/j.ajic.2007.10.007
6. **Roy CJ, Milton DK**. Airborne transmission of communicable infection—the elusive pathway. N Engl J Med 2004; 350(17):1710–1712. doi:10.1056/NEJMp048051
7. **Kutter JS, Spronken MI, Fraaij PL, Fouchier RA, Herfst S**. Transmission routes of respiratory viruses among humans. Curr Opin Virol 2018; 28:142–151. doi:10.1016/j.coviro.2018.01.001
8. **Gralton J, Tovey E, McLaws ML, Rawlinson WD**. The role of particle size in aerosolised pathogen transmission: a review. J Infect 2011; 62(1):1–13. doi:10.1016/j.jinf.2010.11.010
9. **Zhou J, Wei J, Choy KT, et al**. Defining the sizes of airborne particles that mediate influenza transmission in ferrets. Proc Natl Acad Sci USA 2018; 115(10):E2386–E2392. doi:10.1073/pnas.1716771115
10. **Hung LS**. The SARS epidemic in Hong Kong: what lessons have we learned? J R Soc Med 2003; 96(8):374–378. doi:10.1258/jrsm.96.8.374
11. **Simmerman JM, Suntarattiwong P, Levy J, et al**. Findings from a household randomized controlled trial of hand washing and face masks to reduce influenza transmission in Bangkok, Thailand. Influenza Other Respir Viruses 2011; 5(4):256–267. doi:10.1111/j.1750-2659.2011.00205.x
12. **MacIntyre CR, Chughtai AA**. Facemasks for the prevention of infection in healthcare and community settings. BMJ 2015; 350:h694. doi:10.1136/bmj.h694
13. **MacIntyre CR, Wang Q, Seale H, et al**. A randomized clinical trial of three options for N95 respirators and medical masks in health workers. Am J Respir Crit Care Med 2013; 187(9):960–966. doi:10.1164/rccm.201207-1164OC
14. **Smith JD, MacDougall CC, Johnstone J, Copes RA, Schwartz B, Garber GE**. Effectiveness of N95 respirators versus surgical masks in protecting health care workers from acute respiratory infection: a systematic review and meta-analysis. CMAJ 2016; 188(8):567–574. doi:10.1503/cmaj.150835
15. **Radonovich LJ Jr, Simberkoff MS, Bessesen MT, et al; ResPECT investigators**. N95 respirators vs medical masks for preventing influenza among health care personnel: a randomized clinical trial. JAMA 2019; 322(9):824–833. doi:10.1001/jama.2019.11645
16. **Loeb M, Dafoe N, Mahony J, et al**. Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial. JAMA 2009; 302(17):1865–1871. doi:10.1001/jama.2009.1466
17. **MacIntyre CR, Wang Q, Rahman B, et al**. Efficacy of face masks and respirators in preventing upper respiratory tract bacterial colonization and co-infection in hospital healthcare workers. Prev Med 2014; 62:1–7. doi:10.1016/j.ypmed.2014.01.015
18. **MacIntyre CR, Wang Q, Cauchemez S, et al**. A cluster randomized clinical trial comparing fit-tested and non-fit-tested N95 respirators to medical masks to prevent respiratory virus infection in health care workers. Influenza Other Respir Viruses 2011; 5(3):170–179. doi:10.1111/j.1750-2659.2011.00198.x
19. **Loeb M, McGeer A, Henry B, et al**. SARS among critical care nurses, Toronto. Emerg Infect Dis 2004; 10(2):251–255. doi:10.3201/eid1002.030838
20. **Seto WH, Tsang D, Yung RW, et al; Advisors of Expert SARS group of Hospital Authority**. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 2003; 361(9368):1519–1520. doi:10.1016/s0140-6736(03)13168-6
21. **Zhang Y, Seale H, Yang P, et al**. Factors associated with the transmission of pandemic (H1N1) 2009 among hospital healthcare workers in Beijing, China. Influenza Other Respir Viruses 2013; 7(3):466–471. doi:10.1111/irv.12025
22. **Rebmann T, Carrico R, Wang J**. Physiologic and other effects and compliance with long-term respirator use among medical intensive care unit nurses. Am J Infect Control 2013; 41(12):1218–1223. doi:10.1016/j.ajic.2013.02.017
23. **US Centers for Disease Control and Prevention**. Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings. https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html#adhere. Accessed April 3, 2020.
24. **World Health Organization**. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care, WHO guidelines. https://www.who.int/csr/bioriskreduction/infection_control/publication/en/. Accessed April 3, 2020.
25. **Centers for Disease Control and Prevention**. Prevention strategies for seasonal influenza in healthcare settings. https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm. Accessed April 3,2020.


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CME MOC

# 2020

## JUNE

**INTENSIVE REVIEW OF INTERNAL MEDICINE (LIVE STREAM)**
June 1–5

**INNOVATIONS IN CEREBROVASCULAR CARE (CANCELED)**
June 4–5
Cleveland, OH

**MELLEN CENTER UPDATE IN MULTIPLE SCLEROSIS (CANCELED)**
June 12
Cleveland, OH

**INTERDISCIPLINARY APPROACH TO MANAGEMENT OF CRITICALLY ILL LIVER PATIENTS (CANCELED)**
June 15–16
Cleveland, OH

**INTERNAL MEDICINE BOARD REVIEW COURSE (LIVE STREAM)**
June 16–20

**WASOG/AASOG 2020: MULTIDISCIPLINARY MEETING FOR SARCOIDOSIS AND ILD**
June 24–27
Hollywood, FL

## JULY

**MAKE THE DIAGNOSIS! POINT-OF-CARE ULTRASOUND FOR BEDSIDE CLINICIANS**
July 16–17
Cleveland, OH

**MULTIDISCIPLINARY APPROACH TO THE CONTEMPORARY MANAGEMENT OF HEART FAILURE**
July 31
Cleveland, OH

## AUGUST

**HOSPITAL MEDICINE 2020**
August 6–7
Beachwood, OH

**NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN**
August 7–9
Washington, DC

**INTENSIVE REVIEW OF CARDIOLOGY**
August 15–19
Cleveland, OH

## SEPTEMBER

**MEDICAL DERMATOLOGY THERAPY UPDATE**
September 3–5
Cleveland, OH

**CLEVELAND CLINIC EPILEPSY UPDATE AND REVIEW COURSE**
September 9–11
Cleveland, OH

**PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND**
September 10–11
Cleveland, OH

**WOMEN IN HEALTHCARE FORUM (CANCELED)**
September 17
Beachwood, OH

**DIABETES, OBESITY, AND CARDIOVASCULAR DISEASE SUMMIT**
September 22–23
Cleveland, OH, and Baton Rouge, LA

**GENETICS EDUCATION SYMPOSIUM—GENETICS AND GENOMICS: APPLICATIONS FOR THE PREVENTION, DETECTION, AND TREATMENT OF CANCER**
September 24
Cleveland, OH

**INTENSIVE REVIEW FOR THE GI BOARDS**
September 25–28
Las Vegas, NV

## OCTOBER

**NEPHROLOGY UPDATE**
October 1–3
Cleveland, OH

**PRACTICAL MANAGEMENT OF STROKE**
October 2
Cleveland, OH

**STATE-OF-THE-ART ECHOCARDIOGRAPHY 2020**
October 2–4
Cleveland, OH

**INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM**
October 9–11
Cleveland, OH

**FIRST EUROPEAN CLEVELAND CLINIC ENDOCRINOLOGY AND DIABETES UPDATE**
October 15–18
Split, Croatia

**ORTHOBIOLOGICS SUMMIT 2020: SCIENCE AND EVIDENCE BEHIND BIOLOGICS IN ORTHOPEDICS**
October 16–17
Miami, FL

**WAKE UP TO SLEEP DISORDERS 2020: A CLEVELAND CLINIC SLEEP DISORDERS CENTER UPDATE**
October 16–17
Beachwood, OH

**PRIMARY CARE EVIDENCE-BASED MEDICINE**
October 23–24
Beachwood, OH

## DECEMBER

**A CASE-BASED APPROACH TO MASTERING THE MITRAL VALVE: IMAGING, INNOVATION, INTERVENTION**
December 4–5
New York, NY

# 2021

## JANUARY

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

**FOR SCHEDULE UPDATES AND TO REGISTER, VISIT: WWW.CCFCME.ORG/LIVE**

COMMENTARY

**Kenneth G. Poole Jr, MD, MBA, CPE, FACP**
Medical Director of Patient Experience, Mayo Clinic Arizona; Chair, Patient Experience Subcommittee, Mayo Clinic Arizona; Chair, Grievance Subcommittee, Mayo Clinic Arizona; Chair, Patient Health Information Subcommittee, Mayo Clinic; Member, Admissions Operating Committee, Mayo Clinic Alix School of Medicine

# 'I want a doctor who looks like me': The dilemma of race-based requests

PATIENT EXPERIENCE has found its way to the top of the list of priorities for healthcare organizations, which are now obliged to gather and interpret patient feedback in a way that optimizes medical care. Requests for providers based on race and ethnicity create an uncomfortable, delicate situation that hard-line policies fail to adequately address. Ideally, the race of a provider shouldn't matter in providing the best care to patients. But what if it does?

**Ideally, the provider's race shouldn't matter, but what if it does?**

## PATIENT EXPERIENCE HAS BECOME A TOP PRIORITY

The consumer-centric shift of healthcare has moved patient attitudes, preferences, and experience to the top of the list of priorities for healthcare organizations. As such, patient experience has become an important part of healthcare administration and management, with organizations dedicating personnel and resources to maintain a competitive advantage. Healthcare organizations track patient experience data with automated postcare surveys, patient advisory councils, online consumer communities, and direct patient feedback. Patient-centered healthcare organizations use this information to drive operational strategies and continual practice redesign, and some of the data are used to determine insurance reimbursement.

## MINORITY PHYSICIANS FACE BIAS

Not surprisingly, bias often finds its way into patient experience data. Patients tend to prefer healthcare providers of similar race and ethnicity.[1] Thus, minority providers, particularly those from groups that are underrepresented in medicine in the United States, such as African Americans and Latinos, at times find themselves receiving lower patient experience scores than their white colleagues.[2,3] Besides potentially lowering the performance evaluations and reimbursement for minority physicians, such systemic implicit bias contributes to the feelings of frustration, isolation, and burnout faced by minority physicians in healthcare.

Online provider profiles and information have aided patients in selecting healthcare providers. However, you can't always get the doctor you want: limited access, narrowing insurance provider networks, and team-based models of care create a situation in which many patients are still assigned providers without knowing their race, ethnicity, sex, or other characteristics.

It is thus not uncommon for patients to request to be seen by a different provider of a specific race or ethnicity for future visits. Healthcare system and practice leaders now find themselves in the uncomfortable position of deciding how to manage such requests, finding a balance between accommodating patient preference and protecting their providers from bigotry.

Small medical practices, particularly those not affiliated with integrated delivery systems, may lack the brand recognition of large medical groups. Therefore, a substantial proportion of their initial patient appointment requests could be provider-specific, making random assignment based on availability less likely. Still, depending on the racial and ethnic diversity of the practice, the challenge of managing patient preferences could mirror that of large healthcare systems.

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## NOT ALL REQUESTS ARE ROOTED IN RACISM

Many would argue that patient requests for providers on the basis of race, ethnicity, and other personal characteristics should not be accommodated. Perhaps it would be better to try to create a safe, ethnically diverse, culturally competent environment where all patients and providers feel welcome. But what if such selection is in the best interest of a particular patient? What if accommodating a request rooted in bias translates into better health outcomes?

The life expectancy of African Americans continues to lag behind that of white Americans—74.8 years vs 78.5 years. The current life expectancy of African American males is 71.5 years.[4] Additionally, black Americans have a higher rate of death for 9 of the 15 leading causes of death, including many preventable conditions such as heart disease, malignant neoplasms, cerebrovascular diseases, diabetes, renal disease, and hypertension.[5]

Among the factors contributing to these healthcare disparities is the low number of African American physicians. Currently, just over 4% of practicing physicians and less than 6% of US medical school graduates are black.[6] Moreover, African American applicants to US medical schools have a lower rate of acceptance than other racial and ethnic groups, contributing to the small pool of black healthcare providers.

In the early 2000s, LaVeist et al[7] showed that patient-provider race concordance resulted in increased utilization of health services and fewer delays in seeking care, particularly among African Americans. Last year, researchers in Oakland, CA, found that black men were more likely to engage in preventive services when recommended by black physicians.[8] They estimated that such a change in behavior could translate to a 19% reduction in the cardiovascular mortality gap between white and black men.[8] It is thus deduced that increased access to African American male physicians could improve health outcomes in African American male patients.

## CONSIDER THIS PATIENT

A middle-aged black man calls a healthcare system to make an appointment to establish care and asks, "Do you have any black physicians on staff? If so, I would like to see one." How a safe, ethnically diverse, culturally competent hospital system responds to this type of request from such a patient is a complex undertaking. Ideally, the race of a provider shouldn't matter in providing the best care that this patient has the right to seek. But what if it does? What if accommodating such a request is something that we know can result in not just an improved patient experience, but also improved engagement in preventive services and potentially better health outcomes? Would it then be unethical to automatically deny such a request?

Furthermore, why would this patient have such a request? Does the request come from bigotry, racism, or hatred? Alternatively, does it matter that he is part of a community that has been the victim of enslavement and subsequent political, social, and economic disenfranchisement in this country? Does it matter that he comes from a community that has a history of being discriminated against and abused, notably in the healthcare system? Does it matter that the patient likely has experienced explicit and implicit bias in and out of the healthcare setting?

Particularly if the volume of requests for providers on the basis of race and ethnicity is not overwhelming, it would be reasonable to seek to understand the reason behind each request. Requests deemed inappropriate could present an opportunity to provide education and to reduce bias. For those deemed befitting and free of discriminatory intent, it is hard to argue against accommodation.

It is comforting to think that optimal medical care is color-blind, and it is easy and convenient to assume that patient requests for providers on the basis of race and ethnicity are inappropriate. However, there are data and trends that suggest otherwise. Not all patient requests are rooted in bigotry and racism. Some are rooted in history, pain, and survival.

**It is comforting to think that medical care is color-blind, but data suggest otherwise**

## REFERENCES


1. **LaVeist TA, Nuru-Jeter A**. Is doctor-patient race concordance associated with greater satisfaction with care? J Health Soc Behav 2002; 43(3):296–306. pmid:12467254
2. **Poole KG Jr**. Patient-experience data and bias—what ratings don't tell us. N Engl J Med 2019; 380(9):801–803. doi:10.1056/NEJMp1813418
3. **Sotto-Santiago S, Slaven JE, Rohr-Kirchgraber T**. (Dis) incentivizing patient satisfaction metrics: the unintended consequences of institutional bias. Health Equity 2019; 3(1):13–18. doi:10.1089/heq.2018.0065
4. **Centers for Disease Control and Prevention**. Health, United States, 2017. https://www.cdc.gov/nchs/data/hus/2017/fig01.pdf. Accessed February 13, 2020.
5. **Xu J, Murphy SL, Kochanek KD, Bastian B, Arias E**. Deaths: final data for 2016. Natl Vital Stat Rep 2018; 67(5):1–76. pmid:30248015
6. **Association of American Medical Colleges**. Figure 6. Percentage of U.S. medical school applicants by Black subgroups, 2015. http://www.aamcdiversityfactsandfigures2016.org/report-section/section-3/. Accessed February 13, 2020.
7. **LaVeist TA, Nuru-Jeter A, Jones KE**. The association of doctor-patient race concordance with health services utilization. J Public Health Policy 2003; 24(3–4):312–323. pmid:15015865
8. **Alsan M, Garrick O, Graziani G; National Bureau of Economic Research**. Does diversity matter for health? Experimental evidence from Oakland. NBER Working Paper No. 24787. https://www.nber.org/papers/w24787. Accessed February 13, 2020.


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# Page kidney after a renal biopsy

A 25-year-old man presented with sudden onset of left flank pain upon standing up from a chair 3 weeks after undergoing renal biopsy. The procedure had been an ultrasonographically guided percutaneous renal biopsy of the lower pole of the left kidney, with 3 passes, to evaluate hematuria and nephritic-range proteinuria and had resulted in the diagnosis of immunoglobulin A (IgA) nephropathy.

The patient had a history of hypertension, for which he was taking nifedipine 40 mg daily, which had been keeping his blood pressure below 130/80 mm Hg. As an infant he had had congenital hydrocephalus, for which a ventriculoperitoneal shunt had been placed.

On examination, his blood pressure was elevated at 160/80 mm Hg; other vital signs were stable. Abdominal examination revealed left flank tenderness and left costovertebral angle tenderness. The rest of the physical examination was unremarkable.

His blood urea nitrogen level was 13 mg/dL (reference range 8–20), and his serum creatinine was 1.40 mg/dL, up from 1.20 mg/dL before the biopsy (reference range 0.65–1.07). His electrolyte levels, liver function test results, and complete blood cell counts were normal.

Computed tomography (CT) with contrast revealed a large pericapsular collection with high attenuation (70 Hounsfield units [HU]) in the left kidney, compressing the renal parenchyma (**Figures 1 and 2**).

In view of his worsening hypertension and the pericapsular hematoma in his left kidney, we suspected Page kidney as a complication of renal biopsy.

Two days after admission, his creatinine level had increased to 2.75 mg/dL. Four days

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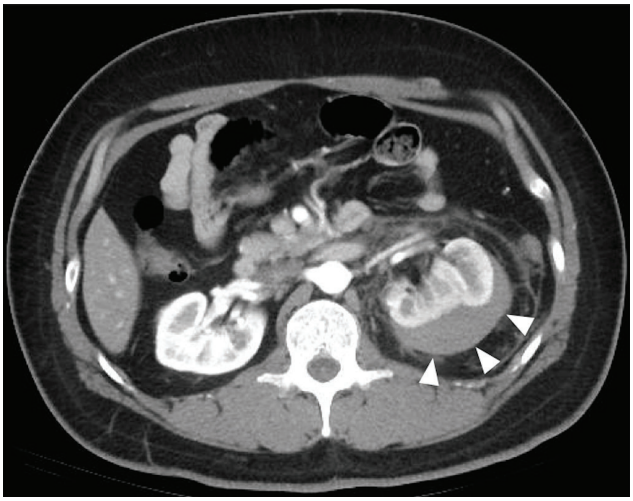

**Figure 1.** Axial computed tomography with contrast of the mid-kidney shows that the renal parenchyma is compressed by a contained, high-attenuation (70 HU), pericapsular collection (arrowheads).

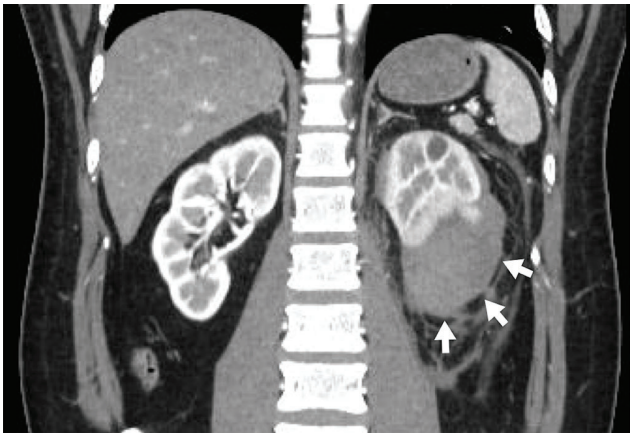

**Figure 2.** Coronal computed tomography with contrast shows that the lower pole is compressed by a contained, high-attenuation, pericapsular collection (arrows).

after admission, his plasma renin activity was elevated to 11 µg/L/hour (reference range 0.3–2.9) and his serum aldosterone level was 337 pg/mL (reference range 29.9–159), establishing the diagnosis of Page kidney.

Intravenous nicardipine and fentanyl were given. Although his pain subsided significantly, his blood pressure remained high. Renin-angiotensin-aldosterone system (RAAS) inhibitors were initially deferred in view of his acute kidney injury, and nicardipine was continued.

The patient subsequently underwent laparoscopic evacuation of the hematoma. Afterward, CT confirmed that the hematoma was gone, but his kidney function did not improve. Therefore, 6 days after admission, enalapril 2.5 mg daily was added to his regimen, and his blood pressure returned to normal over the next several days. One month later, his serum creatinine level was down to 1.28 mg/dL, his plasma renin activity was 0.3 µg/L/hour, and his aldosterone level was 59.7 pg/mL.

## PAGE KIDNEY

**A patient presents with flank pain, worsening hypertension, and acute kidney injury after renal biopsy**

Page kidney, a condition in which an affected kidney is compressed by external force, is an uncommon cause of secondary hypertension and renal insufficiency. Other possible causes of secondary hypertension include renal artery stenosis, juxtaglomerular cell tumor, and malignant hypertension.

Page kidney was first reported in 1939 by Irvine Page,[1] who induced it in a dog by wrapping the animal's kidney in cellophane. The presumed mechanism is that direct external compression of the kidney causes decreased renal perfusion and increased renin secretion, resulting in activation of the RAAS system and secondary hypertension.[2]

The most common cause of constrictive pressure on the kidney is hematoma due to abdominal trauma, surgery, or percutaneous interventions. Page kidney has often been reported after traumatic biopsy of kidney allografts, but more rarely after native kidney biopsy.

Ultrasonography and CT are useful for detecting hematoma.

As activation of the RAAS is the central mechanism of hypertension in Page kidney, we deemed it suitable to give enalapril, a drug that blocks the RAAS, and nicardipine, a calcium channel blocker, to control hypertension and prevent further kidney damage. However, few studies have investigated optimal antihypertensive therapy in Page kidney. Percutaneous or open drainage of the hematoma may be needed for patients with uncontrolled hypertension or worsening renal function. Surgical nephrectomy is occasionally required to control hypertension.[3]

Page kidney should be considered in a patient with new-onset hypertension and flank pain after native kidney biopsy. Early recognition can allow for conservative treatment, which can improve this condition and preserve kidney function.[4]

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## REFERENCES

1. **Page IH**. The production of persistent arterial hypertension by cellophane perinephritis. JAMA 1939; 113(23):2046–2048. doi:10.1001/jama.1939.02800480032008
2. **Wahdat R, Schwartz C, Espinosa J, Lucerna A**. Page kidney: taking a page from history. Am J Emerg Med 2017; 35(1):193.e1–193.e2. doi:10.1016/j.ajem.2016.06.095
3. **Kiczek M, Udayasankar U**. Page kidney. J Urol 2015; 194(4):1109–1110. doi:10.1016/j.juro.2015.07.035
4. **Sokhal AK, Prakash G, Saini DK, Singh K, Sankhwar S, Singh BP**. Page kidney: a rare but surgically treatable cause of hypertension. Saudi J Kidney Dis Transpl 2018; 29(1):193–197. doi:10.4103/1319-2442.225183

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CME MOC

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# Perinatal depression: A review

## ABSTRACT

Perinatal depression affects 10% to 20% of women in the United States during pregnancy, the postpartum period, or both, but it can be difficult to recognize. Identifying and treating this problem can reduce the alarming number of suicides among depressed perinatal women and the possible adverse effects of untreated maternal depression on their child's cognitive and behavioral development. In this review, we discuss the latest developments in screening, treatment, and prevention methods.

## KEY POINTS

Screening for perinatal depression is recommended for all pregnant and postpartum women and is now a covered medical expense; the tools can be completed by patients in 2 minutes in the waiting room.

Perinatal depression can be prevented in some patients with regular counseling sessions.

Newly approved parenteral medications work immediately to ameliorate symptoms in moderate to severe disease.

Promising research suggests that we may be able to predict the likelihood of perinatal depression using biomarkers such as epigenetically modified genes.

Dr. Payne has disclosed membership on advisory committees or review panels for Janssen Pharmaceuticals Inc.

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Depression is a common medical condition in women during the perinatal period and is associated with serious consequences. It can cause intense sadness and anxiety in the mother and prevent her from bonding with or breastfeeding her baby. In severe cases, women may think about or actually harm themselves or their baby. Untreated perinatal depression in the mother can result in low birth weight and impaired social, cognitive, and emotional development in the baby.

Although it is imperative to recognize perinatal depression for these and other reasons, it is often overlooked in the primary care setting, especially since patients may be reluctant to reveal their symptoms. Therefore, many women with perinatal depression go undiagnosed, and even when it is detected, only some receive follow-up treatment.[1]

In this review, we discuss the latest methods for preventing, identifying, and treating perinatal depression.

## DEFINITION AND PRESENTATION

Perinatal depression can occur during pregnancy (prenatally), the year following birth (postpartum), or both. Although feelings of weepiness and labile emotions, called the "baby blues," occur in up to 80% of new mothers within several days of delivery because of regulatory biochemical changes, these symptoms are usually brief and last no longer than 10 days.[2] Perinatal depression, on the other hand, lasts more than 14 days and impairs a woman's quality of life. **Table 1** lists common symptoms.

## INCIDENCE, ETIOLOGY, AND RISK FACTORS

The incidence of perinatal depressive disorder is surprisingly high in the United States.

**TABLE 1**

**Common symptoms of perinatal depression**

Patients with perinatal depression may present with some or many of the following:

- Sadness
- Depressed mood and energy
- Weepiness
- Impaired appetite or overeating
- Either excessive sleep or insomnia
- Feelings of unworthiness
- Anxiety
- Panic attacks
- Worrying constantly about the well-being of the baby, engaging in obsessive or ritualistic activities
- Being afraid to leave the house
- Feeling numb, wooden, and void of feelings
- Indifferent mood, with neither joy nor sadness
- No attachment or interest in the baby
- Inertia
- Hopelessness or thoughts of harming self or baby
- Somatic complaints
- Presentation of vague and continuous body symptoms that persist for weeks, including headaches, body pains, feeling of racing heart, constant fatigue
- Active anger and resentment of the baby
- Constant irritability and negative mood

**The mean rate of depression in the perinatal period is 11.5%**

One of every 7 to 10 pregnant women and 1 of every 5 to 8 postpartum women develop a depressive disorder, which is more than a half million women each year. The mean rate of depression during the perinatal period is 11.5%.[3]

Perinatal depression is thought to be the result of a complex interaction involving genetics, epigenetics, the neuroendocrine hypothalamic-pituitary-adrenal axis, and environmental and social factors. No race or socioeconomic group is spared.[4,5] Some women are more sensitive to changes in their reproductive hormone levels during pregnancy and after delivery, which may make them more susceptible to perinatal depression. Some may also have an unrecognized underlying mood disorder.[2]

Risk factors for perinatal depression include:

- A history of depressive, bipolar, or anxiety disorders
- A family history of depressive disorders or perinatal disorders
- An unwanted or teenage pregnancy
- A multiple birth
- A difficult or traumatic pregnancy or birth
- An ongoing health problem with the baby
- A lack of social support with low socioeconomic status and financial difficulties
- A history of physical or sexual abuse
- A diagnosis of substance abuse disorder.[3,6–8]
- American Indian/Alaska and Hawaii Native heritage; these groups have a 30% higher incidence of perinatal depression.

Of note, other perinatal mental health conditions such as anxiety disorders, bipolar spectrum disorder, or postpartum psychosis may also occur. Perinatal anxiety disorders are common and can frequently coexist with depressive disorders.[9] In patients with pre-existing bipolar disorder, depressive, hypomanic, and manic episodes can occur, especially in the setting of sleep deprivation.[2]

Postpartum psychosis is characterized by a delirium-like presentation with disorganized behavior and psychotic symptoms and is considered a medical emergency, though it is a rare event. It may also, in rare cases, be accompanied by hallucinations that tell the woman to harm herself or her baby.[10]

## SERIOUS CONSEQUENCES IF UNTREATED

Untreated perinatal depression has serious consequences for mothers, their children and families, and society as a whole. During pregnancy, untreated depression is associated with a higher incidence of preterm delivery, preeclampsia, low birth weight, behavior disturbances in the baby at birth, and maternal suicide.[11,12]

Untreated depression during the postpartum period also has repercussions for both the mother and her baby. For the mother, it can lead to intense sadness, marked anxiety, and

a lack of interest in life and the child, often resulting in poor or absent maternal bonding with the infant. It is also associated with failure to initiate breastfeeding or a shortened duration of breastfeeding.[13]

When perinatal depression is severe, the mother's symptoms can progress to ideation of self-harm or of harming the infant, or at its worst, suicide or infanticide. Suicide is the second-leading cause of death for women in the postpartum period, leading to 20% of deaths during the first year after birth.[14,15] Thoughts of harming the baby occur in 41% of depressed mothers vs 7% of controls.[16] Although infanticide is a rare event, at least 1 case occurs every 3 days in this country.[17]

The absence of maternal bonding can have a significant impact on the infant's development. Numerous controlled studies have shown that children born to mothers with untreated postpartum mood disorders are more likely to have impaired cognitive, behavioral, and emotional development and delayed social and communication skills.[18–21] The problem then becomes a serious public health issue, with consequences spanning several generations.

## SCREENING IS KEY TO DIAGNOSING PERINATAL DEPRESSION

Perinatal depression is frequently missed because many of the signs, including acute and chronic stress, lack of sleep, and hormone swings, are present in all pregnant women. In addition, new mothers may not admit to having symptoms because they feel an overwhelming sense of shame and embarrassment about being "less of a mother" than they believe they should be.[22] Furthermore, family members may not understand that their partner's or relative's behavior constitutes a clinical depression that requires treatment.

Primary care clinicians can dramatically increase the rate of detection and diagnosis by screening pregnant and postpartum patients for mood and anxiety disorders. Trials in the United States have concluded that screening improves outcomes in the depressed mother.[23,24] Therefore, screening is recommended for all women in the perinatal period by a number of organizations, including the US Preventive Services Task Force (USPSTF),[25–27] the American College of Obstetricians and Gynecologists, the American Psychiatric Association, and the American Academy of Pediatrics.

One of the simplest and most reliable screening tools is the Edinburgh Postnatal Depression Scale (EPDS).[28] The EPDS is a cross-culturally validated 10-question form that a woman can complete in 2 to 3 minutes in a waiting room, online, or with a clinician. Sensitivity and specificity range from 70% to 88%,[29] and studies have found that the EPDS is twice as effective as a clinician's interview in detecting depression.[30]

The Patient Health Questionnaire (PHQ-9)[31] is also an effective tool for screening, but it does not contain questions about anxiety as the EPDS does.

It is also important to screen for intimate partner violence, which may contribute to or cause the patient's depression.

Pregnant women should be screened at the initial prenatal visit and again in the last trimester. Postpartum mothers should be screened during the 6-week postpartum visit and again by the primary care physician who takes over the care of the patient after the final postpartum visit. Birth classes, prenatal visits, postpartum checks, and monthly well-baby visits all provide easy points of contact with a woman before and after she gives birth.[24,25] Screening is now a covered medical expense during a medical visit, both under the Affordable Care Act and with private insurance.

**Suicide is the second-leading cause of death for women in the postpartum period**

Particular attention should be paid to women of color or those from lower socioeconomic groups since their incidence of perinatal depression is significantly higher, and inadequate research has been done to study effective remedies in these groups. Women from minority groups and women from lower socioeconomic communities suffer disproportionately from these failures to diagnose and treat.[32]

Once a patient screens positive, she should undergo further clinical evaluation to make the diagnosis of depression. It is important for screening programs to include follow-up and support systems.[25] Additionally, all women diagnosed with perinatal depression should be counseled that their condition is a medical illness, that there are good treatments, and that they are "no less of a mother" for experiencing it.

## BIOMARKERS PREDICT

Promising research is focusing on the use of biomarkers to predict which patients will develop perinatal depression. One set of studies identified 2 epigenetically modified genes that can predict with 80% accuracy if a woman will develop depression in the immediate postpartum period.[33,34] While further validation is needed, these studies indicate that in the future, women may be able to be screened for postpartum depression while still pregnant.

## PERINATAL DEPRESSION CAN BE PREVENTED IN SOME PATIENTS

The USPSTF reviewed 50 scientific studies that met their rigorous methodologic criteria and found good evidence that counseling interventions during pregnancy and the postpartum period are effective in preventing perinatal depression in some women.[35,36] Interventions were associated with a 39% decrease in the likelihood of perinatal depression in women who were at risk for depression and had been involved in therapeutic interventions before the onset of depression. Women who received counseling had one of the following risk factors: a personal or family history of depression, a history of physical or sexual abuse, socioeconomic insecurity, or recent negative life events.

**All women should be screened for depression before and after they give birth**

Two specific treatments had the greatest effect: interpersonal therapy and cognitive behavioral therapy, in either an individual or a group setting. Counseling sessions averaged 8 weeks in duration. The USPSTF concluded that counseling interventions can be effective in preventing perinatal depression in pregnant or postpartum women with an elevated risk of perinatal depression.[34]

## WHAT IS THE TREATMENT FOR PERINATAL DEPRESSION?

Although screening is important for detecting perinatal depression, screening itself is not sufficient to improve outcomes unless mechanisms are in place to respond to a positive screen, and treatment and follow-up occur. Individual psychotherapy and other modalities—such as postpartum support groups, family therapy, remote video conferencing, phone check-ins, and home visits with trained mental health providers—are often effective in treating these disorders without the use of medication.[5,24,36]

Primary care and internal medicine hospital departments and outpatient practices have had success in treating these patients using an integrated care model developed in a collaboration between the Health Resources and Services Administration and the Substance Abuse and Mental Health Services Administration.[37]

Despite progress in using nonpharmacologic modalities to treat perinatal depression, medication is sometimes necessary. In current practice, many women are often advised to stop taking all psychotropic medications when they become pregnant or breastfeed, but research has shown that a more nuanced and tailored approach is necessary. Many psychiatric medications have been shown to pose a low risk during pregnancy and lactation. Many reproductive psychiatrists have found that, for some women, taking medication is more advantageous to the mother's health and to the child's development than not taking it, given the data on the effects of untreated depression on pregnancy and child development.[13]

Thus, when a woman needs to consider taking medication during pregnancy and lactation, it is best to refer her to a psychiatrist or reproductive psychiatrist for care during the perinatal period. At this time, whether to take medication is a decision that the patient and her treating physicians should make after considering her unique circumstances and psychiatric history.[13,38,39]

Brexanolone, a new parenteral medication, was approved by the US Food and Drug Administration in March 2019 for moderate to severe depression.[40] Brexanolone has been studied in 2 multicenter, randomized, placebo-controlled trials[41] and can produce rapid and in some cases immediate symptom relief, including reducing acute suicidal ideation. At this point, the medication is infused under supervision over 3 days. Research continues to focus on developing an oral preparation that would allow a more practical and less costly route of administration.[40]

***Dedication**: This article is dedicated to Paul and Margaret Burke.*

## REFERENCES


1. **Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T**. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol 2005; 106(5 pt 1):1071–1083. doi:10.1097/01.AOG.0000183597.31630.db
2. **Henshaw C**. Mood disturbance in the early puerperium: a review. Arch Womens Ment Health 2003; 6(suppl 2):S33–S42. doi:10.1007/s00737-003-0004-x
3. **Ko JY, Rockhill KM, Tong VT, Morrow B, Farr SL**. Trends in postpartum depressive symptoms—27 states, 2004, 2008, and 2012. MMWR Morb Mortal Wkly Rep 2017; 66(6):153–158. doi:10.15585/mmwr.mm6606a1
4. **Couto TC, Brancaglion MY, Alvim-Soares A, et al**. Postpartum depression: a systematic review of the genetics involved. World J Psychiatry 2015; 5(1):103–111. doi:10.5498/wjp.v5.i1.103
5. **Meltzer-Brody S**. New insights into perinatal depression: pathogenesis and treatment during pregnancy and postpartum. Dialogues Clin Neurosci 2011; 13(1):89–100. pmid:21485749
6. **O'Hara MW, Swain AM**. Rates and risk of postpartum depression—a meta-analysis. Int Rev Psychiatry 1996; 8:37–54.
7. **Jeong HG, Lim JS, Lee MS, Kim SH, Jung IK, Joe SH**. The association of psychosocial factors and obstetric history with depression in pregnant women: focus on the role of emotional support. Gen Hosp Psychiatry 2013; 35(4):354–358. doi:10.1016/j.genhosppsych.2013.02.009
8. **Biaggi A, Conroy S, Pawlby S, Pariante CM**. Identifying the women at risk of antenatal anxiety and depression: a systematic review. J Affect Disord 2016; 191:62–77. doi:10.1016/j.jad.2015.11.014
9. **Fairbrother N, Young AH, Janssen P, Antony MM, Tucker E**. Depression and anxiety during the perinatal period. BMC Psychiatry 2015; 15:206. doi:10.1186/s12888-015-0526-6
10. **Bergink V, Rasgon N, Wisner KL**. Postpartum psychosis: madness, mania and melancholia in motherhood. Am J Psychiatry 2016; 173(12):1179–1188. doi:10.1176/appi.ajp.2016.16040454
11. **Jarde A, Morais M, Kingston D, et al**. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry 2016; 73(8):826–837. doi:10.1001/jamapsychiatry.2016.0934
12. **Field T, Diego M, Hernandez-Reif M**. Prenatal depression effects and interventions: a review. Infant Behav Dev 2010; 33(4):409–418. doi:10.1016/j.infbeh.2010.04.005
13. **Payne JL**. Psychopharmacology in pregnancy and breastfeeding. Psychiatr Clin North Am 2017; 40(2):217–238. doi:10.1016/j.psc.2017.01.001
14. **Lindahl V, Pearson JL, Colpe L**. Prevalence of suicidality during pregnancy and the postpartum. Arch Womens Ment Health 2005; 8(2):77–87. doi:10.1007/s00737-005-0080-1
15. **Orsolini L, Valchera A, Vecchiotti R, et al**. Suicide during perinatal period: epidemiology, risk factors, and clinical correlates. Front Psychiatry 2016; 7:138. doi:10.3389/fpsyt.2016.00138
16. **Jennings KD, Ross S, Popper S, Elmore M**. Thoughts of harming infants in depressed and nondepressed mothers. J Affect Disord 1999; 54(1–2):21–28. doi:10.1016/s0165-0327(98)00185-2
17. **Meyer CL, Oberman M**. Mothers who kill their children: understanding the acts of moms from Susan Smith to the "prom mom." New York, NY: NYU Press; 2001.
18. **Grace SL, Evindar A, Stewart DE**. The effect of postpartum depression on child cognitive development and behavior: a review and critical analysis of the literature. Arch Womens Ment Health 2003; 6(4):263–274. doi:10.1007/s00737-003-0024-6
19. **Pilowsky DJ, Wickramaratne P, Talati A, et al**. Children of depressed mothers 1 year after the initiation of maternal treatment: findings from the STAR*D-Child Study. Am J Psychiatry 2008; 165(9):1136–1147. doi:10.1176/appi.ajp.2008.07081286
20. **Dunkel Schetter C, Tanner L**. Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. Curr Opin Psychiatry 2012; 25(2):141–148. doi:10.1097/YCO.0b013e3283503680
21. **Mughal MK, Giallo R, Arnold PD, et al**. Trajectories of maternal distress and risk of child developmental delays: findings from the All Our Families (AOF) pregnancy cohort. J Affect Disord 2019; 248:1–12. doi:10.1016/j.jad.2018.12.132
22. **Edwards E, Timmons S**. A qualitative study of stigma among women suffering postnatal illness. J Mental Health 2009; 14(5):471–481.
23. **Leung SS, Leung C, Lam TH, et al**. Outcome of a postnatal depression screening programme using the Edinburgh Postnatal Depression Scale: a randomized controlled trial. J Public Health (Oxf) 2011; 33(2):292–301. doi:10.1093/pubmed/fdq075
24. **Yawn BP, Olson AL, Bertram S, Pace W, Wollan P, Dietrich AJ**. Postpartum depression: screening, diagnosis, and management programs 2000 through 2010. Depress Res Treat 2012; 2012:363964. doi:10.1155/2012/363964
25. **US Preventive Services Task Force**. Final recommendation statement: depression in adults: screening. http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/depression-in-adults-screening1. Accessed April 4, 2020.
26. **Siu AL, US Preventive Services Task Force, Bibbins-Domingo K, et al**. Screening for depression in adults: US Preventive Services Task Force recommendation statement. JAMA 2016; 315(4):380–387. doi:10.1001/jama.2015.18392
27. **O'Connor E, Rossom RC, Henninger M, Groom HC, Burda BU**. Primary care screening for and treatment of depression in pregnant and postpartum women: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016; 315(4):388–406. doi:10.1001/jama.2015.18948
28. **Cox JL, Holden JM, Sagovsky R**. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987; 150:782–786. doi:10.1192/bjp.150.6.782
29. **Cox JL, Chapman G, Murray D, Jones B**. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord 1996; 39(3):185–189. doi:10.1016/0165-0327(96)00008-0
30. **Evins GG, Theofrastous JP, Galvin SL**. Postpartum depression: a comparison of screening and routine clinical evaluation. Am J Obstet Gynecol 2000; 182(5):1080–1082. doi:10.1067/mob.2000.105409
31. **Kroenke K, Spitzer RL, Williams JB**. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16(9):606–613. doi:10.1046/j.1525-1497.2001.016009606.x
32. **Kozhimannil KB, Trinacty CM, Busch A, Huskamp HA, Adams AS**. Racial and ethnic disparities in postpartum depression care among low-income women. Psychiatr Serv 2011; 62(6):619–625. doi:10.1176/ps.62.6.pss6206_0619
33. **Guintivano J, Arad M, Gould TD, Payne JL, Kaminsky ZA**. Antenatal prediction of postpartum depression with blood DNA methylation biomarkers. Mol Psychiatry 2014; 19(5):560–567. doi:10.1038/mp.2013.62
34. **Osborne L, Clive M, Kimmel M, et al**. Replication of epigenetic postpartum depression biomarkers and variation with hormone levels. Neuropsychopharmacology 2016; 41(6):1648–1658. doi:10.1038/npp.2015.333
35. **US Preventive Services Task Force; Curry SJ, Krist AH, Owens DK, et al**. Interventions to prevent perinatal depression. US Preventive Services Task Force recommendation statement. JAMA 2019; 321(6):580–587. doi:10.1001/jama.2019.0007
36. **Dennis CL, Hodnett E, Kenton L, et al**. Effect of peer support on prevention of postnatal depression among high risk women: multisite randomised controlled trial. BMJ 2009; 338:a3064. doi:10.1136/bmj.a3064
37. **SAMHSA-HRSA Center for Integrated Health Solutions**. Behavioral health in primary care. https://www.integration.samhsa.gov/integrated-care-models/behavioral-health-in-primary-care. Accessed April 4, 2020.
38. **Wisner KL, Gelenberg AJ, Leonard H, Zarin D, Frank E**. Pharmacologic treatment of depression during pregnancy. JAMA 1999; 282(13):1264–1269. doi:10.1001/jama.282.13.1264
39. **Yonkers KA, Wisner KL, Steward DE, et al**. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Obstet Gynecol 2009; 114(3):703–713. doi:10.1097/AOG.0b013e3181ba0632
40. **US Food and Drug Administration**. FDA approves first treatment for postpartum depression. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633919.htm. Accessed April 4, 2020.
41. **Meltzer-Brody S, Colquhoun H, Riesenberg R, et al**. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet 2018; 392(10152):1058–1070. doi:10.1016/S0140-6736(18)31551-4


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REVIEW

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# Bronchoscopic lung volume reduction with valves: What should the internist know?

## ABSTRACT

Traditional therapies for emphysema such as bronchodilators and anti-inflammatory drugs have limited value due to permanent structural changes in the emphysematous lung that result in hyperinflation. Surgical lung volume reduction partially corrects hyperinflation by removing emphysematous lung and is an option in selected patients, but it carries a risk of morbidity and death. Valve therapy is a less-invasive option that involves bronchoscopic implantation of 1-way valves in emphysematous lung segments to allow air flow and mucus clearance in the direction of central airways. The authors review the rationale, evidence, and applications of valve therapy.

## KEY POINTS

After valve placement, the 1-way flow gradually leads to selective de-aeration and collapse of treated areas, thus reducing hyperinflation.

The US Food and Drug Administration has approved valve therapy for the treatment of emphysema.

This procedure may work best for patients who have heterogeneous involvement and complete separation between affected and unaffected lobes.

Dr. Machuzak has disclosed consulting for Olympus.

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Treatment of emphysema remains challenging. Standard therapies for chronic obstructive pulmonary disease (COPD) such as bronchodilators, anti-inflammatory drugs, oxygen, and pulmonary rehabilitation are of limited efficacy in the face of permanent structural changes of emphysema in the lung.

Some patients can get some relief from procedures that reduce lung volume to restore normal mechanics of the diaphragm and chest wall.[1] Today, lung volume reduction is done primarily through surgery or by bronchoscopically placing 1-way valves in the airways.

In this review, we provide a clinical overview of valve therapy, the only approved bronchoscopic lung volume reduction procedure in the United States for palliation of dyspnea in selected patients with emphysema.

## LUNG CHANGES IN EMPHYSEMA

Emphysema is progressive and characterized by destruction of alveolar walls distal to the terminal bronchioles, resulting in permanent enlargement of airspaces. Loss of connective tissue corresponds to loss of elastic lung recoil and reduced tethering of the small airways with consequent air trapping, hyperinflation, and collapse of small airways.

Hyperinflation increases the work of breathing by pushing the tidal volume loop to the less compliant portion of the respiratory volume-pressure curve, so that patients must generate more pressure to breathe in or out (**Figure 1**).[2]

Hyperinflation and air trapping are aggravated during exertion in a process called

*dynamic hyperinflation*, caused by progressive shortening of expiratory time at high respiratory rates and consequent impaired lung emptying. At increased lung volumes, respiratory muscle fibers are shortened, creating a mechanical disadvantage in the ability to produce force. Moreover, in heterogeneous emphysema, in which emphysema is localized to a certain region of the lung, hyperinflation of the more affected areas results in compression atelectasis of other "healthier" areas, creating unfavorable ventilation-perfusion matching and poor gas exchange.[1]

Hyperinflation and air trapping are often seen on chest imaging and can be recognized on pulmonary function testing as increases in total lung capacity (TLC), residual volume (RV), and ratio of RV to TLC.

## A BRIEF HISTORY OF LUNG VOLUME REDUCTION

In 1959, Brantigan et al[3] reported that surgically removing emphysematous lung increased elastic recoil, increased radial traction on airways and restoration of a more normal configuration of the respiratory muscles. But despite subsequent improvements in surgical technique,[4] lung volume reduction surgery produced varying clinical results and had a mortality rate of 4% to 17%.[5]

Uncertainty persisted about the risks vs benefits of this surgery, the degree and duration of clinical improvement, and patient selection criteria.

**The National Emphysema Treatment Trial**[6] of the US Centers for Medicare and Medicaid Services and the National Heart, Lung, and Blood Institute, a multicenter randomized controlled trial, was designed to address these issues by assessing survival and exercise capacity 2 years after lung volume reduction surgery in 1,218 patients randomized (after pulmonary rehabilitation) to either undergo the procedure or continue medical therapy.

Key inclusion criteria were:

- Severe emphysema: forced expiratory volume in 1 second ($FEV_1$) ≤ 45% of predicted, TLC ≥ 100% of predicted, RV ≥ 150% of predicted
- Resting partial pressure of arterial carbon dioxide ($Paco_2$) ≤ 60 mm Hg

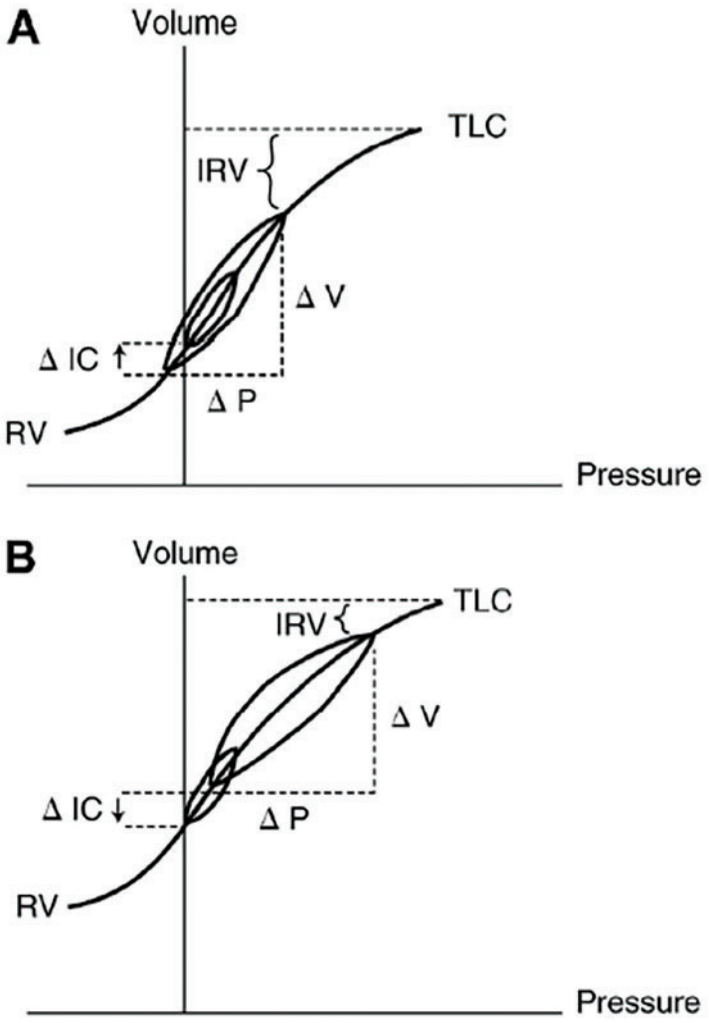


**Figure 1.** Pressure-volume loops while breathing at rest and during exercise in a healthy individual (A) and in a patient with chronic obstructive pulmonary disease (COPD) (B). Inspiratory capacity (maximum volume of breath that can be taken in after exhalation) increases in healthy people during exercise owing to a fall in lung volume at the end of exhalation. The volume loop during normal breathing is situated in the central linear portion of the pressure-volume relationship, which means that relatively small changes in pressure produce comparatively large changes in volume. In COPD, inspiratory capacity declines due to progressive air-trapping during exercise; thus, patients have to breathe at the upper and less compliant portion of the pressure-volume relationship. This means that increasingly higher pressures must be generated for any given breath, increasing the work of breathing.

IC = inspiratory capacity; IRV = inspiratory reserve volume; P = pressure; RV = residual volume; TLC = total lung capacity; V = volume

**TABLE 1**

**Bronchoscopic approaches to lung volume reduction**

| |
|---|
| Valve therapy: Zephyr and Spiration |
| Lung volume reduction coils: PneumRx[10] |
| Airway bypass stents (abandoned due to lack of efficacy and high complication rate)[11] |
| Bronchoscopic thermal vapor ablation (inducing scarring in the diseased airways leading to lung volume reduction)[12] |
| Biologic or polymeric lung volume reduction: fibrin-thombin mixtures, glue, polymeric foam sealant (the AeriSeal System)[13–16] |

- Resting partial pressure of arterial oxygen ($Pao_2$) on room air ≥ 45 mm Hg
- Body mass index ≤ 31 kg/m$^2$ for men, ≤ 32 kg/m$^2$ for women
- Abstinence from smoking for at least 6 months
- Completion of pulmonary rehabilitation.

Exclusion criteria were significant cardiac morbidity, pulmonary hypertension (mean pulmonary artery pressure ≥ 35 mm Hg or systolic pulmonary artery pressure ≥ 45 mm Hg), severe functional impairment (6-minute walk distance < 140 m), chronic prednisone use, and need for high volumes of supplemental oxygen at baseline (≥ 6 L/minute).

**In emphysema, hyperinflation increases the work of breathing**

At an early stage in the trial, a high-risk group with a 30-day mortality rate of 16% was identified. These patients had very severe homogeneous emphysema ($FEV_1$ < 20% of predicted, emphysema distributed evenly throughout the lungs), or poor gas exchange (diffusion capacity < 20% of predicted). These features were added as trial exclusion criteria.[6]

Overall, the National Emphysema Treatment Trial showed an improvement in exercise capacity in the surgery group and no difference in mortality rate between the surgical and medical therapy groups, even after excluding the high-risk group. In subgroup analysis, patients with low baseline exercise capacity (determined by cardiopulmonary exercise testing before surgery) and upper-lobe-predominant emphysema had lower mortality risk if they received surgery (risk ratio for death 0.47, $P$ = .005). In contrast, a higher mortality rate was observed in the surgical group in the subset of patients with high baseline exercise capacity and homogeneous emphysema (risk ratio 2.06, $P$ = .02).[7] These findings were reaffirmed after a median follow-up of 5 years.[8]

Therefore, lung volume reduction surgery, when performed in a select group of patients with heterogeneous emphysema and low baseline exercise capacity, is a therapeutic option that prolongs survival in COPD. Patients with heterogeneous emphysema and high exercise tolerance did not derive survival benefit, although their quality-of-life scores improved.

## THE NEED FOR NONSURGICAL OPTIONS

Lung volume reduction surgery has several limitations. It is associated with considerable rates of mortality (90-day mortality rate 5.2% for patients not at high risk) and morbidity (prolonged hospital stay and air leak in up to 50% of patients).[7] A study performed between 2007 and 2013 showed that the in-hospital mortality rate was 5.5% and that 5.5% of patients required tracheostomy.[9]

While suboptimal patient selection may also have played a role in poor outcomes in this report (eg, secondary pulmonary hypertension, a relative contraindication to this surgery, was prevalent in surgery patients), alternative nonsurgical approaches to lung volume reduction are desirable.

Over the past 3 decades, several nonsurgical methods have been devised (**Table 1**).[10–16] Among these, endobronchial valve implantation (valve therapy) is considered the most promising and is currently the only approved bronchoscopic lung volume reduction procedure in the United States.

## VALVE THERAPY

Valve therapy involves implantation of 1-way valves that allow air flow and mucus clearance in the direction of central airways—out, but not in. The 1-way flow gradually leads to selective de-aeration and collapse of treated areas and reduces hyperinflation and air trapping, theoretically conducive to all the gains

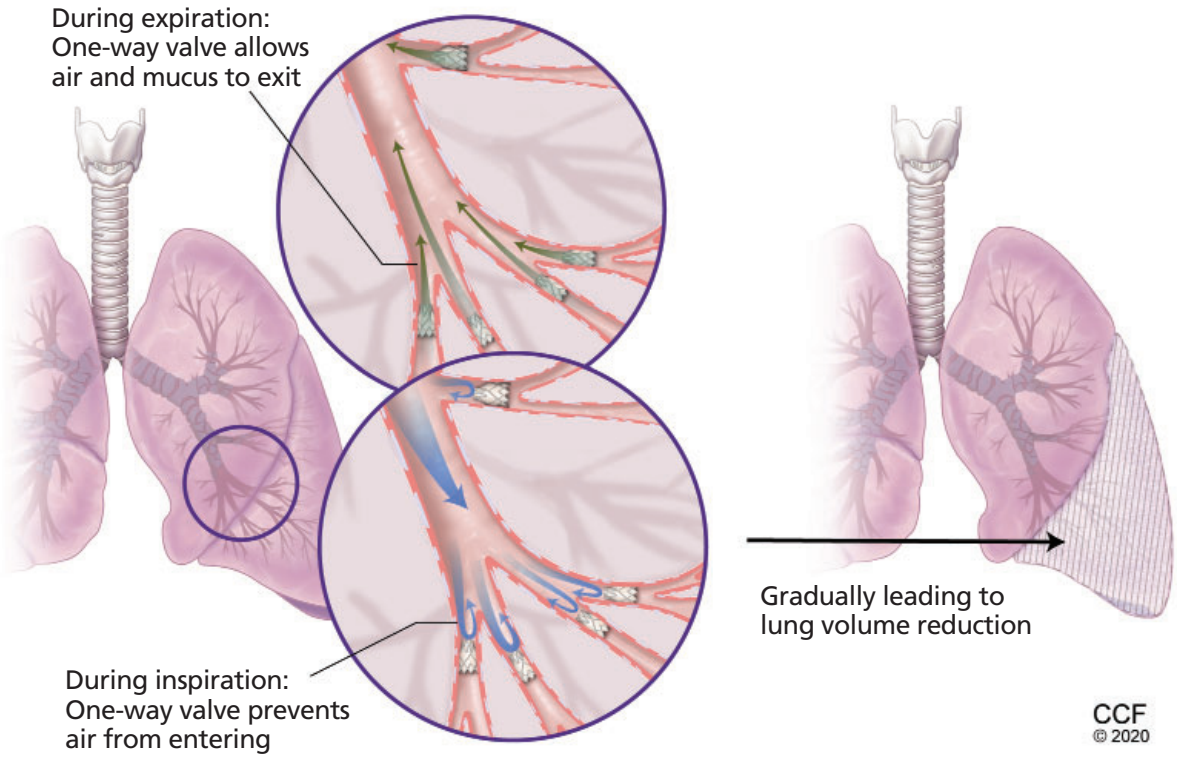


**Figure 2.** Valve therapy for bronchoscopic lung volume reduction involves implantation of 1-way valves to allow air flow and mucus clearance outward to central airways. The 1-way flow leads to selective de-aeration and collapse of treated areas, reducing hyperinflation and air trapping. Unlike lung volume reduction surgery, the procedure is performed unilaterally due to the inherent procedural risk of pneumothorax.

from lung volume reduction surgery (**Figure 2**). Valve therapy, unlike in lung volume reduction surgery, is performed unilaterally due to the inherent procedural risk of pneumothorax.

There are currently 2 valve therapy options approved in the United States: the Zephyr valve system (PulmonX, Redwood City, CA) and the Spiration valve system (Olympus, Center Valley, PA).

### The VENT trial of valve therapy

The Endobronchial Valve for Emphysema Palliation Trial (VENT) was the first multicenter randomized controlled trial to assess the efficacy and safety of lung volume reduction with Zephyr endobronchial valves.[17] The trial had 2 cohorts, 1 in the United States and 1 in Europe.

In the US cohort, 321 patients with severe and very severe heterogeneous emphysema were randomized in a 2:1 fashion to undergo valve placement (n = 220) or medical treatment (n = 101). Compared with medical therapy, the valve group had a modest 6.8% between-group difference in $FEV_1$ and a 5.8% difference in 6-minute walk distance. Although statistically significant, these improvements were not considered as reaching a minimal clinically important difference. Adverse events, including pneumothorax, were more common in the valve therapy group (6.1% vs 1.2%, $P = .08$).[17] Similar results were obtained in the European cohort.[18]

Given the modest benefit and substantial risk of adverse events, the US Food and Drug Administration recommended against approval of the Zephyr endobronchial valve based on the results of VENT.[17]

### Further lessons from VENT

Post hoc analyses from VENT laid the groundwork for trials that delineated the role of endobronchial valve implantation in the treat-

**Endobronchial valve implantation is currently the only approved bronchoscopic lung volume reduction procedure in the United States**

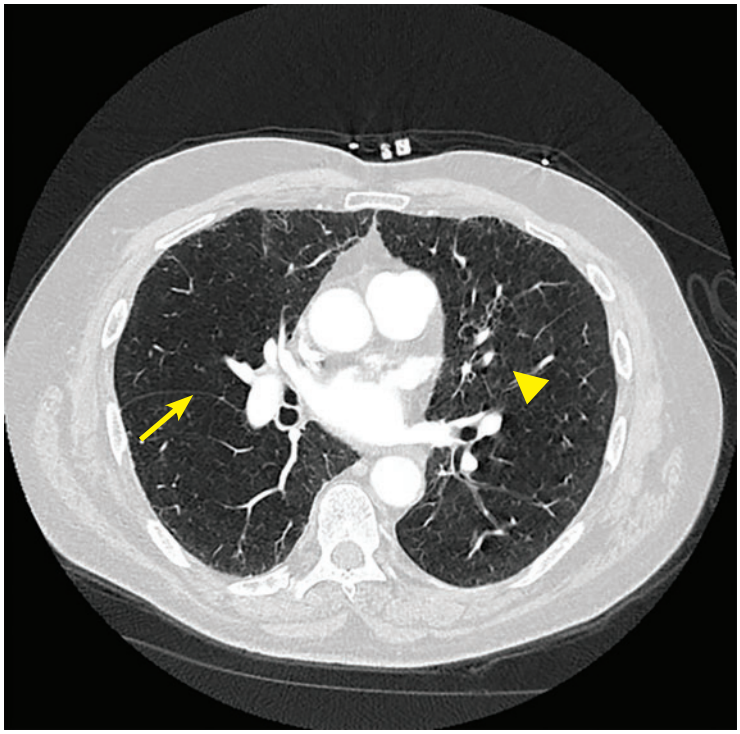

**Figure 3.** Specialized computed tomography software allows objective quantification of fissure integrity. The arrow indicates a complete fissure, and the arrowhead indicates incomplete fissure. Collateral ventilation is considered highly likely when the fissure is incomplete by > 20% across its span. This is a contraindication to valve therapy.

ment of emphysema.

First, improvement in lung function and 6-minute walk distance correlated with the heterogeneity of emphysema: ie, the higher the difference of emphysematous involvement between the treated lobe and neighboring lobes, the more robust the clinical improvement.[17]

Second, the presence of complete fissures between the lobes was associated with greater reductions in lung volume and improvement in lung function.[17] This finding emphasized the importance of absence of collateral ventilation in determining success of the procedure. In essence, despite endobronchial occlusion, the treated lobe could back-fill from the neighboring lobes through collateral ventilation, thereby abrogating lung volume reduction. Absence of any interruption in the pleural lining between the lobes (so-called "fissure integrity") was a surrogate for the absence of collateral ventilation.

Third, complete lobar occlusion was necessary for optimal results. In the VENT study, 44% of the patients had incomplete occlusion of the treated lobe, which likely lessened the benefits from the procedure.[17]

Fissure integrity (a surrogate for absence of collateral ventilation) can be assessed visually or by software analysis on high-resolution CT (**Figure 3**). Collateral ventilation can be directly investigated with diagnostic tools that can measure pressure and flow within the lung.

The Chartis Pulmonary Assessment System (PulmonX) can assess for collateral ventilation during bronchoscopy. The system consists of a balloon catheter that is used to occlude the target airway. When the balloon is inflated at the orifice of the target airway, only unidirectional (expiratory) airflow is allowed through a catheter built into the balloon. The presence of continuous expiratory airflow after balloon occlusion indicates the presence of collateral ventilation. In the absence of collateral ventilation, expiratory flow diminishes over time.

## CLINICAL TRIALS OF VALVE THERAPY AFTER THE VENT STUDY

There were 7 randomized controlled trials of the clinical efficacy of valve therapy with designs that considered the experience from the VENT study (**Table 2**).[19–25] Five of these trials used the Zephyr system,[19–23] and 2 used the Spiration system.[24,25] All assessed collateral ventilation during bronchoscopy using fissure analysis, the Chartis system, or both. All but 1 trial[21] enrolled patients with heterogeneous emphysema in whom the treated lobe had 10% to 15% more destruction from emphysema than the neighboring lobes, based on quantitative CT analysis. One trial enrolled both heterogeneous and homogeneous emphysema patients.[20]

These trials utilized clinical responder analysis as efficacy end points, defined as the proportion of patients who exhibited improvements over the minimal clinically important difference—ie, the smallest measured difference that the patient would deem significant, representing the value patients placed on the change.[26] Several thresholds were used in these trials.[26–29]

These 7 trials recruited patients with severe to very severe COPD (mean $FEV_1$ 28% to 31% of predicted) and severe hyperinflation (mean TLC 130–144 and RV 216–277% of predicted).[19–24] Compared with baseline values, patients who received valve therapy experienced lung volume reduction (mean RV reduction 0.26–0.86 L), improvement in lung function (mean increase in $FEV_1$ 8.7% to 20.9% of predicted), exertional capacity (mean intergroup difference in 6-minute walk distance 6.9–60 m) and quality-of-life scores (mean reduction of 7.2–17.3 in St. George Respiratory Questionnaire score).

Pneumothorax was the most common serious complication, occurring in 8.6% to 34.3% of patients. Some patients required the removal of valves due to recurrent pneumothorax. Two-thirds of cases occurred within the first 3 days. Consequently, patients are typically hospitalized for 3 to 5 days in anticipation of this adverse event.

Other complications included COPD exacerbations, arrhythmia, pneumonia, respiratory failure, empyema, hemoptysis, chest pain, valve expectoration or migration, bronchial trauma, and bronchial torsion. Importantly, death related to postprocedural pneumothorax was reported in some trials.

In 6 of the 7 trials, investigators and patients were not blinded to group assignment, thus introducing performance bias. In the double-blinded trial by Davey et al,[19] a sham procedure was performed for the control group; this was the only study not to show a significant improvement in quality-of-life scores.[19] The design of the study by Davey et al provided insight into the relative importance of performing both high-resolution CT and the Chartis procedure to assess collateral ventilation. The presence of collateral ventilation was confirmed by the Chartis system when compared with high-resolution CT, but the decision to proceed with bronchoscopic lung volume reduction was based on findings on high-resolution CT. Accordingly, 4 of the 25 patients who had intact fissures on CT were found to have collateral ventilation on assessment with the Chartis system. These patients did not experience complete lobar collapse and consequent benefits from the procedure.[19] Therefore, concurrent use of the 2 assessment modalities has been advocated to increase the detection of collateral ventilation.

In the Endobronchial Valves for Emphysema Without Interlobar Collateral Ventilation (STELVIO) trial, valve replacement was needed in 17% of patients and valve removal in 22% due to recurrent pneumothorax, lack of clinical efficacy, or malpositioning.[20] This finding underscores the importance of continued follow-up and personalization of care for valve therapy patients. Initial experience suggested that valve therapy worked better in patients with heterogeneous emphysema, as was seen in studies of lung volume reduction surgery.[20]

Both the STELVIO study and the Improving Patient Outcomes by Selective Implantation of the Zephyr EBV Study (IMPACT)[21] recruited patients with homogeneous emphysema, with STELVIO using a higher threshold for air-trapping (RV > 200%) for inclusion.[20,21] A meta-analysis of these data for homogeneous patients[30] suggested reduction in lung volume reduction and improvement in lung function, walking distance, and quality-of-life scores comparable to that seen in patients with heterogeneous emphysema. These findings are promising for patients with homogeneous emphysema and severe hyperinflation.

In the 2 randomized controlled trials using the Spiration valve system,[24,25] fissure integrity was assessed by CT. Patients were included in the trial if they had greater than 90% fissure integrity. Bronchoscopic confirmation of the absence of collateral ventilation was not required. Improvements in lung function and quality of life were similar to those in trials of the Zephyr valve. Of note, 6-minute walk distance did not improve compared with controls in the EMPROVE trial (Improving Lung Function in Severe Heterogeneous Emphysema With the Spiration Valve System).[25] This was attributed to a lack of pulmonary rehabilitation in the study protocol. The pneumothorax rate was 7.6% to 28.3% in these 2 trials.[24,25]

**Pneumothorax was the most common serious complication of endobronchial valve placement**

## PATIENT SELECTION IS KEY

Valve therapy is not for all emphysema patients. Strict adherence to clinical selection guidelines is necessary for optimal results.

Internists should consider referral for lung

**TABLE 2**

## Randomized controlled trials of bronchoscopic lung volume reduction

| | BELIEVER-HIFI[19] 2015 (N=50) | STELVIO[20] 2015 (N=68) | IMPACT[21] 2016 (N=93) | TRANSFORM[22] 2017 (N=97) | LIBERATE[23] 2018 (N=190) | REACH[24] 2019 (N=107) | EMPROVE[25] 2018 (N=172) |
|---|---|---|---|---|---|---|---|
| Design | Single-center 1:1; BLVR vs sham procedure over 3 months | Single-center 1:1;BLVR vs standard care over 6 months | Multicenter 1:1; BLVR vs standard care over 3 months | Multicenter 2:1; BLVR vs standard of care over 3 months | Multicenter 2:1; BLVR vs standard care over 12 months | Multicenter 2:1; BLVR vs standard care over 3 months | Multicenter 2:1; BLVR vs standard care over 12 months |
| Emphysema type | Heterogeneous[a] | Heterogeneous, homogeneous | Homogeneous[b] | Heterogeneous[c] | Heterogeneous[d] | Heterogeneous[d] | Heterogeneous[c] |
| Valve system | Zephyr | Zephyr | Zephyr | Zephyr | Zephyr | Spiration | Spiration |
| Pulmonary function test criteria | $FEV_1 \leq 50\%$<br>TLC ≥ 100%<br>RV ≥ 150% | $FEV_1 \leq 60\%$<br>TLC ≥ 100%<br>RV ≥ 150% | $FEV_1 \leq$ 15–45%<br>TLC ≥ 100%<br>RV ≥ 200% | $FEV_1 \leq$ 15–45%<br>TLC ≥ 100%<br>RV ≥ 180% | $FEV_1 \leq$ 15–45%<br>TLC ≥ 100%<br>RV ≥ 150%<br>DLCO ≥ 20% | $FEV_1 \leq 45\%$<br>TLC ≥ 100%<br>RV ≥ 150% | $FEV_1 \leq 45\%$<br>TLC ≥ 100%<br>RV ≥ 150% |
| Collateral ventilation, fissure integrity assessment | High-resolution CT | Chartis system | Chartis system | Chartis system | Chartis system | High-resolution CT | High-resolution CT |
| Clinical outcome, change from baseline | | | | | | | |
| $FEV_1$, % of predicted | 8.7 | 20.9 | 13.7 | 20.7 | 17.1 | 13.5 | 12.1 |
| 6-min walk distance (m) | 25 | 60 | 22.6 | 36.2 | 12.9 | 27.1 | 6.9 |
| Reduction in RV (L) | 0.26 | 0.86 | 0.42 | 0.66 | 0.49 | 0.52 | 0.36 |
| Quality of life score[e] | 8.6 | 17.3 | 8.6 | 7.2 | 7.5 | 7.6 | 9.5 |
| Pneumothorax occurrence, % | 8.6 | 17.6 | 27.9 | 23 | 34.3 | 7.6 | 12.4 |

[a] Defined as a National Emphysema Treatment Trial score of > 2 and a difference of > 1 emphysema score from ipsilateral lobes. Emphysema score ranges from 0–4; 0 represents absence of emphysema, and 1–4 represents quartiles of emphysematous lung involvement. For example, a score of 3 means 50% to 75% involvement with emphysema.
[b] Defined as a < 15% difference in destruction score by quantitative high-resolution computed tomography (CT).
[c] Defined as a > 10% difference in destruction score by quantitative high-resolution computed tomography.
[d] Defined as a ≥ 15% difference in destruction score by quantitative high-resolution computed tomography.
[e] St. George Respiratory Questionnaire score.

DLCO = diffusing capacity for carbon monoxide; $FEV_1$ = forced expiratory volume in 1 second; RV = residual volume; TLC = total lung capacity

volume reduction for patients with severe emphysema and poor quality of life despite optimal pharmacologic treatment and pulmonary rehabilitation.

The key elements for patient selection for valve therapy are listed in **Table 3**.

Valve therapy is approved for patients with severe obstruction, hyperinflation, and air trapping and with no collateral ventilation to ensure complete lobar collapse. Collateral ventilation is assessed serially by high-resolution CT and the Chartis procedure before placement of the Zephyr valve. For the Spiration valve system, this is accomplished visually using high-resolution CT, and fissure integrity greater than 90% is required. For the Zephyr valve, if the fissure analysis indicates less than 80% completeness of the fissure adjacent to the target lobe, the likelihood of collateral ventilation is high enough that

the patient should not be considered for valve therapy. For fissure integrity between 80% and 95%, patients undergo the Chartis procedure as the definitive diagnostic study for collateral ventilation. Patients with fissure integrity of 95% or greater can proceed to valve placement without the Chartis procedure.

Valves are placed in the lobe with the highest emphysema destruction score and with a greater than 10% to 15% difference compared with the neighboring lobe. These analyses are available through software systems that automatically assess fissure integrity and degree of emphysematous destruction based on x-ray attenuation.

## CONCLUSION AND FUTURE DIRECTIONS

While valve therapy is a revolutionary advance in emphysema treatment, several issues deserve special attention.

First, when selection criteria are followed, only a minority of patients qualify for the procedure, principally due to lack of fissure integrity and thus the presence of collateral ventilation. For instance, in a multicenter randomized controlled trial of the Zephyr valve in patients with heterogeneous emphysema,[23] of the 909 patients screened, only 190 qualified for the procedure (280 did not meet destruction score and heterogeneity criteria, 156 did not meet pulmonary function test criteria, and 65 had positive collateral ventilation, among other reasons).[23]

Consequently, patients should be informed about the need to have a thorough evaluation to determine candidacy. The evaluation should be holistic, exploring other options including maximizing current medical therapy, pulmonary rehabilitation, lung volume reduction surgery, and lung transplant.

Second, the impact of endobronchial valve placement on mortality rates in emphysema has not been established. None of the valve trials had death as an end point, but procedure-related deaths have been reported. The initial reports regarding mortality are encouraging[31,32] but not conclusive due to the absence of an appropriate control group.

Third, valve therapy is associated with less periprocedural morbidity compared with lung volume reduction surgery. Nonetheless, surgery remains the treatment gold standard, with established benefits for selected patients. Although air leak remains very common after lung volume reduction surgery, perioperative mortality has been drastically reduced in experienced centers.[33–36] The CELEB study (ISRCTN19684749) in the United Kingdom is prospectively comparing surgery vs valve placement; it completed recruitment in March 2020 and will provide important clinical insight to patient selection.[37] Even so, most patients who do not qualify for valve therapy due to collateral ventilation will remain viable candidates for lung volume reduction surgery.

Fourth, the clinical trials to date have not addressed the effects of the procedure on exacerbations and on the need for less-intense pharmacotherapy. Since the procedure is as-

**TABLE 3**

### Selection criteria for valve therapy in emphysema

| |
|---|
| Severe airflow obstruction:<br>$FEV_1$ between 15% and 45% of predicted |
| Severe air trapping and hyperinflation:<br>TLC > 100% and RV > 175% of predicted |
| Severe emphysematous destruction in target lobe:<br>> 50% involvement |
| Absence of collateral ventilation between target lobe and neighboring lobe or lobes |
| Adequate gas exchange:<br>diffusion capacity > 20% of predicted, $PaCO_2$ < 50 mm Hg,<br>$PaO_2$ > 45 mm Hg at baseline |
| No history of frequent severe exacerbations:<br>≥ 2 hospitalizations over the past year |
| Absence of clinically significant sputum production:<br>"significant" production, > 4 tablespoons per day |
| No significant comorbidities:<br>eg, cor pulmonale, ejection fraction < 45%,<br>recent myocardial infarction |
| No prior lung volume reduction surgery, lobectomy, lung transplant |

$FEV_1$ = forced expiratory volume in 1 second; $PaCO_2$ = partial arterial pressure of carbon dioxide; $PaO_2$ = partial arterial pressure of oxygen; RV = residual volume; TLC = total lung capacity

Adapted from reference 23.

sociated with exacerbations of COPD, studies with longer follow-up are needed to assess the end point of COPD exacerbations, in particular.

Finally, the cost-effectiveness of the bronchoscopic procedure has not yet been established, although preliminary estimates provide optimisim.[38]

Valve therapy offers new hope for palliation for some patients with emphysema. A recent iteration of the Global Initiative for Chronic Obstructive Lung Disease report included valve therapy in the treatment algorithm.[39] The treatment also represents an advance in personalized care for COPD. Patient selection, procedural expertise, and postprocedural care are equally important components of a successful outcome. We recommend that COPD patients undergo a thorough evaluation in specialized centers to determine the appropriate therapy for optimal outcome.

## REFERENCES


1. **Russi EW, Stammberger U, Weder W**. Lung volume reduction surgery for emphysema. Eur Respir J 1997; 10(1):208–218. doi:10.1183/09031936.97.10010208
2. **O'Donnell DE**. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2006; 3(2):180–184. doi:10.1513/pats.200508-093DO
3. **Brantigan OC, Mueller E, Kress MB**. A surgical approach to pulmonary emphysema. Am Rev Respir Dis 1959; 80(1, Part 2):194–206. doi:10.1164/arrd.1959.80.1P2.194
4. **Cooper JD, Patterson GA, Sundaresan RS, et al**. Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. J Thorac Cardiovasc Surg 1996; 112(5):1319–1330. doi:10.1016/S0022-5223(96)70147-2
5. **Geddes D, Davies M, Koyama H, et al**. Effect of lung-volume-reduction surgery in patients with severe emphysema. N Engl J Med 2000; 343(4):239–245. doi:10.1056/NEJM200007273430402
6. **National Emphysema Treatment Trial Research Group; Fishman A, Fessler H, Martinez F, et al**. Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med 2001; 345(15):1075–1083. doi:10.1056/NEJMoa11798
7. **Fishman A, Martinez F, Naunheim K, et al; National Emphysema Treatment Trial Research Group**. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003; 348(21):2059–2073. doi:10.1056/NEJMoa030287
8. **Naunheim KS, Wood DE, Mohsenifar Z, et al; National Emphysema Treatment Trial Research Group**. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg 2006; 82(2):431–443. doi:10.1016/j.athoracsur.2006.05.069
9. **Attaway AH, Hatipoglu U, Murthy S, Zein J**. Lung volume reduction surgery in the United States from 2007 to 2013: increasing volumes and reason for caution. Chest 2019; 155(5):1080–1081. doi:10.1016/j.chest.2019.01.032
10. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**. 2020 Global strategy for the diagnosis, management and prevention of COPD. https://goldcopd.org/gold-reports/. Accessed April 3, 2020.
11. **Sciurba FC, Criner GJ, Strange C, et al; RENEW Study Research Group**. Effect of endobronchial coils vs usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial. JAMA 2016; 315(20):2178–2189. doi:10.1001/jama.2016.6261
12. **Shah PL, Slebos DJ, Cardoso PF, et al; EASE Trial Study Group**. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. Lancet 2011; 378(9795):997–1005. doi:10.1016/S0140-6736(11)61050-7
13. **Herth FJ, Valipour A, Shah PL, et al**. Segmental volume reduction using thermal vapour ablation in patients with severe emphysema: 6-month results of the multicentre, parallel-group, open-label, randomised controlled STEP-UP trial. Lancet Respir Med 2016; 4(3):185–193. doi:10.1016/S2213-2600(16)00045-X
14. **Reilly J, Washko G, Pinto-Plata V, et al**. Biological lung volume reduction: a new bronchoscopic therapy for advanced emphysema. Chest 2007; 131(4):1108–1113. doi:10.1378/chest.06-1754
15. **Criner GJ, Pinto-Plata V, Strange C, et al**. Biologic lung volume reduction in advanced upper lobe emphysema phase 2 results. Am J Respir Crit Care Med 2009; 179(9):791–798. doi:10.1164/rccm.200810-1639OC
16. **Refaely Y, Dransfield M, Kramer MR, et al**. Biologic lung volume reduction therapy for advanced homogeneous emphysema. Eur Respir J 2010; 36(1):20–27. doi:10.1183/09031936.00106009
17. **Sciurba FC, Ernst A, Herth FJ, et al; VENT Study Research Group**. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010; 363(13):1233–1244. doi:10.1056/NEJMoa0900928
18. **Herth FJ, Noppen M, Valipour A, et al; International VENT Study Group**. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J 2012; 39(6):1334–1342. doi:10.1183/09031936.00161611
19. **Davey C, Zoumot Z, Jordan S, et al**. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet 2015; 386(9998):1066–1073. doi:10.1016/S0140-6736(15)60001-0
20. **Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ**. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med 2015; 373(24):2325–2335. doi:10.1056/NEJMoa1507807
21. **Valipour A, Slebos DJ, Herth F, et al**. Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT Study. Am J Respir Crit Care Med 2016; 194(9):1073–1082. doi:10.1164/rccm.201607-1383OC
22. **Kemp SV, Slebos DJ, Kirk A, et al; TRANSFORM Study Team**. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). Am J Respir Crit Care Med 2017; 196(12):1535–1543. doi:10.1164/rccm.201707-1327OC
23. **Criner GJ, Sue R, Wright S, et al; LIBERATE Study Group**. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med 2018; 198(9):1151–1164. doi:10.1164/rccm.201803-0590OC
24. **Li S, Wang G, Wang C, et al**. The REACH trial: a randomized controlled trial assessing the safety and effectiveness of the Spiration valve system in the treatment of severe emphysema. Respiration 2019; 97(5):416–427. doi:10.1159/000494327
25. **Criner GJ, Delage A,Voelker KG; for the EMPROVE Trial Investigator Group**. The EMPROVE trial – a randomized, controlled multicenter clinical study to evaluate the safety and effectiveness of the Spiration® valve system for single lobe treatment of severe emphysema. Am J Respir Crit Care Med 2018; 197:A7753. https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2018.197.1_MeetingAb-

stracts.A7753. Accessed April 3, 2020.
26. **McGlothlin AE, Lewis RJ**. Minimal clinically important difference: defining what really matters to patients. JAMA 2014; 312(13):1342–1343. doi:10.1001/jama.2014.13128
27. **Donohue JF**. Minimal clinically important differences in COPD lung function. COPD 2005; 2(1):111–124. doi:10.1081/copd-200053377
28. **Puhan MA, Chandra D, Mosenifar Z, et al; National Emphysema Treatment Trial (NETT) Research Group**. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011; 37(4):784–790. doi:10.1183/09031936.00063810
29. **Jones PW**. St. George's Respiratory Questionnaire: MCID. COPD 2005; 2(1):75–79. doi:10.1081/copd-200050513
30. **Hartman JE, Ten Hacken NH, Klooster K, Boezen HM, De Greef MH, Slebos DJ**. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J 2012; 40(5):1137–1141. doi:10.1183/09031936.00219111
31. **Labarca G, Uribe JP, Pacheco C, et al**. Bronchoscopic lung volume reduction with endobronchial Zephyr valves for severe emphysema: a systematic review and meta-analysis. Respiration 2019; 98(3):268–278. doi:10.1159/000499508
32. **Garner J, Kemp SV, Toma TP, et al**. Survival after endobronchial valve placement for emphysema: a 10-year follow-up study. Am J Respir Crit Care Med 2016; 194(4):519–521. doi:10.1164/rccm.201604-0852LE
33. **Gompelmann D, Benjamin N, Bischoff E, et al**. Survival after endoscopic valve therapy in patients with severe emphysema. Respiration 2019; 97(2):145–152. doi:10.1159/000492274
34. **Ciccone AM, Meyers BF, Guthrie TJ, et al**. Long-term outcome of bilateral lung volume reduction in 250 consecutive patients with emphysema. J Thorac Cardiovasc Surg 2003; 125(3):513–525. doi:10.1067/mtc.2003.147
35. **Clark SJ, Zoumot Z, Bamsey O, et al**. Surgical approaches for lung volume reduction in emphysema. Clin Med (Lond) 2014; 14(2):122–127. doi:10.7861/clinmedicine.14-2-122
36. **Caviezel C, Schaffter N, Schneiter D, et al**. Outcome after lung volume reduction surgery in patients with severely impaired diffusion capacity. Ann Thorac Surg 2018; 105(2):379–385. doi:10.1016/j.athoracsur.2017.09.006
37. **Horwood CR, Mansour D, Abdel-Rasoul M, et al**. Long-term results after lung volume reduction surgery: a single institution's experience. Ann Thorac Surg 2019; 107(4):1068–1073. doi:10.1016/j.athoracsur.2018.10.014
38. **Buttery S, Kemp SV, Shah PL, et al**. CELEB trial: comparative effectiveness of lung volume reduction surgery for emphysema and bronchoscopic lung volume reduction with valve placement: a protocol for a randomised controlled trial. BMJ Open 2018; 8(10):e021368. doi:10.1136/bmjopen-2017-021368
39. **Pietzsch JB, Garner A, Herth FJ**. Cost-effectiveness of endobronchial valve therapy for severe emphysema: a model-based projection based on the VENT study. Respiration 2014; 88(5):389–398. doi:10.1159/000368088

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# Cutaneous adverse effects of biologic medications

## ABSTRACT

Biologic therapies have become widely used but often cause cutaneous adverse effects. The authors discuss the cutaneous adverse effects of tumor necrosis factor (TNF) alpha inhibitors, epidermal growth factor receptor (EGFR) inhibitors, small-molecule tyrosine kinase inhibitors (TKIs), and cell surface-targeted monoclonal antibodies, including how to manage these reactions and when to refer to a dermatologist.

## KEY POINTS

TNF alpha inhibitors (infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab) have been implicated in infusion and injection site reactions, infection, inflammatory dermatoses, and malignancy.

The most common cutaneous reaction with EGFR inhibitors (eg, gefitinib, cetuximab, erlotinib, and panitumumab) is a widespread papulopustular acneiform eruption.

Small-molecule TKIs include imatinib, dasatinib, nilotinib, ponatinib, bosutinib, sorafenib, sunitinib, pazopanib, axitinib, vandetanib, dovitinib, vemurafenib, dabrafenib, and ruxolitinib.

Commonly used monoclonal antibodies include rituximab, anakinra, tocilizumab, ipilimumab, nivolumab, pembrolizumab, and avelumab.

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Biologic therapy encompasses an exponentially expanding arena of medicine. As the name implies, biologic therapies are derived from living organisms and consist largely of proteins, sugars, and nucleic acids. A classic example of an early biologic medication is insulin. These therapies have revolutionized medicine and offer targeted therapy for an increasing number of diseases, particularly in rheumatology, gastroenterology, hematology-oncology, and dermatology.

But along with these advances and the ensuing expanded use of biologic and targeted therapies have come many unique adverse effects, and some of the most commonly reported adverse effects with these new therapies are cutaneous. Cutaneous adverse effects can potentially limit the use of these agents and add cost to already expensive treatment regimens.[1]

It is important for physicians and other healthcare providers to be aware of these effects, have a basic understanding of how to manage patients with these reactions, and to know when to refer to a dermatologist.

This article reviews recent literature on cutaneous adverse reactions experienced with commonly prescribed biologic and targeted therapies, specifically tumor necrosis factor (TNF) alpha inhibitors, epidermal growth factor receptor (EGFR) inhibitors, small-molecule tyrosine kinase inhibitors (TKIs), and frequently used cell surface-targeted monoclonal antibodies.

## TNF ALPHA INHIBITORS

TNF alpha is a proinflammatory cytokine that plays an important role in regulation of immune cells. Dysregulation of TNF alpha is involved in the pathogenesis of numer-

**TABLE 1**

**Cutaneous adverse effects of tumor necrosis factor alpha antagonists**

| Examples | Cutaneous side effects | Management strategies |
|---|---|---|
| Adalimumab<br>Certolizumab<br>Etanercept<br>Golimumab<br>Infliximab | Infusion reactions and injection site reactions | Preinfusion treatment with oral antihistamines, acetaminophen, and intravenous steroids |
| | Cutaneous infections (bacterial, viral) | Frequent skin examinations, low threshold to perform cultures and initiate bacterial or fungal-targeted topical or oral therapy<br>Consider varicella zoster vaccination before starting therapy |
| | Psoriasis | Topical therapy, methotrexate, cyclosporine, phototherapy |
| | Eczematous dermatitis | Gentle skin care, liberal emollients, topical steroids |
| | Lichenoid reactions | Discontinuation or reduction of therapy dose, topical steroids |
| | Cutaneous leukocytoclastic vasculitis | Discontinuation of therapy, initiation of systemic prednisone, switch to other immunosuppressive medication |
| | Nonmelanoma and melanoma skin cancer | Routine skin cancer surveillance, broad-spectrum sunscreen, sun avoidance, skin self-examination |

ous inflammatory conditions, most notably rheumatoid arthritis, inflammatory bowel disease, psoriasis vulgaris, and psoriatic arthritis. Therefore, TNF alpha inhibitors have been successfully used to treat numerous autoimmune and inflammatory conditions.

However, these medications also have been implicated in a number of cutaneous adverse events, including infusion and injection site reactions, infection, inflammatory dermatoses, and malignancy.

Five TNF alpha inhibitors are currently available: infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab (**Table 1**).

### Infusion reactions with infliximab

Infusion reactions associated with infliximab have been reported to occur in as many as 18% of recipients.[2] These reactions may be acute (onset within minutes to hours) or delayed (days to weeks), with cutaneous manifestations of flushing, urticaria, pruritus, angioedema, and a serum sickness-like reaction.

In a Danish cohort of patients with inflammatory bowel disease receiving infliximab, infusion reactions were most strongly associated with younger patients and with episodic therapy.[2]

Treatment for these infusion reactions is largely supportive. Preventive measures include preinfusion treatment with oral antihistamines, acetaminophen, and occasionally intravenous steroids and slowing the rate of infusion. Adding concomitant immunosuppressive medications and avoiding drug-free intervals have also been recommended.

### Injection site reactions

Injection site reactions have been reported to occur in 6% to 37% of patients receiving adalimumab, 17% to 37% of patients receiving etanercept, 6% of patients receiving golimumab, and 3.1% of those receiving certolizumab pegol.[3,4]

Patients can experience itching, pain, redness, irritation, bruising, or swelling at the in-

**Biologic therapies have revolutionized medicine, but come with many unique adverse effects**

jection site. This can be seen during the first month of treatment and can last 3 to 5 days. Absence of warmth or drainage and improvement within a few days can distinguish injection site reactions from infection.

Management of these reactions is again primarily supportive. Preventive therapies similar to those described for infusion reactions, as well as cooling pads or ice packs for symptomatic relief, may be helpful. Varying the site of injection is another useful strategy. Most of these reactions are considered moderate, and rarely do patients need to discontinue the TNF alpha inhibitor because of them.

### Cutaneous infections

TNF alpha plays an important role in numerous complex immune signaling pathways, including cell proliferation, differentiation, apoptosis, macrophage activation, and morphogenesis of lymphoid tissue. Not surprisingly, inhibition of this cytokine leads to increased risk of cutaneous infection. Risk factors for increased cutaneous infections during TNF alpha inhibitor therapy include additional immunosuppressive therapy, malnutrition, age, and comorbidities such as chronic lung disease, alcoholism, organic brain disease, and diabetes mellitus.

**Dysregulation of TNF alpha is involved in the pathogenesis of numerous inflammatory conditions**

A single-center, retrospective cohort study[5] of 583 patients with inflammatory bowel disease treated with TNF alpha inhibitors (primarily infliximab) found cutaneous infections to be the most common dermatologic complication of therapy. The cumulative incidence of cutaneous infection was 1.1% at 1 year of therapy, 6.4% at 5 years, and 17.6% at 10 years; the median time to onset was 3 years. Bacterial infections (overwhelmingly staphylococcal) were the most common and manifested as folliculitis, erysipelas, cellulitis, and abscess formation. Cutaneous infection led to discontinuation of therapy in 2.9% of those affected.[5] Fungal cutaneous infections, particularly with *Candida* species, are more common when a corticosteroid is combined with a TNF alpha inhibitor, but the exact incidence is not known.

Another large cohort study of patients treated with TNF alpha inhibitors[6] also found an increased incidence of bacterial skin infections, as well as a high incidence of herpesvirus skin infections. This population-based study from Spain[6] found cutaneous bacterial infections occurred at an incidence of 10.4 per 1,000 patient-years, and zoster infections at an incidence of 7.2 per 1,000 patient-years. Zoster infections were found more often in those receiving infliximab and adalimumab. In addition, immunosuppressive therapy in conjunction with a TNF alpha inhibitor increased the risk of zoster dissemination and complications, including bacterial superinfection and postherpetic neuralgia.

Cutaneous infections during anti-TNF alpha therapy are rarely serious, and management should include frequent skin examinations and initiation of appropriate antibacterial or antifungal topical or oral therapy. For example, acyclovir, valacyclovir, and famciclovir can be used for acute varicella zoster virus infection.

Given the current guidelines and the incidence of herpes zoster in patients receiving TNF alpha inhibitors, clinicians should strongly consider vaccination before starting therapy.[6] Safe use and efficacy of the recombinant vaccine in these individuals are not entirely clear. There are currently no contraindications to the recombinant vaccine in patients on moderate- to high-dose immunosuppressive therapy. However, data on efficacy and safety are not yet sufficient to recommend routinely giving the recombinant vaccine to patients actively treated with TNF alpha inhibitors.[7]

Human papillomavirus infections can cause anogenital warts and cervical dysplasia and may have an increased incidence in patients on TNF alpha inhibitors. A study of women with inflammatory bowel disease found that those receiving a TNF alpha inhibitor were more likely to have abnormal Papanicolaou smears than were controls (odds ratio [OR] 4.5) and those with inflammatory bowel disease not on TNF alpha inhibitors (OR 1.9).[8]

However, another study of 222 patients on TNF alpha inhibitors found that even after a mean of 31.4 months on the medication, there was no increase in detectable anogenital human papillomavirus infection or disease. Given the mixed findings, standard vaccination and screening schedules should be adhered to in this population.

## Dermatitis

Numerous inflammatory and autoimmune-like cutaneous reactions have been reported during anti-TNF alpha therapy; they include psoriasis, eczema, lupus erythematosus, vasculitis, and others.

The terms *psoriasiform dermatitis* and *psoriasis* are sometimes used interchangeably when describing psoriasis-like lesions in the setting of anti-TNF alpha agents. We have therefore kept the terminology consistent with that used by the authors of the study being discussed.

**Psoriasiform lesions.** A case-control study[9] involving 521 patients with inflammatory bowel disease treated with TNF alpha inhibitors examined those within the cohort who developed psoriasiform skin lesions. Psoriasiform lesions were reported in 3.5% of patients and most commonly involved the palms, soles, and scalp (**Figure 1**). Other areas that can be affected are the intertriginous and genital skin (**Figure 2**).

On biopsy, psoriasiform lesions have histologic features similar to those of psoriasis, and further, can resemble allergic contact dermatitis, seborrheic dermatitis, atopic dermatitis, pityriasis rubra, and lichen simplex chronicus.

One study[5] found a cumulative incidence of psoriasiform dermatitis of 1.1% at 1 year, 6.75% at 5 years, and 28.9% at 10 years in a cohort of patients with inflammatory bowel disease treated with TNF alpha inhibitors. In those who developed psoriasiform dermatitis, topical therapy was required in 78% and systemic therapy (methotrexate or phototherapy) in 15.2%. Remission occurred in 20.3%, and 18.6% of patients needed to discontinue TNF alpha inhibitor therapy.

Another study[10] examined 102 patients with TNF alpha inhibitor-induced psoriasis and found the most common forms to be plaque-type (49.5%) and scalp (47.5%). Palmoplantar pustulosis (whose differential diagnosis can include dyshidrotic eczema, contact dermatitis, pityriasis rubra pilaris, acquired palmoplantar keratoderma, tinea pedis, and tinea manuum) was also found in 41% of these patients. Topical medications alone improved the eruption in 63.5% of patients, with cyclosporine and methotrexate often successful when topical treatments alone failed.[10] Discontinuation of

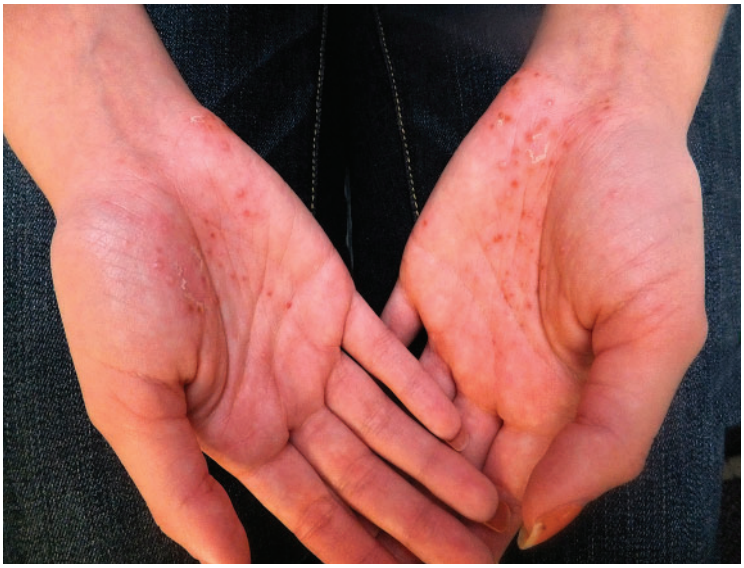

**Figure 1.** Palmar psoriasis eruption in a patient receiving infliximab treatment for Crohn disease.

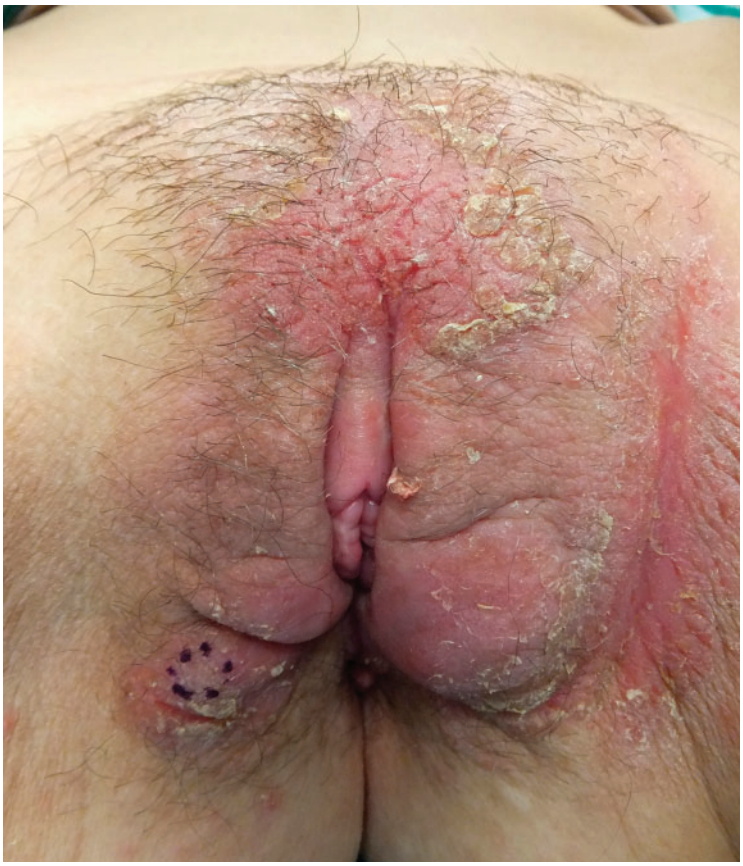

**Figure 2.** Inverse psoriasis induced by infliximab treatment for Crohn disease.

the TNF alpha inhibitor was required in 10.6% of those who developed lesions.

Notably, however, lesions commonly recur if a TNF alpha inhibitor, either the same drug or a different one, is restarted after discontinuation. In a study of patients with inflammatory bowel disease treated with TNF alpha inhibitors, 9 patients had to stop the medication because of psoriasiform lesions. Three of those were retreated with a second TNF alpha inhibitor, and all had recurrence of the lesions.[9] Current experience has found that there is high risk of recurrence with use of the same TNF alpha agent, and about a 50% recurrence rate if using another drug in the same class.[9,10]

**An algorithm for treating TNF alpha inhibitor psoriasiform eruptions** has been proposed and is based on severity of skin eruption and control of the underlying disease[11]:

- If the skin eruption is mild and the underlying disease is controlled, continue the TNF alpha inhibitor and treat the eruption topically
- If the skin eruption is mild but the underlying disease is not controlled, switching within the same class is reasonable
- If the skin eruption is moderate to severe and the underlying disease is controlled, switching within the same class is reasonable
- If the skin eruption is moderate to severe and the disease is not well controlled, discontinuing TNF alpha inhibitors altogether is warranted.

**Other forms of dermatoses** reported in association with TNF alpha inhibitors tend to occur less often than psoriasiform eruptions and include eczema, leukocytoclastic vasculitis, lupus erythematosus, and granulomatous dermatitis. Eczematous dermatitis, for example, has an incidence ranging from 2.2% to 23.5% in patients undergoing anti-TNF alpha therapy.[12] Depending on severity, gentle skin care, liberal emollients, topical steroids, biopsy, or referral to dermatology is recommended.

**Autoimmunity.** Patients on TNF alpha inhibitors can develop autoimmune conditions that include alopecia (both autoimmune and scarring), dermatomyositis, sarcoidosis, and antiphospholipid syndrome. Specifically, leukocytoclastic vasculitis and TNF alpha inhibitor-induced lupuslike syndrome (TAILS) will be discussed below.

**Evidence is mixed on whether TNF alpha inhibitors increase the risk of skin cancer, but caution is reasonable**

**Leukocytoclastic vasculitis** associated with TNF alpha inhibitors typically manifests as a cutaneous small-vessel vasculitis. Discontinuation of therapy is required in 94% to 100% of patients with TNF alpha inhibitor-induced leukocytoclastic vasculitis, and initiation of systemic prednisone or other immunosuppressive medication or both is sometimes required or recommended.[13]

**TAILS,** a form of drug-induced lupus, is rare (incidence ≤ 1%), most commonly affects middle-aged women, and presents weeks to years after starting the TNF alpha inhibitor, particularly infliximab and etanercept.[13] A maculopapular rash, malar rash, photosensitivity, and alopecia are common skin manifestations, seen in 72% of patients. Noncutaneous manifestations include arthritis, serositis, myositis, anemia, leukopenia, renal, and neurologic disorders.

If TAILS is suspected, patients can be screened for laboratory findings seen in lupus. Positive results for antibodies occur as follows: antinuclear antibody 91%, anti-dsDNA 64%, and antiphospholipid antibody 11% to 50%.[13] Antihistone is also frequently found. In a study of 53 patients with rheumatoid arthritis receiving infliximab, the prevalence of antinuclear antibody at a dilution greater than 1:100 increased from 24% at baseline to 77% at 30 weeks and 69% at 54 weeks.[13] Other studies in patients with rheumatoid arthritis have shown induction of antinuclear antibody and anti-dsDNA after the use of infliximab and etanercept.[13]

Of note, in some conditions such as rheumatoid arthritis, patients may already have underlying lupus features. However, TNF alpha inhibitors may trigger additional lupus features, leading to a diagnosis of TAILS. Withdrawal of the TNF alpha inhibitor and referral to dermatology or rheumatology are recommended in these cases.

Treatment for TAILS generally includes topical steroids, antimalarials, and possibly switching to another TNF alpha inhibitor.

## Malignancy risk

Findings are mixed on whether TNF alpha inhibitors increase the risk of nonmelanoma skin cancer.[14] In a meta-analysis of 4 observational studies with 28,000 patients, the risk of non-

TABLE 2

**Cutaneous adverse effects of epidermal growth factor receptor inhibitors**

| Examples | Cutaneous side effects | Management strategies |
|---|---|---|
| Cetuximab<br>Erlotinib<br>Gefitinib<br>Panitumumab | Papulopustular acneiform eruption | Prevention with minocycline or doxycycline<br>Topical and systemic corticosteroids, antibiotics, oral isotretinoin<br>Oral histamine 1 (H1) antihistamines and gamma aminobutyric acid agonists for pruritus |
| | Paronychial inflammation | Topical antibiotics, topical corticosteroids, electrodessication for larger lesions, rarely photodynamic therapy |
| | Stevens-Johnson syndrome–toxic epidermal necrolysis | Discontinue therapy |

melanoma skin cancer was significantly higher among patients exposed to these drugs.[14] However, the data are confounded by past or concomitant use of phototherapy or other immunosuppressive agents.

There is some evidence to suggest that patients receiving methotrexate, commonly used in rheumatoid arthritis, are at increased risk of nonmelanoma skin cancer, possibly due to the photosensitizing nature of methotrexate.[15] One study in particular[15] examined the rate of development of a second nonmelanoma skin cancer in 9,460 patients with rheumatoid arthritis or inflammatory bowel disease. It found that anti-TNF use may increase the nonmelanoma skin cancer risk when used in combination with methotrexate. However, further study is needed to eliminate confounding factors.

The link between melanoma and TNF alpha inhibitors is also not straightforward. In a Swedish cohort study,[16] there was a higher risk of a first invasive melanoma in patients with rheumatoid arthritis receiving TNF alpha inhibitors than in those not treated with them. Another study,[16] however, examined 130,315 patients who had rheumatoid arthritis and found 287 first-time melanomas. The risk was slightly higher than in the general population in the entire cohort and in those on TNF alpha inhibitors, but the differences were not statistically significant, and the overall absolute incidence was quite low.

Given the mixed findings, it is therefore reasonable that all patients treated with a TNF alpha inhibitor undergo skin cancer surveillance for both melanoma and nonmelanoma skin cancer, use broad-spectrum sunscreens, and practice sun avoidance and skin self-examination. If malignant melanoma is found, it is reasonable to stop the TNF inhibitor.

## EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

EGFR is a transmembrane glycoprotein that, when activated, leads to the autophosphorylation of tyrosine kinase receptor, initiating a cascade of downstream signaling pathways involved in regulating cellular proliferation, differentiation, and survival. EGFR inhibitors block this pathway in tumor cells and are predominantly used in non-small cell lung cancer, colorectal cancer, pancreatic cancer, and head and neck cancer. Examples include gefitinib, cetuximab, erlotinib, and panitumumab (**Table 2**).

**The most common skin reaction to EGFR inhibitors is a widespread papulopustular, acneiform eruption**

### Acneiform reactions

The most common cutaneous reaction with EGFR inhibitors is a widespread papulopustular acneiform eruption consisting of erythematous follicle-based papules and pustules without comedones.

TABLE 3

**Cutaneous adverse effects of small-molecule tyrosine kinase inhibitors**

| Examples | Adverse effects | Management strategies |
|---|---|---|
| Axitinib<br>Bosutinib<br>Dabrafenib<br>Dasatinib<br>Dovitinib<br>Imatinib<br>Nilotinib<br>Pazopanib<br>Ponatinib<br>Ruxolitinib<br>Sorafenib<br>Sunitinib<br>Vandetanib<br>Vemurafenib | Rash (exanthematous papular eruption) | Discontinue and then reintroduce at lower dose, temporary course of oral corticosteroid |
| | Hand-foot skin reactions | Topical emollients, topical urea, salicylic acid, topical corticosteroid |
| | Keratoacanthoma, squamous cell carcinoma | Phototherapy, intralesional methotrexate, retinoids and excision |
| | Acneiform eruption | Topical antiseptics and antibiotics, oral antibiotics, systemic isotretinoin, short course of a low-dose systemic corticosteroid |

More than half of patients taking these drugs experience an acneiform eruption. It is usually mild or moderate but can be severe in a minority of cases. The acneiform eruption is often dose-dependent and begins within 1 week of treatment.[17]

The lesions commonly present on the face and trunk, spare the palms and soles, and are associated with pruritus.

While management depends on the severity, consultation with a dermatologist is recommended for most patients, particularly if the reaction lasts more than 2 weeks or is severe. Prevention can include medications such as minocycline or doxycycline. Treatment can include topical and systemic corticosteroids, antibiotics, and oral isotretinoin. If there is pruritus, oral histamine 1 (H1) antihistamines can be used. Gamma aminobutyric acid agonists such as gabapentin and pregabalin can be used as second-line treatments for itching.

### Toenail inflammation

A study of 10 patients suggested paronychial inflammation, commonly with pyogenic granuloma-like lesions, as another cutaneous manifestation.[18] Paronychia in the great toe often occurs first, and secondary bacterial infection (commonly *Staphylococcus aureus*) can occur as well.

Treatment with topical antibiotics, topical corticosteroids, electrodessication for larger lesions, and, more rarely, photodynamic therapy, can be effective.

### Other reactions

EGFR inhibitors have also been associated with hair changes including development of brittle, fine, and curly hair on the scalp and extremities.

Xerosis with desquamation, small aphthous ulcerations of the oral and nasal mucosa, photosensitivity, and urticaria have also been noted.

Cases of Stevens-Johnson syndrome–toxic epidermal necrolysis have been associated with erlotinib therapy, but the incidence is low.[19] Discontinuation is recommended if any sign of a bullous or exfoliative eruption occurs.

## SMALL-MOLECULE TYROSINE KINASE INHIBITORS

**Small-molecule tyrosine kinase inhibitors block intracellular signaling pathways in tumor cells**

TKIs block intracellular signaling pathways that regulate cellular functions such as proliferation and differentiation in tumor cells. Different small molecules may target different components of the tyrosine kinase signaling cascade. Examples include imatinib, dasatinib, nilotinib, ponatinib, bosutinib, sorafenib, sunitinib, pazopanib, axitinib, vandetanib, dovitinib, vemurafenib, dabrafenib, and ruxolitinib (**Table 3**).

### Imatinib

Imatinib is commonly used to treat Philadelphia-chromosome–positive chronic myelogenous leukemia (Ph+CML) and gastrointestinal stromal tumors. It can trigger skin eruptions, sometimes in up to 1 in 5 (20%) treated patients. A study of 532 patients with chronic-phase CML treated with imatinib daily found that 32% reported a rash or related cutaneous event.[20] Most commonly, the rash presented as an exanthematous papular eruption.

When mild, this rash will resolve spontaneously. However, more severe skin eruptions may require stopping treatment for 2 weeks, and then restarting at a lower dose. Upon reintroduction, a potential strategy is to temporarily add an oral corticosteroid to minimize risk of a repeat cutaneous reaction.

Beyond rash, one prospective study of 54 patients on imatinib found that 7% developed photosensitivity and 7% developed a psoriasiform eruption.[21] Imatinib has also been linked to Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and Sweet syndrome (acute febrile neutrophilic dermatosis). Discontinuation is recommended in these cases. For the latter two, the decision to attempt retreatment depends on the extent of the reaction and if there are therapeutic alternatives.

### Second-generation TKIs

Dasatinib, nilotinib, ponatinib, and bosutinib are second-generation TKIs that are used for treatment of Ph+CML. There are a number of cutaneous findings to be aware of when encountering these drugs.

Phase 1 and 2 studies of dasatinib found that of 911 patients, 35% had cutaneous eruptions, including localized and generalized erythema, papular eruptions, and pruritus.[22]

In phase 1 and 2 studies of nilotinib, 20% to 28% suffered a nonspecific rash, 15% to 24% had pruritus, and 12% had dry skin.[23]

Bosutinib can cause adverse dermatologic concerns in 20% to 44% of patients, including erythema, maculopapular eruption, pruritic rash, allergic dermatitis, acne, folliculitis, and skin exfoliation.[24]

Treatments for the above reactions generally include topical and systemic corticosteroids, isotretinoin, and oral H1 antihistamines, depending on the specific concern.

**Figure 3.** Acneiform eruption in a patient receiving dovitinib for glioblastoma.

Sorafenib and sunitinib are multitargeted TKIs whose most common cutaneous effects involve hand-foot skin reactions. A meta-analysis involving 6,011 patients on sorafenib found hand-foot skin reactions occurred in 39%, while less common cutaneous reactions included all-grade rash or desquamation (35.4%), alopecia (25.5%), pruritus (14%), and dry skin (14.1%).[25] Patients treated with sunitinib or sorafenib who develop hand-foot skin reactions tend to develop localized tender lesions in friction areas that can become blistered or hyperkeratotic. Hand-foot skin reactions appear more commonly with sorafenib than with sunitinib, and their severity with higher doses is a pattern found specifically in sorafenib recipients.[26] For mild hand-foot skin reactions, dosing of the medication can remain the same, and topical emollients, topical urea, or salicylic acid may be effective. In more severe cases, treatment may require a topical corticosteroid or temporary reduction in dose.

**Knowing when to reduce the dose, stop the drug, give steroids or antibiotics, or refer to a dermatologist will be highly useful**

Sorafenib has also been associated with cutaneous squamoproliferative lesions such as keratoacanthomas and squamous cell carcinomas.[27] Of note, lesions have the potential to regress upon cessation of therapy. Complete surgical excision, similar to treatment of those not

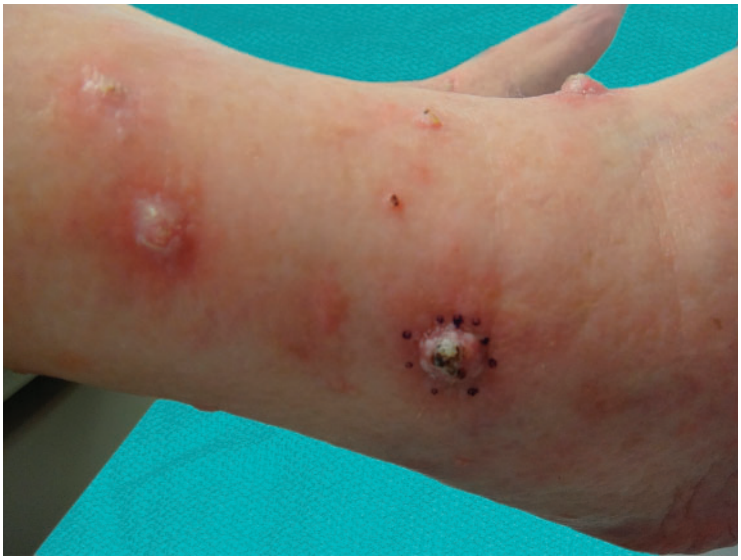

**Figure 4.** Eruptive squamous cell carcinoma keratoacanthomas in a patient receiving ruxolitinib for primary myelofibrosis.

on the drug, can be employed in these cases.

Pazopanib, axitinib, vandetanib, and dovitinib are all multitargeted TKIs. Pazopanib is used for advanced renal cell carcinoma and soft-tissue sarcoma. When studied in 290 patients with renal cell carcinoma, changes in hair color occurred in 38% of recipients.[28]

Axitinib is approved for the treatment of advanced renal cell carcinoma. Of 984 patients, 29.2% had hand-foot skin reactions.[29] Vandetanib is used for patients with medullary thyroid cancer and lung cancer. It can present with skin reactions of dermatitis, acneiform eruption, dry skin, pruritus, photosensitivity, or hand-foot skin reactions in 28% to 71% of patients.[30]

**Rituximab, relatively benign dermatologically, has been reported to cause infusion reactions**

Dovitinib is used in renal cell carcinoma and melanoma. It has been reported to cause acneiform eruptions and eruptive facial milia and comedones (**Figure 3**).[31] Topical antiseptics, topical antibiotics, oral antibiotics, and systemic isotretinoin can be used for treatment. A short course of a low-dose systemic corticosteroid can also be useful to control inflammation.[31]

Vemurafenib and dabrafenib are inhibitors of the kinase domain in mutant BRAF (a serine-threonine kinase) and are used for treatment of metastatic melanoma with a V600E BRAF mutation. In clinical trials in 675 patients, vemurafenib was associated with a rash in 18% of patients, photosensitivity in 12%, squamous cell carcinoma or keratoacanthoma in 18% to 26%, and alopecia in 8%.[32] Dabrafenib also has been associated with development of keratoacanthomas or well-differentiated cutaneous squamous cell carcinoma in 6% to 26% of patients.[33] Treatment of these skin lesions can include phototherapy, intralesional methotrexate, retinoids, or surgical excision.

Ruxolitinib is a Janus-associated kinase inhibitor used in the treatment of myelofibrosis and polycythemia vera. Ruxolitinib is particularly associated with the development of skin cancer, as 17.1% of patients on the therapy developed basal cell carcinoma or squamous cell carcinoma compared with 2.7% of patients on alternate available therapy for myelofibrosis (**Figure 4**).[34] A case series reported 5 patients with a history of myelofibrosis treated with ruxolitinib who developed multiple skin cancers with aggressive features, including a lentigo maligna melanoma.[34]

## CELL SURFACE-TARGETED MONOCLONAL ANTIBODIES

Monoclonal antibodies are drugs directed against specific antigens on cells that cause disease. These drugs may assist in immune modulation, cell killing, or blocking a physiologic ligand-receptor interaction. Not surprisingly, monoclonal antibodies are used in the treatment of immunologic diseases and cancer therapy. Although the number of monoclonal antibodies designed as drugs has been increasing substantially since 1985, common ones include rituximab, anakinra, tocilizumab, ipilimumab, nivolumab, pembrolizumab, avelumab, and tofacitinib (**Table 4**).

### Rituximab, an anti-CD20 monoclonal antibody

Rituximab is a chimeric murine-human monoclonal antibody against CD20 used in rheumatoid arthritis, autoimmune disorders, and lymphoproliferative disorders. While dermatologically it is relatively benign, it has been reported to cause infusion reactions. Standard practice is to premedicate with acetaminophen and diphenhydramine 30 minutes before the first and second infusions.

TABLE 4

**Cutaneous adverse effects of cell surface-targeted monoclonal antibodies**

| Examples | Adverse effects | Management strategies |
|---|---|---|
| Anakinra<br>Avelumab<br>Ipilimumab<br>Nivolumab<br>Pembrolizumab<br>Rituximab<br>Tocilizumab<br>Tofacitinib | Infusion reactions | Premedicate with acetaminophen and diphenhydramine 30 minutes before the first and second infusions |
| | Serum sickness | Pulse methylprednisolone therapy |
| | Stevens-Johnson syndrome/toxic endothelial necrolysis and vesiculobullous dermatitis | Discontinue therapy |
| | Rash (lichenoid, bullous, psoriasiform, macular, morbiliform morphologies) | Topical corticosteroids, systemic steroids |

Serum sickness has also been reported with rituximab, and is seen visibly as a morbilliform skin eruption with acral accentuation.[35] Treatment for this reaction includes pulse methylprednisolone therapy, which can be effective in resolving symptoms over 48 hours.

Less commonly, Stevens-Johnson syndrome–toxic epidermal necrolysis and vesiculobullous dermatitis can occur with rituximab, in which case discontinuation is recommended.

### Other monoclonal antibodies

Other commonly used monoclonal antibodies include anakinra, tocilizumab, and ipilimumab.

**Anakinra** is a recombinant human interleukin 1 receptor antagonist used to treat rheumatoid arthritis, systemic juvenile idiopathic arthritis, adult-onset Still disease, and, in select patients, recurrent pericarditis. Case reports note new-onset psoriasis with this drug, as well as injection-site reactions.[36]

**Tocilizumab** is an anti-human interleukin 6 receptor antibody used for rheumatoid arthritis and giant cell arteritis. It rarely presents with skin rash, but is most notable for hypersensitivity reactions upon infusion.[37]

**Ipilimumab** is a monoclonal antibody directed against cytotoxic T-lymphocyte antigen 4 used to treat patients with advanced melanoma.

In 41 patients treated with ipilimumab, 34.1% developed cutaneous adverse events that included rash (7.3%), folliculitis (7.3%), mucositis (2.4%), rosacea (2.4%), eczema (2.4%), acneiform eruption (2.4%), syringometaplasia mucinosa (2.4%;), Stevens-Johnson syndrome (2.4%), and vitiligo (4.9%). Approximately 5% of the patients complained of severe xerosis and 10% of pruritus.[38]

Treatment for these cutaneous manifestations is similar to that described in previous sections.

**Nivolumab, pembrolizumab, and avelumab** bind to programmed cell death ligand-1 (PD-L1), enhancing the host immune response by preventing tumor cells from suppressing endogenous T-cell activity. Cutaneous eruptions described with these medications include lichenoid, bullous, psoriasiform, macular, and morbilliform morphologies. Cases of Stevens-Johnson syndrome–toxic epidermal necrolysis have also been reported (**Figure 5**).

Treatment with topical corticosteroids, systemic steroids, or discontinuation of the anti-PD-L1 inhibitor may be effective depending on the severity of the eruption.[39]

## BE ON THE LOOKOUT

Biologic medications are becoming critical in medicine, for treating conditions ranging from autoimmune diseases to metastatic cancers. They are reducing mortality and substantially

**Biologic medications are becoming critical in medicine for conditions ranging from autoimmune disease to metastatic cancer**

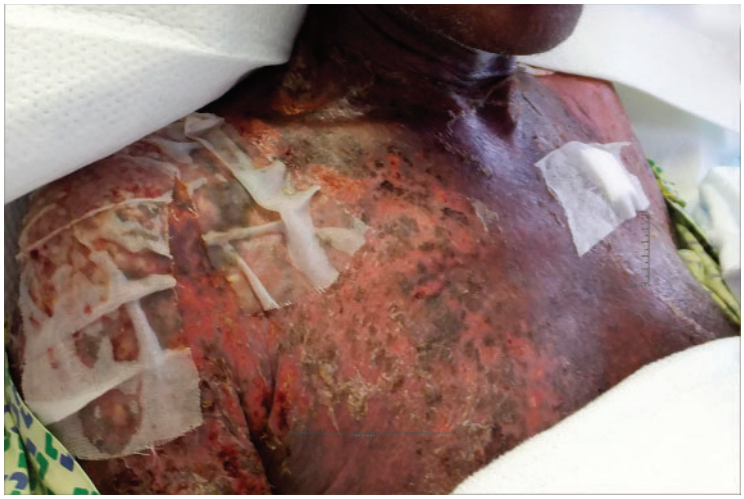

**Figure 5.** Toxic epidermal necrolysis in a patient receiving pembrolizumab for Sézary syndrome.

improving quality of life.

It is therefore important that physicians be armed with knowledge about the cutaneous adverse events of these medications and basic treatment steps. For example, knowing when to reduce the dose or discontinue the drug, supplement with topical or oral steroids or antibiotics, or refer to a dermatologist will be highly useful when caring for patients on these biologics. These innovative medications will only reach their maximum effectiveness when we as providers understand and manage adverse events appropriately.

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## REFERENCES


1. **Treudler R**. New drug therapies and their effect on the skin. J Dtsch Dermatol Ges 2009; 7(7):623–637. doi:10.1111/j.1610-0387.2009.07139.x
2. **Steenholdt C, Svenson M, Bendtzen K, Thomsen O, Brynskov J, Ainsworth M**. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2011; 34(1):51–58. doi:10.1111/j.1365-2036.2011.04682.x
3. **AbbVie, Inc**. HUMIRA (adalimumab) injection, for subcutaneous use. Highlights of prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/125057s399lbl.pdf. Accessed April 7, 2020.
4. **Capogrosso Sansone A, Mantarro S, Tuccori M, et al**. Safety profile of certolizumab pegol in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. Drug Saf 2015; 38(10):869–888. doi:10.1007/s40264-015-0336-2
5. **Fréling E, Baumann C, Cuny JF, et al**. Cumulative incidence of, risk factors for, and outcome of dermatological complications of anti-TNF therapy in inflammatory bowel disease: a 14-year experience. Am J Gastroenterol 2015; 110(8):1186–1196. doi:10.1038/ajg.2015.205
6. **Hernández MV, Sanmartí R, Cañete JD, et al; BIOBADASER 2**.0 Study Group. Cutaneous adverse events during treatment of chronic inflammatory rheumatic conditions with tumor necrosis factor antagonists: study using the Spanish registry of adverse events of biological therapies in rheumatic diseases. Arthritis Care Res (Hoboken) 2013; 65(12):2024–2031. doi:10.1002/acr.22096
7. **Mocci G, Marzo M, Papa A, Armuzzi A, Guidi L**. Dermatological adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. J Crohns Colitis 2013; 7(10):769–779. doi:10.1016/j.crohns.2013.01.009
8. **Kane S, Khatibi B, Reddy D**. Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. Am J Gastroenterol 2008; 103(3):631–636. doi:10.1111/j.1572-0241.2007.01582.x
9. **George LA, Gadani A, Cross RK, Jambaulikar G, Ghazi LJ**. Psoriasiform skin lesions are caused by anti-TNF agents used for the treatment of inflammatory bowel disease. Dig Dis Sci 2015; 60(11):3424–3430. doi:10.1007/s10620-015-3763-0
10. **Mazloom SE, Yan D, Hu JZ, et al**. TNF-a inhibitor-induced psoriasis: a decade of experience at the Cleveland Clinic. J Am Acad Dermatol 2018. doi:10.1016/j.jaad.2018.12.018. Epub ahead of print.
11. **Li SJ, Perez-Chada LM, Merola JF**. TNF inhibitor-induced psoriasis: proposed algorithm for treatment and management. J Psoriasis Psoriatic Arthritis 2019; 4(2):70–80. doi:10.1177/2475530318810851
12. **Cleynen I, Van Moerkercke W, Billiet T, et al**. Characteristics of skin lesions associated with anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: a cohort study. Ann Intern Med 2016; 164(1):10–22. doi:10.7326/M15-0729
13. **Ramos-Casals M, Brito-Zerón P, Soto MJ, Cuadrado MJ, Khamashta MA**. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol 2008; 22(5):847–861. doi:10.1016/j.berh.2008.09.008
14. **Mariette X, Matucci-Cerinic M, Pavelka K, et al**. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011; 70(11):1895–1904. doi:10.1136/ard.2010.149419
15. **Scott FI, Mamtani R, Brensinger CM, et al**. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA Dermatol 2016; 152(2):164–172. doi:10.1001/jamadermatol.2015.3029
16. **Mercer LK, Askling J, Raaschou P, et al**. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. Ann Rheum Dis 2017; 76(2):386–391. doi:10.1136/annrheumdis-2016-209285
17. **Fabbrocini G, Panariello L, Caro G, Cacciapuoti S**. Acneiform rash induced by EGFR inhibitors: review of the literature and new insights. Skin Appendage Disord 2015; 1(1):31–37. doi:10.1159/000371821
18. **Busam KJ, Capodieci P, Motzer R, Kiehn T, Phelan D, Halpern AC**. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. Br J Dermatol 2001; 144(6):1169–1176. doi:10.1046/j.1365-2133.2001.04226.x
19. **Jatoi A, Nguyen PL**. Do patients die from rashes from epidermal growth factor receptor inhibitors? A systematic review to help counsel patients about holding therapy. Oncologist 2008; 13(11):1201–1204. doi:10.1634/theoncologist.2008-0149
20. **Druker BJ, Talpaz M, Resta DJ, et al**. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001; 344(14):1031–1037. doi:10.1056/NEJM200104053441401
21. **Kantarjian H, Sawyers C, Hochhaus A, et al; International STI571 CML Study Group**. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002; 346(9):645–652. doi:10.1056/NEJMoa011573
22. **Heidary N, Naik H, Burgin S**. Chemotherapeutic agents and the skin: an update. J Am Acad Dermatol 2008; 58(4):545–570. doi:10.1016/j.jaad.2008.01.001
23. **Kantarjian H, Giles F, Wunderle L, et al**. Nilotinib in imatinib-resistant

CML and Philadelphia chromosome-positive ALL. N Engl J Med 2006; 354(24):2542–2551. doi:10.1056/NEJMoa055104
24. **Cortes JE, Kantarjian HM, Brümmendorf TH, et al**. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011; 118(17):4567–4576. doi:10.1182/blood-2011-05-355594
25. **Abdel-Rahman O, Fouad M**. Risk of mucocutaneous toxicities in patients with solid tumors treated with sunitinib: a critical review and meta analysis. Expert Rev Anticancer Ther 2015; 15(1):129–141. doi:10.1586/14737140.2015.985660
26. **Strumberg D, Awada A, Hirte H, et al**. Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: is rash associated with treatment outcome? Eur J Cancer 2006; 42(4):548–556. doi:10.1016/j.ejca.2005.11.014
27. **Arnault JP, Wechsler J, Escudier B, et al**. Keratoacanthomas and squamous cell carcinomas in patients receiving sorafenib. J Clin Oncol 2009; 27(23):e59–e61. doi:10.1200/JCO.2009.23.4823
28. **Sternberg CN, Davis ID, Mardiak J, et al**. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28(6):1061–1068. doi:10.1200/JCO.2009.23.9764
29. **Fischer A, Wu S, Ho AL, Lacouture ME**. The risk of hand-foot skin reaction to axitinib, a novel VEGF inhibitor: a systematic review of literature and meta-analysis. Invest New Drugs 2013; 31(3):787–797. doi:10.1007/s10637-013-9927-x
30. **Wells SA Jr, Gosnell JE, Gagel RF, et al**. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010; 28(5):767–772. doi:10.1200/JCO.2009.23.6604
31. **Hsiao YW, Lin YC, Hui RC, Yang CH**. Fulminant acneiform eruptions after administration of dovitinib in a patient with renal cell carcinoma. J Clin Oncol 2011; 29(12):e340–e341. doi:10.1200/JCO.2010.32.9458
32. **Chapman PB, Hauschild A, Robert C, et al; BRIM-3 Study Group**. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364(26):2507–2516. doi:10.1056/NEJMoa1103782
33. **Ascierto PA, Minor D, Ribas A, et al**. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol 2013; 31(26):3205–3211. doi:10.1200/JCO.2013.49.8691
34. **Blechman AB, Cabell CE, Weinberger CH, et al**. Aggressive skin cancers occurring in patients treated with the Janus kinase inhibitor ruxolitinib. J Drugs Dermatol 2017; 16(5):508–511. pmid:28628689
35. **Guan M, Zhou YP, Sun JL, Chen SC**. Adverse events of monoclonal antibodies used for cancer therapy. Biomed Res Int 2015; 2015:428169. doi:10.1155/2015/428169
36. **Vila AT, Puig L, Fernández-Figueras MT, Laiz AM, Vidal D, Alomar A**. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. Br J Dermatol 2005; 153(2):417–423. doi:10.1111/j.1365-2133.2005.06635.x
37. **Rocchi V, Puxeddu I, Cataldo G, et al**. Hypersensitivity reactions to tocilizumab: role of skin tests in diagnosis. Rheumatology (Oxford) 2014; 53(8):1527–1529. doi:10.1093/rheumatology/keu181
38. **Dika E, Ravaioli GM, Fanti PA, et al**. Cutaneous adverse effects during ipilimumab treatment for metastatic melanoma: a prospective study. Eur J Dermatol 2017; 27(3):266–270. doi:10.1684/ejd.2017.3023
39. **Shen J, Chang J, Mendenhall M, Cherry G, Goldman JW, Kulkarni RP**. Diverse cutaneous adverse eruptions caused by anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) immunotherapies: clinical features and management. Ther Adv Med Oncol 2018; 10:1758834017751634. doi:10.1177/1758834017751634

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REVIEW

CME MOC

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# Aspirin for primary prevention of atherosclerotic cardiovascular events

## ABSTRACT

Recent trials evaluated the impact of aspirin for primary prevention of cardiovascular events in patients at intermediate risk, patients with diabetes, and the elderly, and the results have been incorporated into the most recent professional guidelines. For the most part, the role of aspirin in primary prevention remains limited, albeit not adequately tested in those at higher risk.

## KEY POINTS

Using aspirin for the sole purpose of primary prevention is discouraged in healthy elderly patients (age > 70) and those at high risk of bleeding, including patients on anticoagulation.

Routine use of aspirin for the sole purpose of primary prevention is best deferred in patients at low risk (< 5% 10-year risk) and borderline risk (5%–7.5% 10-year risk). However, in selected patients at borderline risk, such as those with a strong family history, clinicians could also consider risk-enhancers such as coronary calcium.

A shared decision to initiate aspirin in those at intermediate risk (7.5%–20% 10-year risk) could be considered for patients with a risk-enhancer such as an elevated coronary calcium score (> 100) or elevated lipoprotein(a) (> 50 mg/dL).

In patients age 40 to 70 at high risk (> 20% at 10 years), it is reasonable to consider starting low-dose aspirin as a shared decision if the patient is thought to be at low risk of bleeding.

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Aspirin is one of the most widely used drugs in cardiovascular medicine, with one-third of adults over the age of 40 using it for either primary or secondary prevention of major cardiovascular events. But does this widespread use achieve the intended goal of reducing the incidence of cardiovascular events and death?

The use of aspirin undoubtedly reduces the risk of a subsequent cardiovascular event or death from vascular causes when used for secondary prevention—eg, in patients who have had a myocardial infarction, stroke, or symptomatic peripheral arterial disease or who have undergone coronary revascularization.[1–5] However, its net impact in primary prevention (ie, in patients without established cardiovascular disease or previous coronary revascularization) has been debated for years.[5–7]

Recent clinical trials have reevaluated the role of aspirin in primary prevention.[8–12] The results suggest that aspirin should play a more limited role than in the past, and this evidence has resulted in an update in the recommendations from the American Heart Association (AHA) and American College of Cardiology (ACC).[13]

This review examines the evidence on the risk-benefit profile of aspirin in primary prevention of cardiovascular events (**Table 1**),[8–12,14–24] summarizes current recommendations on this topic, and proposes an evidence-based algorithm to guide the use of aspirin for primary prevention in clinical practice.

## CONFLICTING EVIDENCE FROM OLDER TRIALS

### ATC meta-analysis, 2009

The Anti-thrombotic Trialists' Collaboration (ATC) meta-analysis, published in 2009, was a landmark study of the role of aspirin in pri-

TABLE 1

## Trials of aspirin as primary prevention

| Trial | Year | Population | Number needed to treat or harm[a] | | |
|---|---|---|---|---|---|
| | | | Nonfatal myocardial infarction | Nonfatal ischemic stroke | Major gastrointestinal bleed |
| **BDS**[14] | 1988 | 5,139 healthy male physicians | [143] | [250] | ND |
| **PHS**[15] | 1989 | 22,071 healthy male physicians | 67 | [333] | [250] |
| **TPT**[16] | 1998 | 5,085 men at high risk | 40 | 125 | [250] |
| **HOT**[17] | 1998 | 18,790 people with hypertension | 77 | 1,000 | [71] |
| **PPP**[19] | 2003 | 4,495 people with risk factors | 143 | 250 | 333 |
| **WHS**[18] | 2005 | 39,876 healthy female nurses | ND | 500 | 1,000 |
| **POPADAD**[21] | 2008 | 1,276 people with diabetes, ABI ≤ 0.99 | 500 | 36 | 143 |
| **JPAD**[23] | 2008 | 2,539 people with diabetes | [167] | 1,000 | [200] |
| **AAA**[24] | 2010 | 3,350 people with ABI ≤ 0.91 | 200 | 1,000 | [1,000] |
| **JPPP**[22] | 2014 | 14,000 people with ≥ 1 risk factor | 250 | ND | [50] |
| **ARRIVE**[8] | 2018 | 12,526 men with 2–4 risk factors or women with ≥ 3 risk factors | 333 | 333 | [100] |
| **ASCEND**[9] | 2018 | 15,480 people with diabetes | 1,000 | 333 | [167] |
| **ASPREE**[10–12] | 2018 | 19,114 healthy elderly | 333 | 250 | 42 |

[a]The number of patients who would need to be treated for 10 years to prevent or cause 1 event, calculated as the inverse of the absolute difference in the proportion of patients with events per year between the aspirin and placebo groups. Numbers in brackets indicate harm, ie, higher rates in the aspirin group.

AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle-brachial index; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = A Study of Cardiovascular Events in Diabetes (ASCEND) and Aspirin in Reducing Events in the Elderly; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; BDS = British Doctors Study; HOT = Hypertension Optimal Treatment; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; ND = no difference; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

**Aspirin is one of the most widely used drugs in cardiovascular medicine**

mary prevention.[5] It analyzed patient-level data from 6 trials published between 1988 and 2005,[14–19] mostly addressing the impact of aspirin in patients at low risk, with an event rate of about 0.5% per year (or 5% in 10 years).

Serious vascular events (myocardial infarction, stroke, and vascular death) occurred at a rate of 0.51% per year in the aspirin groups and 0.57% in the placebo groups. Although this represented a 12% reduction in relative risk (relative risk [RR] 0.88, 95% confidence interval [CI] 0.82–0.94, $P$ = .0001), the absolute risk reduction was very modest: 1,667 patients would need to be treated for 1 year (or 167 for 10 years) to prevent 1 major cardiovascular event. This reduction was primarily driven by a reduction in nonfatal myocardial infarctions and ischemic strokes but not in vascular mortality.

Although all the prespecified subgroups showed a similar proportional reduction in major cardiovascular events, the data suggested that men and women might benefit differently from aspirin. Men primarily experienced a reduction in nonfatal myocardial infarctions, while women benefited from a reduction in ischemic strokes.[5,20] However, this differential effect was not noted in the secondary prevention cohort of the meta-analysis and was no longer statistically significant when accounting for multiple comparisons.

The modest reduction in nonfatal cardiovascular events came at the cost of excess bleeding—and 1 in every 4 events was a hemorrhagic stroke. Major extracranial bleeding occurred in 0.10% of the aspirin recipients and 0.07% of the placebo recipients, and hemorrhagic stroke occurred in 0.04% vs 0.03%, for an increase of 0.04% per year in the rate of major bleeding. Thus, 1 major bleeding event would be caused after treating 333 patients for 10 years. Based on this evidence, 2 nonfatal cardiovascular events would be prevented per major bleed caused.

Hence, the net impact of aspirin for primary prevention of major cardiovascular events was at best marginal in these earlier trials, mainly reducing the incidence of nonfatal cardiovascular events and largely counterbalanced by the risk of bleeding.

Also, at the time these data were gathered, best preventive practices and aspirin dosing significantly differed from the current standard of care. Today, tighter blood pressure control, lower rates of smoking, and widespread use of statins likely make the risk-benefit profile of aspirin in primary prevention less favorable. For instance, using a statin halves the benefit of aspirin without attenuating the bleeding risk, which could completely dissipate the marginal benefit reported in the ATC meta-analysis and perhaps render aspirin harmful in patients at low risk.[5]

**Aspirin would cause about 1 major bleeding event for every 2 cardiovascular events prevented**

Despite the very modest benefits reported in these early trials, debate continued as to whether the net impact would be more favorable in patients at higher risk of cardiovascular events. Evidence supporting this notion was that the relative risk reduction in major cardiovascular events was about the same in both primary prevention (RR 0.88, 95% CI 0.82–0.94) and secondary prevention (RR 0.81, 95% CI 0.82–1.00).[5] For context, giving aspirin in the secondary prevention cohort resulted in a 1.5%-per-year absolute reduction (number needed to treat 7 for 10 years) in the annual rate of major cardiovascular events compared with the marginal absolute reduction of 0.07% per year (number needed to treat 167 for 10 years) in the primary prevention cohort. This difference in absolute benefit is due to the substantially higher baseline rate of cardiovascular events in the secondary prevention group.

### Further studies, 2008–2014

Hence, a second wave of studies, published between 2008 and 2014, sought to evaluate the impact of aspirin for primary prevention in a higher-risk population, ie, patients with diabetes, low ankle-brachial index, or other cardiovascular risk factors.[21–24] Despite this intention, these trials, like the earlier ones, largely studied a low-risk population. Only in the Prevention of Progression of Arterial Disease and Diabetes trial was the event risk greater than 1% per year (or > 10% in 10 years).[21]

Most of these studies were small and therefore lacked the power to detect differences in cardiovascular event rates, with only the Japanese Primary Prevention Project having a sample size comparable to the earlier trials.[22]

Collectively, these studies failed to show any benefit of aspirin for primary prevention of major cardiovascular events, and even the better-powered Japanese Primary Prevention Project was stopped early due to futility regarding the composite end point of death, myocardial infarction, and stroke. Although an overall negative trial, this was the only study from 2008 to 2014 to report a potential reduction in nonfatal myocardial infarction as a secondary end point, a suggested benefit that was largely counterbalanced by a higher rate of major bleeding.[22]

The negative results of these studies came as a surprise and greatly contrasted with the at-least marginal benefit reported by the earlier trials. These results were attributed in part to lack of statistical power but also to improved management of cardiovascular risk factors with tighter blood pressure control, smoking cessation, and statin use.

To overcome the lack of power of these trials, an updated meta-analysis was conducted, pooling all available studies from 1988 through 2014, which replicated the finding of marginal benefit of aspirin reported in the ATC analysis. Yet the results were mainly driven by studies published before 2005, with no benefit found in the later trials.[25,26]

## CONTEMPORARY TRIALS: THE TIEBREAKER?

Three recent clinical trials examined the role of aspirin for primary prevention of major cardiovascular events in a contemporary cohort

of patients thought to be at higher risk of cardiovascular events in 3 distinct populations:

- Patients at moderately elevated risk of cardiovascular events (estimated 10-year risk 10%–20%)[8]
- Patients with diabetes[9]
- The elderly.[10–12]

### The ARRIVE trial: No benefit in patients at low risk

The use of aspirin for primary prevention of cardiovascular events in those with elevated risk has been a point of heated debate in clinical practice.

The ASA to Reduce Risk of Initial Vascular Event (ARRIVE) trial[8] was designed to clarify the benefit of aspirin in patients with an estimated 10-year risk of 10% to 20%. However, the actual rate of events was lower, at about 0.8% per year (or 8% in 10 years). Due to the low rate of events, the original primary end point (myocardial infarction, stroke, and cardiovascular death) had to be modified to include unstable angina and transient ischemic attack to adequately power the study.

The incidence of the primary composite end point and those of each component of the composite end point was no different between the aspirin and control groups. However, aspirin was associated with a significant reduction in myocardial infarction on per-protocol analysis. This finding must be interpreted with caution, given the potential for bias associated with a per-protocol analysis, although it provides an opportunity to explore the impact of aspirin in those that completed the intended intervention.

On the other hand, the use of aspirin was associated with a 2-fold higher rate of gastrointestinal bleeding (0.97% vs 0.46%, $P$ = .0007), predominantly mild gastrointestinal bleeding. Approximately 1 gastrointestinal bleeding event would be caused by treating 196 patients for 10 years. Importantly, the incidence of bleeding was likely underestimated in this study, given the exclusion of patients perceived to be at higher risk of bleeding at enrollment.

In summary, this study found aspirin to have an unfavorable risk-benefit profile when used for primary prevention of cardiovascular events in a contemporary low-risk cohort. In this patient population, aspirin offers no adjunctive cardiovascular preventive benefit and moreover increases the risk of bleeding. Whether the cardiovascular benefit of aspirin in a higher-risk (> 10%–20% estimated 10-year risk) population without diabetes outweighs the bleeding risk remains unknown.

### The ASCEND trial: Modest benefit in patients with diabetes

Preventive use of aspirin in patients with diabetes without established atherosclerotic cardiovascular disease has been another point of controversy. Patients with diabetes suffer a 2- to 3-fold higher rate of cardiovascular events, and they are thus thought to be a population that could benefit from preventive use of aspirin. Although earlier trials in patients with diabetes failed to demonstrate a definite benefit of aspirin in this group, these studies were grossly underpowered.

The larger Study of Cardiovascular Events in Diabetes (ASCEND) trial[9] assessed the benefit of aspirin in men and women age 40 or older with diabetes and without atherosclerotic cardiovascular disease. Once again, the event rate was lower than anticipated, with an annual risk of 1.25% to 1.3% (or estimated 10-year risk of 12%–13%). As a result, the sample size and follow-up had to be increased, and the primary composite end point was modified to include transient ischemic attack to maintain the intended power.

**Statins may dilute the potential benefit of aspirin**

Preventive use of aspirin resulted in an absolute reduction of 0.17% per year in the rate of the composite end point of nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, and vascular death (hazard ratio [HR] 0.88, 95% CI 0.79–0.97, $P$ = .01). A total of 59 patients would need to be treated for 10 years to prevent 1 major cardiovascular event.

However, there was an absolute annual excess in major bleeding of 0.13% per year (HR 1.29, 95% CI 1.09–1.52, $P$ = .003), which included gastrointestinal (62.3%), ocular (21.1%), intracranial (17.2%), and other site (20.4%) bleeds. Thus, 1 major bleeding event would be caused after treating 77 patients for 10 years. Thus, the use of low-dose aspirin in patients with diabetes (> 10% risk at 10 years) led to a modest reduction in cardiovascular

events that was largely offset by an increase in major bleeding.

### The ASPREE trial: Aspirin was harmful in the elderly

Similarly, the elderly are a population at increased risk of cardiovascular events that could, it was thought, profit from preventive use of aspirin.

The ASA in Reducing Events in the Elderly (ASPREE) trial sought to define the role of aspirin in those 70 years or older (or 65 or older if Hispanic or black) without established atherosclerotic cardiovascular disease and having a life expectancy longer than 5 years.[10–12] Those with a clinical diagnosis of dementia, substantial physical disability, or high bleeding risk were excluded, as were those adhering to their medications less than 80% of the time during a run-in period. The main goal of the study was to determine if aspirin 100 mg daily would prolong a healthy life span in this population, using the composite end point of death, dementia, and persistent physical disability.

The study was stopped early due to futility after a mean follow-up of 4.7 years. There were no differences in the rates of the primary end point or individual secondary end points of cardiovascular events, dementia, or disability between the treatment groups.[10,12]

**Many questions remain about the use of aspirin for primary prevention of atherosclerotic cardiovascular disease**

Worse, the use of aspirin translated into a net excess of 0.24% per year in major bleeding events (HR 1.38, 95% CI 1.18–1.62, $P < .001$), resulting in 1 major bleeding event after treating 42 patients for 10 years. Again, this risk is likely underestimated, given the exclusion of patients who could not tolerate aspirin during the run-in period. Aspirin increased the rates of upper gastrointestinal bleeds (HR 1.87, 95% CI 1.32–2.66) and intracranial hemorrhage of any kind (HR 1.50, 95% CI 1.11–2.02).

Surprisingly, a higher rate of all-cause mortality (HR 1.14, 95% CI 1.01–1.29 was noted in the aspirin group, mainly driven by cancer death, particularly colorectal cancers, challenging the theory that aspirin could prevent this type of cancer.

In summary, this contemporary primary prevention trial demonstrated a rather deleterious effect of aspirin in an unselected healthy elderly population (age > 70).

### A new meta-analysis: Modest benefit, unacceptable risk

A 2019 meta-analysis[27] summarized all available evidence, including the contemporary trials.

The use of aspirin for primary prevention of atherosclerotic cardiovascular disease was associated with a 0.3%-per-year reduction in the absolute risk of myocardial infarction but no benefit in reducing the risk of stroke or death, a very modest benefit that disappears when analyzing only studies published after 2008. Further, aspirin use in primary prevention is consistently associated with an absolute increase in the rates of intracranial bleeding at 0.1% per year and major bleeding at 0.2% per year.[27]

Overall, the use of aspirin appears harmful when prescribed for primary prevention of cardiovascular events in lower-risk patients without diabetes and unselected healthy elderly populations (age > 70). In patients without diabetes, a total of 265 patients need to be treated with aspirin for 10 years to prevent 1 cardiovascular event, while 1 major bleeding event would be caused after treating 210 patients.

On the other hand, patients with diabetes without atherosclerotic cardiovascular disease appear to enjoy a modest reduction in cardiovascular events when prescribed aspirin for primary prevention, although this benefit is largely counterbalanced by an increase in bleeding. About 153 diabetic patients would need to be treated for 10 years to prevent 1 major cardiovascular event, while treating 121 patients for 10 years would cause 1 major bleeding event.

Many questions remain regarding the use of aspirin for primary prevention of atherosclerotic cardiovascular disease. For instance it is still largely unknown whether it is justified in a higher-risk primary prevention cohort (> 20% estimated 10-year risk), or those with uncontrolled risk factors or risk enhancers such as coronary calcium, elevated lipoprotein(a), or elevated inflammatory markers.

## PAST GUIDELINE UNCERTAINTIES AND CURRENT RECOMMENDATIONS

Major cardiovascular societies have interpreted the available evidence differently, leading to discrepant recommendations on the use of

TABLE 2

## Aspirin for primary prevention: Recommendations from major societies

**American Heart Association/American College of Cardiology, 2002**[7]

Low-dose aspirin recommended in persons at higher cardiovascular risk, especially those with 1-year risk ≥ 10%

Low-dose aspirin recommended in patients with diabetes at increased cardiovascular risk, including those who are over age 40 or who have additional risk factors

Therapy should not be recommended for patients with diabetes under age 21 because of the increased risk of Reye syndrome associated with aspirin use in this population; patients with diabetes under age 30 have not been studied

**European Society of Cardiology, 2016**[6]

Antiplatelet therapy is not recommended in individuals without cardiovascular disease due to the increased risk of major bleeding

Antiplatelet therapy (eg, aspirin) is not recommended for people with diabetes who do not have cardiovascular disease

**US Preventive Services Task Force, 2017**[34]

Low-dose aspirin is recommended in adults ages 50–59 who have a ≥ 10% 10-year risk, are not at increased risk for bleeding, have a life expectancy of ≥ 10 years, and are willing to take it daily for ≥ 10 years

The decision to initiate low-dose aspirin for primary prevention of cardiovascular disease and colorectal cancer in adults ages 60–69 who have a 10% or greater 10-year cardiovascular disease risk should be an individual one

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in adults under age 50

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for primary prevention of cardiovascular disease and colorectal cancer in adults age 70 or older

**American Academy of Family Physicians, 2016**[33]

Low-dose aspirin use for primary prevention of cardiovascular disease and colorectal cancer is recommended in adults ages 50–59 who have a 10% or greater 10-year cardiovascular disease risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years

The decision to initiate low-dose aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in adults ages 60–69 who have a 10% or greater 10-year cardiovascular disease risk should be an individual one

Evidence is insufficient to assess risk-benefit profile of aspirin for primary prevention of cardiovascular disease and colorectal cancer in adults younger than 50

The current evidence is insufficient to assess the balance of benefits and harms of starting aspirin for primary prevention of cardiovascular disease and colorectal cancer in adults age 70 or older

**American Diabetes Association, 2018**[32]

Low-dose aspirin may be considered as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased cardiovascular risk; this includes most men and women with diabetes age > 50 who have at least 1 additional major risk factor and are not at increased risk of bleeding

**American Heart Association/American College of Cardiology, 2019**[13]

Low-dose aspirin might be considered for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) among select adults ages 40–70 who are at higher ASCVD risk but not at increased bleeding risk

Low-dose aspirin should not be prescribed on a routine basis for primary prevention of ASCVD among adults age > 70

Low-dose aspirin should not be prescribed for primary prevention of ASCVD among adults of any age who are at increased risk of bleeding

aspirin in primary prevention (**Table 2**).[6,13,28–34]

**Earlier guidelines** from the AHA/ACC, US Preventive Services Task Force (USPSTF), and American Diabetes Association supported the use of aspirin for primary prevention of cardiovascular events in those at high risk.[28–32] The USPSTF and AHA/ACC used an estimated 10-year risk higher than 10% as a criterion for prophylactic initiation of aspirin. This recommendation was based on post hoc analysis of older trials that suggested with moderate certainty that the risk-benefit profile of aspirin was more favorable in those with an estimated 10-year risk greater than 10%, particularly in those age 50 to 59.

In contrast, the 2016 European Society of Cardiology guidelines[6] advised against using aspirin for primary prevention, even before the 3 newer trials described above were published. This recommendation was based on a more direct interpretation of the evidence, acknowledging that even if aspirin conferred a very modest reduction in nonfatal cardiovascular events, this was largely offset by an increase in bleeding, with no decrease in mortality.

**The decision to start aspirin should be individualized and shared**

**AHA/ACC 2019.** Most recently, the AHA/ACC updated their recommendations,[13] considering the evidence from the newer trials. The 2019 AHA/ACC guidelines recognized the greatly attenuated benefit of adjunctive aspirin in contemporary optimal medical management and acknowledged the systematic overestimation of risk with the use of pooled cohort equations. Hence, they downgraded the class of recommendation for prophylactic use of aspirin to class IIb ("it may be considered") and removed any specific pooled cohort equation risk levels as criteria for recommending aspirin. In the new guidelines, prophylactic use of aspirin may be considered in selected adults age 40 to 70 at higher risk of atherosclerotic cardiovascular disease without a higher bleeding risk. In contrast, routine use of aspirin in healthy elders age 70 or older and in those at high bleeding risk is discouraged.

These more cautious recommendations highlight the lingering uncertainty about the impact of this intervention in those at the higher end of the cardiovascular risk spectrum such as those with uncontrolled risk factors despite optimal medical management, those with subclinical coronary atherosclerosis, and those with additional risk-enhancing factors such as elevated inflammatory markers or elevated lipoprotein(a).

Ultimately, the guidelines defer the decision to initiate aspirin for primary prevention to the patient-clinician encounter after weighing the risk vs the possible benefit in the patient in question and the totality of the evidence available.[13]

## REMAINING GAPS IN KNOWLEDGE

As previously mentioned, most of the available evidence pertains to a low-risk primary prevention cohort, and no high-quality study has been conducted to assess the net risk-benefit profile of aspirin in selected young patients (age < 40) or in high-risk patients (> 20% 10-year risk) such as those with uncontrolled risk factors or risk enhancers. Therefore, great uncertainty remains about the potential impact of aspirin in selected young patients and those thought to be at the higher end of the risk spectrum.

**Patients at high risk.** Although a larger absolute benefit would be expected in those at higher baseline cardiovascular risk, it is also anticipated that the bleeding risk will increase, given the concomitant increase in bleeding associated with several cardiovascular risk factors such old age, diabetes, obesity, and smoking.[30] Whether these risk factors increase cardiovascular disease and bleeding risk by the same magnitude remains unknown. Hence, the patient profile and the specific risk cutoff at which the primary prevention benefits of aspirin outweigh the bleeding risk remain unknown.

Another area of ambiguity relates to the proper classification (primary vs secondary prevention cohort) and subsequent management of patients without symptoms who are found incidentally to have atherosclerotic cardiovascular disease on coronary angiography or noninvasive imaging such as coronary artery calcium scoring or coronary computed tomographic angiography.

**Coronary calcium.** It is well known that the total burden of coronary plaque directly correlates with the rate of cardiovascular

events. Such plaque burden can be easily estimated by measuring coronary artery calcium, with higher calcium scores resulting in proportional increment in cardiovascular risk.

Therefore, measuring coronary calcium greatly enhances the accuracy in estimating risk of cardiovascular events irrespective of age and comorbidities.[35] For instance, patients with a calcium score greater than 100 experience cardiovascular events at a rate close to that in a stable secondary prevention population, while those with extensive calcium (scores > 1,000) experience event rates that exceed the rates observed in secondary prevention trials.[36,37] On the other hand, absence of coronary calcium (scores of 0) is equally helpful in establishing that patients are not at risk, which is particularly helpful in those with a borderline or intermediate risk estimation based on the pooled cohort equation.[38]

Evidence from the Multi-ethnic Study of Atherosclerosis (MESA)[39] suggested that the coronary calcium score might be of value when deciding whether to start aspirin for primary prevention of cardiovascular disease in patients without diabetes. In this regard, the risk-benefit profile of aspirin appears favorable in those with a calcium score greater than 100, with the odds of preventing vascular events 2 to 4 times higher than the chance of causing a bleed. In contrast, aspirin seems harmful in those with a score of 0, with a chance of bleeding that is 2 to 4 times higher than the likelihood of preventing a vascular event, regardless of traditional risk factors.

**Lipoprotein(a).** Similarly, the utility of lipoprotein(a) to ascertain the benefit of aspirin for the primary prevention of cardiovascular events remains uncertain. In a substudy from the Women's Health Study,[40] an elevated lipoprotein(a) was associated with a 2-fold higher rate of cardiovascular events, which was effectively attenuated by the use of aspirin.

High-quality studies are needed to define the role of coronary calcium and lipoprotein(a) in the decision to start aspirin for primary prevention of atherosclerotic cardiovascular disease in patients both with and without diabetes.

**Aspirin dose.** The optimal aspirin dose for primary prevention events remains uncertain. The current understanding is that low doses (75–100 mg per day) are effective in preventing vascular events while minimizing bleeding rates. On the other hand, the impact of statins and proton-pump inhibitors on the risk-benefit profile of aspirin in primary prevention remains unresolved.[41] Further studies are needed to evaluate the optimal aspirin dosing. The upcoming ASA and Simvastatin Combination for Cardiovascular Events Prevention Trial (ACCEPT-D) is set to evaluate the strongly suspected attenuation effect of statins on the aspirin benefit.[42]

## FROM THE EVIDENCE TO THE PATIENT

The decision to defer or prescribe aspirin in clinical practice for primary prevention of cardiovascular events remains a challenging one and should be individualized. It is important to first emphasize that primary prevention recommendations only apply to those patients without established atherosclerotic cardiovascular disease, namely no prior myocardial infarction, no prior ischemic stroke, no symptomatic peripheral arterial disease, and no prior coronary revascularization. In patients with these conditions, ie, the secondary prevention cohort, the benefit of aspirin is well established.

Primary prevention should always begin with encouragement of healthy life habits and optimal management of cardiovascular risk factors including weight loss, glucose and blood pressure control, and lipid management, per preventive guideline recommendations.[13]

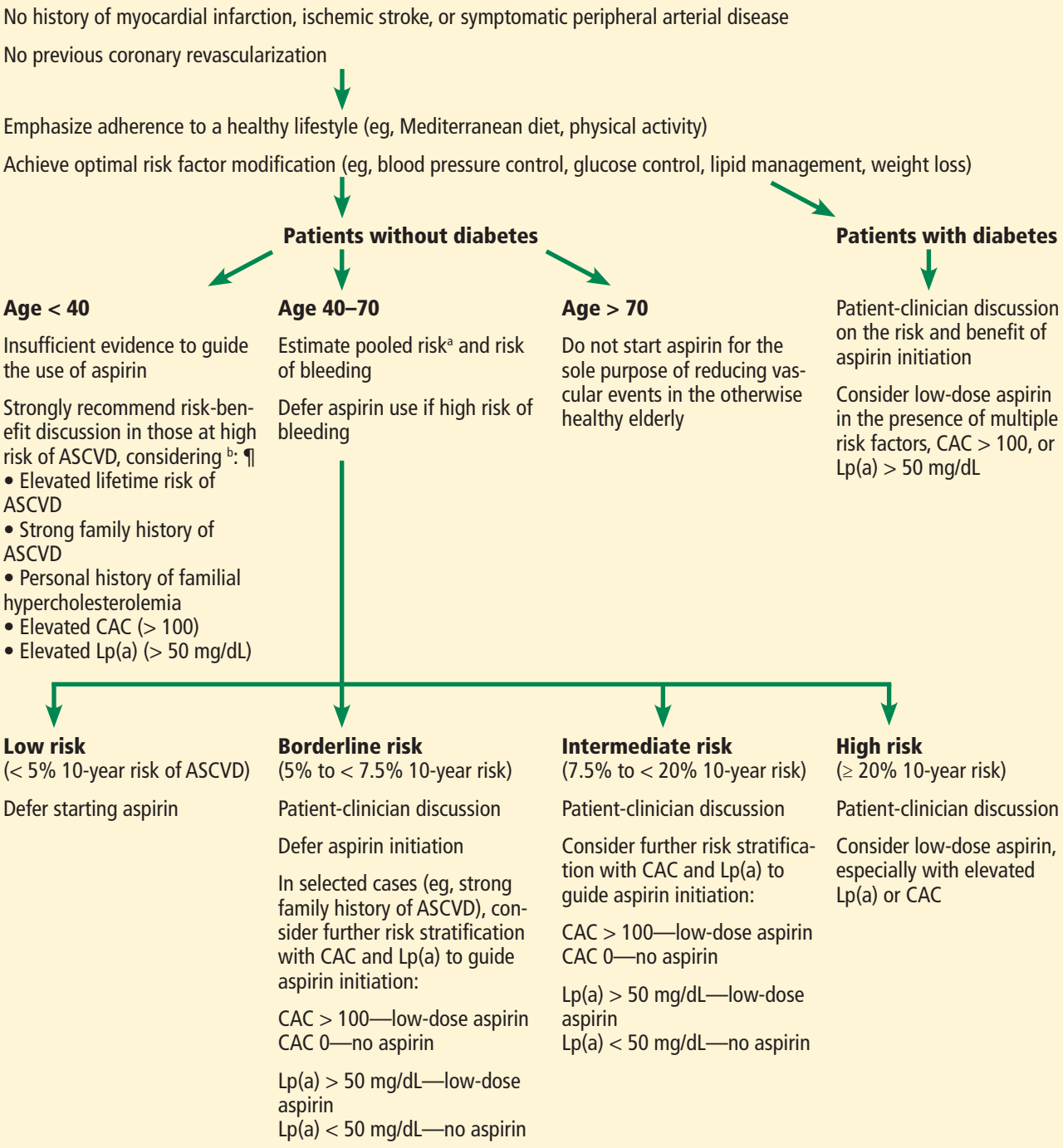
**Primary prevention should always begin with encouragement of healthy life habits and optimal management of cardiovascular risk factors**

The risk of atherosclerotic cardiovascular disease should be estimated using the pooled cohort equation in every patient before deciding on the prophylactic use of aspirin. In the new guidelines, patients are classified into 4 risk categories based on the pooled cohort equation[13]:

- Low risk (10-year risk < 5%)
- Borderline risk (5% to < 7.5%)
- Intermediate risk (7.5% to < 20%)
- High risk (≥ 20%).

Of importance, the current risk estimation tools (including the 10-year pooled cohort equation) systematically overestimate risk.

## Aspirin for primary prevention of cardiovascular disease




[a] Consider the consistent overestimation of cardiovascular risk by current scoring systems.
[b] Defer aspirin in patients with increased risk of bleeding.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium score; Lp(a) = lipoprotein(a)

**Figure 1.** Our recommendations for aspirin use for primary prevention of cardiovascular events.

Hence, incorporation of risk enhancers (eg, positive family history, elevated inflammatory markers, elevated lipoprotein(a), coronary calcium) could further refine the accuracy of the risk estimation and guide the escalation of preventive measures in selected cases. Although the use of such risk enhancers was mainly designed to guide statin therapy, they may also guide the decision to initiate aspirin in primary prevention, particularly coronary calcium and lipoprotein(a) based on available data as described above (**Figure 1**).

Ultimately, a preventive regimen of aspirin must reduce the rate of cardiovascular events by an absolute magnitude that is clinically meaningful, emphasizing the focus on treating those patients at the higher end of the cardiovascular risk spectrum.

It is equally important to estimate the risk of bleeding when considering primary preventive use of aspirin. Such risk might vary among patients based on age, concomitant medications, and comorbidities.[5] The use of aspirin in primary prevention confers a 1.0% risk of bleeding over a 5-year period in men and a 1.1% risk in women. Age, smoking history, and diabetes, as well as a history of previous bleeding, peptic ulcer disease, cancer, and use of nonsteroidal anti-inflammatory drugs are associated with a further increase in the risk of bleeding.[43] Similarly, it is well established that concomitant use of aspirin and anticoagulation is associated with a significant increase in bleeding with no ischemic benefit in a wide range of scenarios including primary prevention and atrial fibrillation.[44,45]

In summary, giving aspirin for primary prevention is to be considered only when the estimated cardioprotective effects of aspirin outweigh the bleeding risk on therapy.

The following recommendations are meant to provide a general guidance on the use of aspirin in clinical practice. However, the ultimate decision on whether to start or defer aspirin for primary prevention must be shared, considering the individual risk-benefit profile and the preferences of the patient at hand.

- The use of aspirin for the sole purpose of primary prevention is discouraged in healthy elderly patients (age > 70) and those at high risk of bleeding, including patients on anticoagulation.
- Similarly, routine use of aspirin for the sole purpose of primary prevention is best deferred in patients at low risk (< 5% 10-year risk) and borderline risk (5%–7.5% 10-year risk). In selected cases in patients at borderline risk such as those with a strong family history, clinicians could also consider risk enhancers such as coronary calcium in the discussion about the risks and benefits of starting aspirin.
- A shared decision to initiate aspirin in those at intermediate risk (7.5%–20% 10-year risk) could be considered for patients with risk enhancers such as an elevated coronary calcium score (> 100) or elevated lipoprotein(a) (> 50 mg/dL).
- In patients ages 40 to 70 at high risk of atherosclerotic cardiovascular disease (> 20% at 10 years), it is reasonable to consider starting low-dose aspirin as a shared decision if the patient is thought to be at low risk of bleeding.
- Finally, scarcity of data in those younger than 40 precludes any recommendation to guide the use of aspirin in this population. A shared decision on the benefit of aspirin in younger patients (age < 40) is recommended in selected cases at high risk of atherosclerotic cardiovascular disease based on an elevated lifetime risk, strong family history, familial hypercholesterolemia, elevated coronary calcium score, or elevated lipoprotein(a).
- Patients with diabetes are a unique population at higher risk of cardiovascular events. Again, risk factor modification is the first step for primary prevention of cardiovascular disease in this population, including glucose control favoring medications with proven cardiovascular benefit. Patient-clinician risk discussion is strongly recommended to decide on the added value of starting aspirin in patients with diabetes, weighing perceived benefits against risks to the patient at hand. It is best to defer aspirin use in those at high risk of bleeding, while starting aspirin is reasonable in those patients with diabetes with multiple additional risk factors or who have risk enhancers such as a coronary calcium score higher than 100 and elevated lipoprotein(a).

**Ultimately, a preventive regimen of aspirin must reduce the rate of cardiovascular events by an absolute magnitude that is clinically meaningful**

## CONCLUSION

Despite the large amount of data, the role of aspirin in contemporary practice for primary prevention of cardiovascular disease remains debatable. In contrast to the modest benefit reported by older trials, the most recent trials largely challenged the benefit of aspirin in current practice. This is in great part explained, as anticipated, by improved best preventive practices (eg, blood pressure control, lipid management with statins, smoking cessation) that dilute the potential benefit from aspirin for primary prevention.[46]

Nonetheless, the existing evidence mainly comes from low-risk populations and fails to definitively ascertain the impact of aspirin in those at higher risk of cardiovascular disease. If aspirin use is to be considered for primary prevention, it must remain limited to selected patients at elevated risk of cardiovascular disease but low risk of bleeding. The use of risk enhancers such as elevated coronary calcium scores and elevated lipoprotein(a) may be useful to accurately identify such patients at the higher end of the risk spectrum.

Further studies are needed to determine the primary prevention subgroups that would benefit from low-dose aspirin.

## REFERENCES


1. **ISIS-2 Collaborative Group**. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 332(8607):349–360. doi:10.1016/S0140-6736(88)92833-4
2. **Sandercock PAG**. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. Lancet 1997; 349(9065):1569–1581. doi:10.1016/S0140-6736(97)04011-7
3. **Lewis HD, Davis JW, Archibald DG, et al**. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration cooperative study. N Engl J Med 1983; 309(7):396–403. doi:10.1056/NEJM198308183090703
4. **Gent M**. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348(9038):1329–1339. doi:10.1016/S0140-6736(96)09457-3
5. **Collins R, Peto R, Hennekens C, et al**. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373(9678):1849–1860. doi:10.1016/S0140-6736(09)60503-1
6. **Piepoli MF, Hoes AW, Agewall S, et al**. 2016 European guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol 2016; 23(11):NP1-NP96. doi:10.1177/2047487316653709
7. **Pearson TA, Blair SN, Daniels SR, et al**. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. Circulation 2002; 106(3):388–391. doi:10.1161/01.CIR.0000020190.45892.75
8. **Gaziano JM, Brotons C, Coppolecchia R, et al**. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018; 392(10152):1036–1046. doi:10.1016/S0140-6736(18)31924-X
9. **ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, et al**. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018; 379(16):1529–1539. doi:10.1056/NEJMoa1804988
10. **McNeil JJ, Wolfe R, Woods RL, et al**. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018; 379(16):1509–1518. doi:10.1056/NEJMoa1805819
11. **McNeil JJ, Woods RL, Nelson MR, et al**. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018; 379(16):1499–1508. doi:10.1056/NEJMoa1800722
12. **McNeil JJ, Nelson MR, Woods RL, et al**. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018; 379(16):1519–1528. doi:10.1056/NEJMoa1803955
13. **Arnett DK, Blumenthal RS, Albert MA, et al**. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. J Am Coll Cardiol 2019. doi:10.1016/j.jacc.2019.03.010
14. **Peto R, Gray R, Collins R, et al**. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1988; 296(6618):313–316. doi:10.1136/bmj.296.6618.313
15. **Steering Committee of the Physicians' Health Study Research Group**. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989; 321(3):129–135. doi:10.1056/NEJM198907203210301
16. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998; 351(9098):233–241. pmid:9457092
17. **Hansson L, Zanchetti A, Carruthers SG, et al**. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 35(9118):1755–1762. doi:10.1016/s0140-6736(98)04311-6
18. **Ridker PM, Cook NR, Lee IM, et al**. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352(13):1293–1304. doi:10.1056/NEJMoa050613
19. **Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A**. Primary prevention of cardiovascular events with low dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care 2003; 26(12):3264–3272. doi:10.2337/diacare.26.12.3264
20. **Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL**. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006; 295(3):306–316. doi:10.1001/jama.295.3.306
21. **Belch J, MacCuish A, Campbell I, et al**. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008; 337:a1840. doi:10.1136/bmj.a1840
22. **Ikeda Y, Shimada K, Teramoto T, et al**. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA 2014; 312(23):2510–2520. doi:10.1001/jama.2014.15690
23. **Ogawa H, Nakayama M, Morimoto T, et al**. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008; 300(18):2134–2141. doi:10.1001/jama.2008.623
24. **Fowkes FGR, Price JF, Stewart MCW, et al**. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010; 303(9):841–848. doi:10.1001/jama.2010.221
25. **Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J**. Effect

of aspirin on mortality in the primary prevention of cardiovascular disease. Am J Med 2011; 124(7):621–629. doi:10.1016/j.amjmed.2011.01.018
26. **Raju N, Sobieraj-Teague M, Bosch J, Eikelboom JW**. Updated meta-analysis of aspirin in primary prevention of cardiovascular disease. Am J Med 2016; 129(5):e35–e36. doi:10.1016/j.amjmed.2015.10.046
27. **Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA**. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. Eur Heart J 2019; 40(7):607–617. doi:10.1093/eurheartj/ehy813
28. **Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP**. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2016; 164(12):804–813. doi:10.7326/M15-2113
29. **Whitlock EP, Williams SB, Burda BU, Feightner A, Beil T**. Aspirin use in adults: cancer, all-cause mortality, and harms: a systematic evidence review for the U.S. Preventive Services Task Force. US Prev Serv Task Force Evid Synth 2015; (132):AHRQ Publication No. 13-05193-EF-1.
30. **Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV**. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2016; 164(12):826–835. doi:10.7326/M15-2112
31. **Buse JB, Ginsberg HN, Bakris GL, et al**. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2007; 115(1):114–126. doi:10.1161/CIRCULATIONAHA.106.179294
32. **American Diabetes Association**. Cardiovascular disease and risk management: standards of medical care in diabetes 2018. Diabetes Care 2018; 41:S86–S104. doi:10.2337/dc18-S009
33. **AAFP**. Clinical preventive service recommendation. Aspirin use to prevent CVD and colorectal cancer. https://www.aafp.org/patient-care/clinical-recommendations/all/aspirin-use-prevention.html. Accessed April 2, 2020.
34. **USPSTF**. Final update summary: aspirin use to prevent cardiovascular disease and colorectal cancer: preventive medication. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer%5Cnhttp://www.cancernetwork.com/colorectal-cancer/uspstf-supports-aspirin-colorectal-cancer-prevention. Published 2016. Accessed February 12, 2018.
35. **Mitchell JD, Paisley R, Moon P, Novak E, Villines TC**. Coronary artery calcium and long-term risk of death, myocardial infarction, and stroke: the Walter Reed Cohort Study. JACC Cardiovasc Imaging 2018. doi:10.1016/j.jcmg.2017.09.003
36. **Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE**. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol 2018; 72(4):434–447. doi:10.1016/j.jacc.2018.05.027
37. **Blankstein R, Chandrashekhar Y**. Extensive coronary artery calcifications: no longer primary prevention! JACC Cardiovasc Imaging 2020; 13(1 pt 10):183–185. doi:10.1016/j.jcmg.2019.12.007
38. **Blaha MJ, Cainzos-Achirica M, Greenland P, et al**. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2016. doi:10.1161/CIRCULATIONAHA.115.018524
39. **Miedema MD, Duprez DA, Misialek JR, et al**. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Qual Outcomes 2014; 7(3):453–460. doi:10.1161/CIRCOUTCOMES.113.000690
40. **Chasman DI, Shiffman D, Zee RYL, et al**. Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. Atherosclerosis 2009; 203(2):371–376. doi:10.1016/j.atherosclerosis.2008.07.019
41. **Rothwell PM, Cook NR, Gaziano JM, et al**. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet 2018; 392(10145):387–399. doi:10.1016/S0140-6736(18)31133-4
42. **De Berardis G, Sacco M, Evangelista V, et al**. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. Trials 2007; 8. doi:10.1186/1745-6215-8-21
43. **Selak V, Jackson R, Poppe K, et al**. Predicting bleeding risk to guide aspirin use for the primary prevention of cardiovascular disease. Ann Intern Med 2019. doi:10.7326/M18-2808
44. **Hamon M, Lemesle G, Tricot O, et al**. Incidence, source, determinants, and prognostic impact of major bleeding in outpatients with stable coronary artery disease. J Am Coll Cardiol 2014; 64(14):1430–1436. doi:10.1016/j.jacc.2014.07.957
45. **Yasuda S, Kaikita K, Akao M, et al; AFIRE Investigators**. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 2019; 381(12):1103–1113. doi:10.1056/NEJMoa1904143
46. **Meyer J, Arps K, Blumenthal RS, Martin SS**. New data on aspirin use in the era of more widespread statin use. American College of Cardiology, September 28, 2018. https://www.acc.org/latest-in-cardiology/articles/2018/09/28/08/08/new-data-on-aspirin-use-in-the-era-of-more-widespread-statin-use. Accessed March 25, 2020.

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## CORRECTION

# Familial hypercholesterolemia

The article, "Familial hypercholesterolemia: Detect, treat, and ask about family" by Drs. N. P. Shah, H. M. Ahmed, and W. H. Tang in the February 2020 issue (Cleve Clin J Med 2020; 87(2):109–120. doi:10.3949/ccjm.87a.19021) contained an error.

On page 118, first column, the last paragraph stated: "If patients strongly suspected of having familial hypercholesterolemia are on maximally tolerated statin therapy and ezetimibe and still have an LDL-C level of 100 mg/dL or higher or are statin-intolerant, then PCSK9 inhibitors can be considered (class IIb recommendation, level of evidence B-R).[50] In secondary prevention cases, LDL-C goals should be 70 mg/dL or less, according to the 2018 American College of Cardiology and American Heart Association cholesterol guidelines, and 55 mg/dL or less according to the American Diabetes Association (class IIa recommendation, level of evidence A [clear evidence]).[50]"

The recommendation for a lower LDL-C goal of 55 mg/dL or less in secondary prevention is not from the American Diabetes Association but rather from the American Association of Clinical Endocrinologists and American College of Endocrinology (recommendation grade A, best level of evidence 1 [strong evidence]), reference 66 in the article. The error has been corrected online.