HOSPITAL MEDICINE™ SUMMIT

Proceedings from the September 26, 2020 Hospital Medicine Summit

INTEGRITY
CONTINUING EDUCATION

Program Overview

The 2020 Hospital Medicine Summit (HMS) is an innovative, multisupported, multifaceted educational initiative designed to provide important educational updates from leading experts on conditions that are commonly encountered by healthcare clinicians practicing in the hospital and internal medicine settings.

This Hospital Medicine Summit Proceedings Monograph summarizes recent clinical trial data, practical strategies and detailed discussions presented by leading experts during the September 26, 2020 virtual symposium.

Program Chair

Alpesh Amin, MD, MBA, FACC, MACP, SFHM
Thomas & Mary Cesario Chair of Medicine
Professor of Medicine, Business, Public Health, Nursing Science, and Biomedical Engineering
Executive Director, Hospitalist Program
Medical Director, Anticoagulation Services
University of California, Irvine
Irvine, California

Editorial Assistance:

Kathleen Wildasin, MA
Medical/Science Writer
Lexington, Kentucky

Target Audience

This educational initiative has been designed for physicians, physician assistants, nurse practitioners, registered nurses, and pharmacists who practice in hospital and internal medicine settings.

Release date: December 30, 2020
Expiration date: December 30, 2021
Estimated time to complete activity: 2.0 hours

Learning Objectives

Drift, Shift, Evolve: Keeping Abreast of the Role of Antiviral Therapy in the Management of Seasonal Influenza

- Appraise the role of vaccination in reducing the spread of influenza and improving patient outcomes
- Employ updated guidelines for the diagnosis of influenza in the hospitalized patient
- Determine appropriate use of antiviral chemoprophylaxis for individuals at risk of influenza and associated complications
- Compare current and emerging antiviral agents based on efficacy and safety, dosage and administration, and reduction in duration of illness and complications in order to make individualized treatment decisions for patients with influenza

Assessment and Management of Hyperkalemia in the Hospital Setting: Optimizing Patient Outcomes

- Identify factors that increase risk for hyperkalemia
- Discuss the relationship between renin-angiotensin system (RAAS) inhibitors and hyperkalemia development in patients with chronic kidney disease, heart failure, hypertension, and/or diabetes mellitus
- Apply to practice an understanding of clinical trial evidence for the efficacy and safety of newer potassium binders approved for treating hyperkalemia
- Employ a multidisciplinary, team-based approach to improve outcomes for patients with hyperkalemia

Optimizing Transitions From Hospital to Home: Best Practices for Reducing Readmissions in Heart Failure

- Apply diagnostic and assessment criteria to the effective management of patients with heart failure (HF)
- Integrate current guideline-directed medical therapy (GDMT) and recent clinical trial outcomes into the effective management of patients with HF
- Develop a comprehensive GDMT approach to HF management in patients who have recently experienced an acute heart failure episode
- Review proven strategies to achieve successful transitions of care in patients with HF

The Impact of COVID-19 on Hospital Medicine

- Discuss the impact of COVID-19 on hospital-based practice in the US
- Describe lessons learned in hospital surge and emergency medical preparedness
- Review and highlight key successes in the US healthcare system response to COVID-19

CME/CE Information

Physician Continuing Education

Accreditation Statement

Integrity Continuing Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation

Integrity Continuing Education designates this enduring material for a maximum of 2.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Pharmacist Continuing Education

Accreditation Statement

Global Education Group is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Credit Designation

Global Education Group designates this continuing education activity for 2.0 contact hours (0.20 CEUs) of the Accreditation Council for Pharmacy Education. (Universal Activity Number - 0530-9999-20-077-H01-P.)

This is a knowledge-based activity.

Nursing Continuing Education

Global Education Group is accredited with distinction as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

This educational activity for 2.0 contact hours is provided by Global Education Group. Nurses should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure of Conflicts of Interest (COI)

Integrity Continuing Education and Global Education Group requires instructors, planners, managers and other individuals who are in a position to control the content of this activity and their spouse/life partner to disclose any real or apparent COI they may have as related to the content of this activity. All identified COI are thoroughly vetted by Integrity Continuing Education and Global Education Group for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations.

Program Chair Disclosures:

Dr. Alpesh Amin, MD, MBA, FACC, MACP, SFHM

- COVID-19 Trials PI/Co-I – Alexion, Blade Therapeutics, Eli Lilly, Fulcrum Therapeutics, Humanigen, NIH/NIAID, NeuroRx Pharma, Novartis, OctaPharma, PTC Therapeutics, Pulmotect, Takeda
- Consulting Fees – AstraZeneca
- Ownership Interest – AseptiScope, Sprightly Health

The following planners and managers (along with their spouses/life partners) reported no financial relationships nor relationships to products or devices with commercial interests related to the content of this CME activity: Lindsay Borvansky, Rachel Brown, PharmD, MPH, Ashley Cann, Andrea Funk, Donna Fausak, Liddy Knight, Ashley Marostica, RN, MSN, Michelle R. Rizzo, ELS, Patima Tanapat, PhD, Kathleen Wildasin, MA.

Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. Integrity Continuing Education and Global Education Group do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of any organization associated with this activity. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Provider Statement

INTEGRITY CONTINUING EDUCATION
www.integrityce.com

global EDUCATION GROUP | UMA
A DIVISION OF ULTIMATE MEDICAL ACADEMY

This CME activity is provided by Integrity Continuing Education.

This CEU/CNE activity is jointly provided by Global Education Group and Integrity Continuing Education.

Supporter Acknowledgement

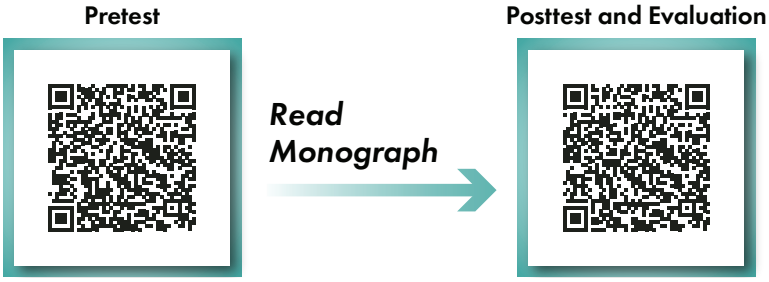
This activity is supported by educational grants from AstraZeneca Pharmaceuticals; Genentech, a member of the Roche Group; and Novartis Pharmaceuticals Corporation.

Instructions to Receive Credit

There are no fees for participating and receiving CME/CE credit for this activity. During the period of December 30, 2020 through December 30, 2021, participants must:

- Read the CME/CE information and the learning objectives
- Complete the pretest
- Study the educational activity
- Complete the posttest and the evaluation form

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Pharmacists must check the CPE monitor for their credits within 60 days of the activity. The pretest and posttest along with the evaluation can be accessed online at **www.integrityce.com/hms-supplement** or by scanning the QR codes below.



Contact Information

For information about ACCME accreditation of this activity, please contact Integrity Continuing Education at (855) 835-4004 or cme@integrityce.com.

For information about ACPE or ANCC accreditation of this activity, please contact Global at (303) 395-1782 or cme@globaleducationgroup.com.

Proceedings from the September 26, 2020 Hospital Medicine Summit

Since 2014, Integrity Continuing Education has produced the Hospital Medicine Summit (HMS), a multidisciplinary, multisupported educational initiative designed specifically for hospital-based and internal medicine clinicians. Now in its 6th year, HMS remains committed to providing clinically relevant educational updates from leading experts on conditions that are commonly encountered by healthcare clinicians practicing in the hospital setting.

This Hospital Medicine Summit Proceedings Monograph summarizes recent clinical trial data, practical strategies and detailed discussions presented by leading experts during the September 26, 2020 virtual symposium. The topics include the use of antiviral therapy in the management of influenza, the management of hyperkalemia in the inpatient setting, best practices for reducing readmissions in patients with heart failure, and last, but certainly not least, the everchanging effects of COVID-19 on healthcare clinicians practicing in the hospital setting.

As Program Chair for Hospital Medicine Summit, I have been excited about this unique educational conference and the feedback obtained from those who attended. The world of hospital medicine not only includes physicians such as hospitalists, intensivists, and emergency physicians that practice within the hospital setting but also other members of the multidisciplinary team such as nurses, pharmacists, case managers, social workers, nurse practitioners, physician assistants, dieticians, etc. Also, hospital-based practitioners not only have significant impact on a patient's care during their acute illness, but also have influence over the chronic management of the patient's care over the long run. Hospital Medicine Summit is an innovative curriculum-based series, focused on current medical trends impacting the delivery of patient care and the well-being of the multidisciplinary healthcare team. It includes a variety of topics focused on innovative systems of delivery, opportunities to improve care, and novel therapeutic strategies to achieve optimal outcomes across the continuum. Hospital Medicine Summit has been designed for the multidisciplinary team fostering the way healthcare should be delivered to optimize patient care outcomes and experience.

-Alpesh Amin, MD, MBA, MACP, SFHM, FACC, FRCP

HOSPITAL MEDICINE™
SUMMIT

Table of Contents

Drift, Shift, Evolve:
Keeping Abreast of the Role of Antiviral Therapy in the Management of Seasonal Influenza

Introduction

Seasonal influenza is an acute respiratory infection caused by influenza viruses that circulate in all parts of the world.[1] In the US, seasonal influenza viruses are detected year round, but are most common during the fall and winter.[2] There are four types of seasonal influenza viruses, A, B, C, and D; influenza viruses A and B circulate and cause seasonal disease epidemics.[1]

The medical burden associated with seasonal influenza is substantial and highly variable due to numerous factors, such as characteristics of the circulating virus, duration of the season, vaccine efficacy, and the number of individuals vaccinated.[3] In the US, influenza has resulted in 9 to 45 million symptomatic illnesses; 4 to 21 million medical visits; 140,000 to 810,000 hospitalizations; and 12,000 to 61,000 deaths annually between the 2010-11 through 2018-19 seasons.[3] Preliminary burden estimates for the 2019-2020 influenza season (October 1, 2019 through April 4, 2020) in the US are as follows: 39 to 56 million symptomatic illnesses; 18 to 26 million medical visits; 410,000 to 740,000 hospitalizations; and 24,000 to 62,000 deaths.[4]

Seasonal influenza in the US is also associated with a substantial economic burden to the healthcare system and society. In 2015, the estimated average annual total cost of influenza was $11.2 billion ($6.3 to $25.3 billion); direct medical costs were estimated to be $3.2 billion ($1.5 to $11.7 billion); and indirect costs were estimated to be $8.0 billion ($4.8 to $13.6 billion).[5]

Influenza Vaccination

The effectiveness of seasonal influenza vaccines in the US in the past 15 years has been highly variable, with rates ranging from 10% effectiveness in 2004-2005 to 60% effectiveness in 2010-2011.[6-8] Indeed, the 2010-2011 influenza season was much less severe than other recent seasons in terms of symptomatic illnesses, medical visits, hospitalizations, and deaths because there was a better match of the vaccine to the circulating virus strain.[8]

The overall influenza vaccination coverage among US adults in the 2018-2019 influenza season was 45.3%; the rate was higher in adults aged ≥65 years (68.1%) compared with those aged 18 to 49 years (34.9%) and 50 to 64 years (47.3%).[9] Notably, the rate of influenza vaccination coverage during the 2018-2019 season prevented an estimated 4.4 million influenza illnesses, 58,000 influenza hospitalizations, and 3500 influenza deaths.[10] Influenza vaccination has broader implications in the upcoming influenza season, as it will not only help to reduce the burden of influenza illness, hospitalization, and death, but also conserve medical resources for individuals with coronavirus disease 2019 (COVID-19).[11]

Diagnosing Influenza

Most patients with influenza have an uncomplicated illness that involves the abrupt onset of respiratory and systemic signs and symptoms, with or without fever.[12,13] General signs and symptoms may include fever, chills, malaise, fatigue, and confusion. Specific signs and symptoms may include headache, nasal congestion, rhinorrhea, sore throat/hoarseness, myalgia/arthralgia, weakness, chest pain, abdominal pain, vomiting, diarrhea, nonproductive cough, and pleuritic chest pain. Complicated influenza may involve the lower respiratory tract, as well as neurologic, cardiac, and musculoskeletal manifestations.[13]

Individuals who are at risk of influenza complications include adults aged ≥65 years, children aged ≤5 years (children aged <2 years face the highest risk, and infants aged <6 months have the highest hospitalization and death rates), pregnant women, women up to 2 weeks postpartum, American Indians, Alaska Natives, and people living in nursing homes and other long-term care facilities.[14] Additional risk factors for complicated influenza include asthma; chronic lung disease; neurological and neurodevelopmental conditions; blood disorders; endocrine disorders; heart disease; kidney, liver, or metabolic disorders; obesity; use of long-term aspirin or salicylate-containing medications in people aged <19 years; and a weakened immune system due to disease or medications.[14]

Influenza is not pathognomonic, thus differentiating it from other illnesses is difficult. The differential diagnosis of

influenza should exclude upper respiratory tract infection, infectious mononucleosis, and COVID-19, all three of which are associated with a more gradual disease onset and longer duration than influenza.[15-18] Numerous tests are available to facilitate the diagnosis of influenza, including rapid antigen-based diagnostic tests, direct and indirect immunofluorescence assays, molecular assays (rapid reverse transcriptase-polymerase chain reaction [RT-PCR]; multiplex), rapid cell cultures (shell vial and cell mixtures), and viral cultures (tissue cell cultures).[12] No diagnostic test is available for upper respiratory tract infection; heterophile antibody testing and Epstein-Barr virus-specific serologies can be used to diagnosis infectious mononucleosis.[19] At present, two types of tests can be used to diagnose COVID-19: molecular tests (eg, RT-PCR), which detect viral genetic material, and antigen tests, which detect specific proteins on the surface of the virus.[18]

The Infectious Diseases Society of America (IDSA) has established recommendations for influenza diagnostic testing based on the level of influenza activity in the community, whether the patient is in an outpatient or hospitalized setting, and whether testing will impact clinical management.[12] To that end, the IDSA recommends the use of rapid molecular-based assays in outpatients and traditional RT-PCR or other molecular assays in hospitalized patients.[12] Influenza diagnostic testing should be implemented in (1) all hospitalized patients with signs and symptoms suggestive of influenza; (2) patients with signs and symptoms suggestive of influenza for whom testing results will influence clinical management; and (3) patients with atypical signs and symptoms or complications associated with influenza for whom influenza testing results will influence clinical management. In all three of the above-mentioned cases, empiric antiviral treatment should commence while results are pending.

Treatment Approaches for Influenza

The goals of influenza treatment are to shorten the duration of illness and to reduce complications, hospitalizations, and adverse outcomes.[12] Treatment for confirmed or suspected influenza should be initiated promptly in hospitalized patients; outpatients who have severe or progressive illness or who are at risk of complications; children aged <2 years; adults aged ≥65 years; pregnant women; and women who are ≤2 weeks postpartum.[12,20] Treatment for confirmed or suspected influenza should also be considered in selected individuals who are not at high risk, including symptomatic healthcare workers, those who have illness onset of ≤2 days, and those with high-risk home contact(s).[12,20]

Six antivirals have been approved by the FDA for use in the US: the neuraminidase inhibitors (NAIs) oseltamivir, peramivir, and zanamivir; the cap-dependent endonuclease (CEN) baloxavir marboxil; and the adamantanes amantadine and rimantadine. The three NAIs work by inhibiting virion release and promoting clumping, whereas baloxavir marboxil works by inhibiting viral RNA replication.[21-24] Recently, the Centers for Disease Control and Prevention (CDC) recommended against the use of amantadine and rimantadine in the US due to widespread antiviral resistance in circulating influenza A viruses.[25] The discussion below therefore focuses on the four recommended agents.

The efficacy of the four recommended antiviral agents has been evaluated in randomized controlled trials and observational studies. Key findings are summarized here.

Oseltamivir

In a meta-analysis of randomized controlled trials, oral oseltamivir was shown to reduce the time to alleviation of symptoms in the intention-to-treat population (N = 2860) infected by seasonal influenza by 21% compared with placebo (median time, 97.5 hours vs 122.7 hours, respectively).[26]

In another meta-analysis—this one involving observational studies in high-risk patients with influenza—oseltamivir versus no treatment was shown to reduce mortality and hospitalization and was associated with fewer complications (eg, pneumonia, otitis media, and cardiovascular events).[27]

Peramivir

Data from a multinational, multicenter, randomized, controlled study in ambulatory patients with influenza showed that median time to alleviation of symptoms was similar with single-dose intravenous peramivir (300 mg and 600 mg) and oseltamivir (75 mg) twice daily for 5 days (78.0, 81.0, and 81.8 hours, respectively).[28]

Zanamivir

In a meta-analysis of unpublished manufacturer studies in patients with influenza-like illness, inhaled zanamivir versus placebo was associated with an improvement in time to first alleviation of symptoms in treatment with zanamivir, however, did not lead to a reduction in influenza complications, and data were inadequate to evaluate the effect of zanamivir on hospitalization.

Baloxavir Marboxil

Baloxavir marboxil was compared with placebo and oseltamivir in the phase 3 CAPSTONE-1 and CAPSTONE-2 trials. In CAPSTONE-1, which was conducted in 1064 patients with uncomplicated influenza, the median time to alleviation of symptoms was 53.7 hours with baloxavir marboxil compared with 53.8 hours with oseltamivir and 80.2 hours with placebo ($P < .001$); furthermore, baloxavir marboxil was associated with a significantly more rapid decline in infectious viral load than were placebo or oseltamivir (median reduction from baseline by 1 day after treatment initiation was 4.8, 2.8, and 1.3 $\log_{10}$ $TCID_{50}$ per milliliter, respectively).[29] In the CAPSTONE-2 study, which was conducted in 1163 assessable patients at increased risk of influenza complications due to existing comorbidities or age ≥65 years, median time to improvement of influenza symptoms was significantly shorter with baloxavir marboxil than with placebo (73.2 vs 102.3 hours, respectively;

Table 1. Recommended Antiviral Therapies[21-24]

Agent	Indications	Dosing for Treatment	Dosing for Prophylaxis	Common AEs
Oseltamivir	Acute uncomplicated influenza A and B in patients aged ≥2 weeks with symptoms for ≤48 hours Prophylaxis of influenza A and B in patients aged ≥1 year	◆ 75 mg BID x 5 days (≥13 years old) ◆ Weight-based BID x 5 days (1-12 years old) ◆ 3 mg/kg BID x 5 days (<2 weeks to 1 year old) ◆ Dose adjustments recommended for patients with renal impairment or ESRD	◆ 75 mg QD for ≥10 days in patients aged ≥13 years ◆ Weight-based QD for 10 days in patients aged 1-12 years ◆ Dose adjustments recommended for community outbreaks and for patients with renal impairment or ESRD	Treatment trials: ◆ Nausea ◆ Vomiting ◆ Headache Prophylaxis trials: ◆ Nausea ◆ Vomiting ◆ Headache ◆ Pain
Peramivir	Acute uncomplicated influenza in patients aged ≥2 years with symptoms for ≤48 hours	◆ Single dose IV infusion for ≤15 minutes » 600 mg in patients aged ≥13 years » 12 mg/kg (up to 600 mg) in patients aged 2-12 years ◆ Dose adjustments recommended for patients with altered creatinine clearance	N/A	Treatment trials: ◆ Diarrhea
Zanamivir	Acute uncomplicated influenza type A and B in patients aged ≥7 years with symptoms for ≤48 hours Prophylaxis in patients aged ≥5 years	◆ 10 mg BID x 5 days; note that the 10-mg dose is provided by 2 inhalations	◆ 10 mg QD for 10 days in the household setting ◆ 10 mg QD for 28 days for community outbreaks	Treatment trials: ◆ Sinusitis ◆ Dizziness Prophylaxis trials: ◆ Fever and/or chills ◆ Arthralgia ◆ Articular rheumatism
Baloxavir marboxil*	Acute uncomplicated influenza in patients aged ≥12 years with symptoms for ≤48 hours who are otherwise healthy or at high risk of developing influenza-related complications Post-exposure prophylaxis in patients aged ≥12 years after contact with an individual who has influenza	◆ Tablet dosage » Two 20-mg tablets taken at the same time for patients with body weight <80 kg » Two 40-mg tablets taken at the same time for patients with body weight ≥80 kg ◆ Oral suspension dosage » 40 mg/20 mL (1 bottle) taken as a single dose for patients with body weight <80 kg » 80 mg/40 mL (2 bottles) taken as a single dose for patients with body weight ≥80 kg		Treatment trials: ◆ Diarrhea ◆ Bronchitis ◆ Nausea ◆ Sinusitis ◆ Headache Prophylaxis trials: ◆ Nasopharyngitis

** The FDA has accepted a New Drug Application (NDA) seeking approval of baloxavir marboxil for the treatment of acute uncomplicated influenza in otherwise healthy children aged 1 year to <12 years who have been symptomatic for ≤48 hours. The FDA also accepted a supplemental NDA for post-exposure prophylaxis of influenza in individuals aged ≥1 year for both the oral suspension and tablet formulations.*

AEs = adverse events; BID = twice a day; ESRD = end-stage renal disease; IV = intravenous; QD = once a day.

P < .0001) and numerically shorter than with oseltamivir (81.0 hours).[30] Median time to improvement of influenza symptoms in patients with influenza B was significantly shorter with baloxavir marboxil (74.6 hours) than with placebo (100.6 hours) or oseltamivir (101.6 hours). The rate of complications with baloxavir marboxil, oseltamivir, and placebo was 3%, 5%, and 10%, respectively.

The phase 3 miniSTONE-2 study compared baloxavir marboxil with oseltamivir. In the study, which was conducted in 173 otherwise healthy children aged 1 to <12 years with a positive influenza test, median time to resolution of signs and symptoms with baloxavir marboxil and oseltamivir was 138.1 versus 150.0 hours, respectively; the median time to cessation of viral shedding was 24.2 versus 75.8 hours, respectively.[31] The incidence of AEs was similar in patients receiving baloxavir marboxil and oseltamivir (46.1% vs 53.4%, respectively), and no deaths, serious AEs, or hospitalizations were reported.[31]

In addition to the currently approved agents, several other antiviral therapies are currently in phase 3 trials, including nitazoxanide (inhibits assembly of hemagglutinin), favipiravir (selectively inhibits viral RNA-dependent RNA polymerase), and pimodivir (inhibits the PB2 subunit of influenza A polymerase).[32,33]

The Timing and Selection of Antiviral Delivery

Timing is important in antiviral delivery partly because of the replication kinetics of the virus: peak virus replication occurs in the first 48 hours from symptom onset and declines over time. Indeed, data from numerous studies show the benefits of early versus late initiation of antiviral treatment. For example, in a study in 1426 patients presenting within 48 hours of the onset of influenza symptoms, early versus late initiation of oral oseltamivir was shown to reduce the duration of illness, duration of fever, severity of symptoms, and time to return to baseline activity and health scores.[34] Initiation of treatment within the first 12 hours after fever onset reduced the total median illness duration by 3.1 days compared with treatment initiation at 48 hours, and intermediate treatment initiation reduced the illness proportionately compared with 48 hours.[34] In another study, insurance claims data from 112,492 individuals in Taiwan showed that treatment with oseltamivir within 1 week of diagnosis versus beyond 1 week of diagnosis was shown to reduce repeat outpatient visits, hospitalization, and mortality by 50%, 46%, and 29%, respectively.[35]

Survival data from intensive care unit (ICU) patients with pandemic influenza showed that those who received NAI treatment lived longer than did those who were not treated (75% vs 58%, respectively); furthermore, earlier initiation of NAI treatment was associated with a higher survival rate than was later treatment.[27] It is also important to note, however, that the survival benefit associated with NAI treatment was increased up to 5 days after the onset of symptoms, thereby highlighting the importance of treating all hospitalized patients regardless of the time of symptom development.

Unfortunately, not all patients with early influenza presentation receive treatment. For example, data from the 2013-2014 influenza season (N = 6004) show a missed opportunity to reduce the complications of influenza. In the study, only 30% of patients who were not at high risk with early presentation (0-2 days) and PCR-positive influenza were treated, and only 43% of high-risk patients with early presentation (0-2 days) and PCR-positive influenza were treated.[36]

Several factors should be considered in selecting an antiviral therapy, including patient characteristics (history of respiratory illness, pregnancy); patient preference (route of administration, dosing frequency); and practical issues (cost, concurrent administration of other intravenous therapy).[12]

Influenza Prophylaxis

The best way to prevent seasonal influenza is through yearly vaccination.[37] Other everyday actions, such as regular handwashing, disinfecting surfaces, covering coughs/sneezes and avoiding contact with individuals who are ill, are also beneficial in preventing influenza infection.[11] Both oseltamivir and baloxavir marboxil have approved indications for influenza prophylaxis.

Several studies have investigated the benefit of influenza prophylaxis with antiviral agents. For example, a systematic review and meta-analysis of four studies examining the effectiveness of NAIs for pre- or postexposure prophylaxis found that treatment with either oseltamivir or zanamivir consistently and significantly lowered the odds or risk of developing symptomatic influenza; two of the studies found that prophylaxis with either oseltamivir or zanamivir did not reduce the odds or risk of secondary transmission of asymptomatic influenza transmission.[38] In the phase 3 BLOCKSTONE study, which examined the impact of prophylaxis on influenza infection among 749 household members who had exposure to an infected household member, 1.9% of those who received baloxavir marboxil versus 13.6% of those who received placebo developed clinical influenza; the incidence of AEs was 22.2% and 20.5%, respectively, and no serious AEs were observed.[39]

Antiviral Resistance

The efficacy of antiviral agents is limited by the development of antiviral resistance, a phenomenon that can be attributable to the virus and the host.[40] Virus-driven factors include both antigenic drift and antigenic shift. Specifically, influenza is a negative-stranded RNA virus with an error-prone viral polymerase that tends to introduce errors and antigenic drifts in influenza proteins, thus it can escape some antiviral strategies; a potential solution is to target host pathways. In addition, dramatic antigenic shifts that occur in surface glycoproteins due to the segmented nature of the viral genome can produce viruses with new combinations of hemagglutinins and neuraminidases; a

potential solution is vigilant surveillance. Host-contributing factors to antiviral resistance include (1) subtherapeutic dosing used for treatment and chemoprophylaxis and (2) prolonged shedding due to virulent strain or infection of high-risk patients; a solution to the former is to confine and check the use of chemoprophylaxis with full dosage, and a solution to the latter is hospitalized isolation, treatment, and maintenance to prevent nosocomial transmission.

Several mutations associated with antiviral resistance have been identified. H274Y is the most common mutation associated with oseltamivir resistance in influenza A H1N1 and H5N1 subtypes, and E119V and R292K are the most common mutations associated with oseltamivir resistance in influenza A H3N2 and H7N9 subtypes.[41] The pattern of oseltamivir resistance has shown wide variability in the past 15 years. For example, in the 2006-2007 influenza season, the level of resistance of H1N1 subtypes to oseltamivir in the US was ~0.9%; however, in the 2007-2008 influenza season, there was a 7% increase in oseltamivir resistance in global H1N1 isolates, but all oseltamivir-resistant H1N1 isolates were sensitive to zanamivir.[41] By the time of the 2008-2009 influenza season, more than 90% of the influenza A H1N1 subtypes circulating globally were resistant to oseltamivir. Remarkably, the 2009 pandemic influenza A H1N1 subtype was sensitive to oseltamivir and has replaced the pre-2009 oseltamivir-resistant H1N1 strains. By 2011, only 1.6% of global pandemic H1N1 isolates were shown to be resistant to oseltamivir. Data from phase 2 and phase 3 trials suggest that resistance to baloxavir marboxil is 2.2% in patients with influenza A H1N1 (pandemic 2009 infection) and 9.7% in patients with influenza A H3N2.[41,42] Resistance to zanamivir has generally remained low, and data are lacking on peramivir resistance.[40]

Conclusions

Seasonal influenza is associated with substantial medical burden, especially among high-risk individuals. Yearly vaccination is critical for reducing the likelihood of illness and poor outcomes in the event of infection. Several antiviral influenza therapies have been shown to be safe and effective for disease prevention, shortening illness duration, minimizing complications, and reducing hospitalizations. Although effective influenza prophylaxis and treatment are perennially important goals, their impact has assumed even greater significance in the wake of the current COVID-19 pandemic.

References

1. World Health Organization. Influenza (seasonal). November 6, 2018. Accessed September 30, 2020. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)
2. Centers for Disease Control and Prevention. The flu season. July 12, 2018. Accessed September 30, 2020.https://www.cdc.gov/flu/about/season/flu-season.htm
3. Centers for Disease Control and Prevention. Disease burden of influenza. April 17, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/about/burden/index.html#:~:text=While%20the%20impact%20of%20flu,61%2C000%20deaths%20annually%20since%202010
4. Centers for Disease Control and Prevention. 2019-2020 US flu season: preliminary burden estimates. April 17, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm
5. Putri WCWS, Muscatello DJ, Stockwell MS, Newall AT. Economic burden of seasonal influenza in the United States. *Vaccine*. 2018;36:3960-3966.
6. Belongia EA, Kieke BA, Donahue JG, et al. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004-2005 season to the 2006-2007 season. *J Infect Dis*. 2009;199:159-167.
7. Centers for Disease Control and Prevention. Past seasons vaccine effectiveness estimates. January 29, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html
8. Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. *Clin Infect Dis*. 2012;55:951-959.
9. Centers for Disease Control and Prevention. Flu vaccination coverage, United States, 2018-19 influenza season. September 26, 2019. Accessed September 30, 2020. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)
10. Chung JR, Rolfes MA, Flannery B, et al. Effects of influenza vaccination in the United States during the 2018-2019 influenza season. *Clin Infect Dis*. 2020:1-9.
11. Centers for Disease Control and Prevention. Preventive steps. September 14, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/prevent/prevention.htm
12. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019:68:895-902.
13. Ghebrehewet S, MacPherson P, Ho A. Influenza. *BMJ*. 2016;355:i6258.
14. Centers for Disease Control and Prevention. People at high risk for flu complications. August 12, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/highrisk/index.htm
15. Centers for Disease Control and Prevention. Similarities and differences between flu and COVID-19. August 31, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm
16. Centers for Disease Control and Prevention. About infectious mononucleosis. May 8, 2018. Accessed September 30, 2020. https://www.cdc.gov/epstein-barr/about-mono.html
17. Centers for Disease Control and Prevention. Cold versus flu. August 31, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/symptoms/coldflu.htm
18. US Food & Drug Administration. Coronavirus testing. July 16, 2020. Accessed September 30, 2020. https://www.fda.gov/consumers/consumer-updates/coronavirus-testing-basics
19. Centers for Disease Control and Prevention. Laboratory testing. May 10, 2018. Accessed September 30, 2020. https://www.cdc.gov/epstein-barr/laboratory-testing.html
20. Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. August 10, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
21. Oseltamivir phosphate (Tamiflu) [prescribing information]. South San Francisco, CA; Genentech, Inc. August 2019.
22. Peramivir (Rapivab) [prescribing information]. Durham, NC: BioCryst Pharmaceuticals. April 2018.
23. Zanamivir (Relenza) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline. June 2018.
24. Baloxavir marboxil (Xofluza) [prescribing information]. South San Francisco, CA: Genentech USA, Inc. October 2019.
25. Centers for Disease Control and Prevention. Influenza antiviral drug resistance. September 3, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/treatment/antiviralresistance.htm
26. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomized controlled trials. *Lancet*. 2015;385:1729-1737.
27. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza. *Ann Intern Med*. 2012;156:512-524.
28. Kohno S, Yen M-Y, Cheong H-J, et al. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2011;55:5267-5276.
29. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated

influenza in adults and adolescents. *N Engl J Med*. 2018;379:913-923.
30. Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomized, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2020;S1473-3099(20)s0004-9.
31. Baker J, Block SL, Matharu B, et al. Baloxavir marboxil single-dose treatment in influenza-infected children. A randomized, double-blind, active controlled phase 3 safety and efficacy trial (miniSTONE-2). *Pediatr Infect Dis J*. 2020;39:700-705.
32. Hayden FG, Shindo N. Influenza virus polymerase inhibitors in clinical development. *Curr Opin Infect Dis*. 2019;32:176-186.
33. Pizzorno A, Padey B, Terrier O, Rosa-Calatrava M. Drug repurposing approaches for the treatment of influenza viral infection: reviving old drugs to fight against a long-lived enemy. *Front Immunol*. 2019;10:531.
34. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother*. 2003;51:123-129.
35. Wang C-B, Chiu M-L, Lin P-C, et al. Prompt oseltamivir therapy reduces medical care and mortality for patients with influenza infection: an Asian population cohort study. *Medicine (Baltimore)*. 2015;94:1-6.
36. Havers F, Flannery B, Clippard JR, et al. Use of influenza antiviral medications among outpatients at high risk for influenza-associated complications during the 2013-2014 influenza season. *Clin Infect Dis*. 2015;60:1677-1680.
37. Centers for Disease Control and Prevention. Prevent seasonal flu. September 21, 2020. Accessed September 30, 2020. https://www.cdc.gov/flu/prevent/index.html
38. Doll MK, Winters N, Boikos C, Kraicer-Melamed H, Gore G, Quach C. Safety and effectiveness of neuraminidase inhibitors for influenza treatment, prophylaxis, and outbreak control: a systematic review of systematic reviews and/or meta-analyses. *J Antimicrob Chemother*. 2017;72:2990-3007.
39. Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir marboxil for prophylaxis against influenza in household contacts. *N Engl J Med*. 2020;383:309-320.
40. Han J, Perez J, Schafer A, et al. Influenza virus: small molecule therapeutics and mechanisms of antiviral resistance. *Curr Med Chem*. 2018;25:5115-5127.
41. Hussain M, Galvin HD, Haw TY, Nutsford AN, Husain M. Drug resistance in influenza A virus: the epidemiology and management. *Infect Drug Resistance*. 2017;10:121-134.
42. Rodriguez T. H1N1/H3N2 influenza variants with reduced susceptibility to baloxavir. Infectious Disease Advisor. February 20, 2020. Accessed September 30, 2020. https://www.infectiousdiseaseadvisor.com/home/topics/respiratory/influenza/mutations-were-noted-frequently-in-influenza-a-h3n2-viruses/

Assessment and Management of Hyperkalemia in the Hospital Setting:
Optimizing Patient Outcomes

Introduction

Hyperkalemia is a common and potentially deadly electrolyte imbalance characterized by an elevated serum potassium level of >5 mEq/L.[1] In the US, the prevalence of hyperkalemia has been on the rise in recent years, affecting 3.0 million individuals in 2010 and 3.7 million individuals in 2014.[2] The 2014 annual prevalence of hyperkalemia in US adults with chronic kidney disease (CKD) and/or heart failure (HF) was 6.35%, and 48.4% of US adults with hyperkalemia had either CKD and/or HF.[2] Hyperkalemia occurs in up to 73% of patients with advanced CKD and up to 40% of patients with chronic HF.[1] Hyperkalemia may be the cause of cardiac arrhythmias that lead to cardiac arrest and death, with a resultant mortality rate of up to 30%.[1]

In addition to CKD and HF, risk factors for hyperkalemia include advanced age, CKD, HF, coronary artery and vascular disease, hypertension, diabetes mellitus, and the use of certain medications (eg, renin-angiotensin-aldosterone system [RAAS] inhibitors and β-blockers).[3] Compared with White patients, Hispanics have a 32% higher risk of hyperkalemia, whereas African-Americans have a 42% lower risk.[4] Men are more likely to develop hyperkalemia than are women.[1]

Hyperkalemia occurs in about 3.0% of hospitalized patients.[5] Acute in-hospital presentations can include any of the following symptoms: cardiac arrhythmia and conduction abnormalities (ventricular tachycardia or fibrillation; sinus bradycardia), muscle weakness, and possible paralysis, fatigue, and vomiting; however, patients with hyperkalemia are often asymptomatic, and some patients develop chronic disease.[6,7] Hyperkalemia is associated with increased hospitalizations and mortality, especially when potassium testing and monitoring are not performed frequently.[1] Severe hyperkalemia, the definition of which is variable (>6 mEq/L or ≥7 mEq/L), is an independent predictor of all-cause and in-hospital mortality.[1]

Potassium Homeostasis: A Balancing Act

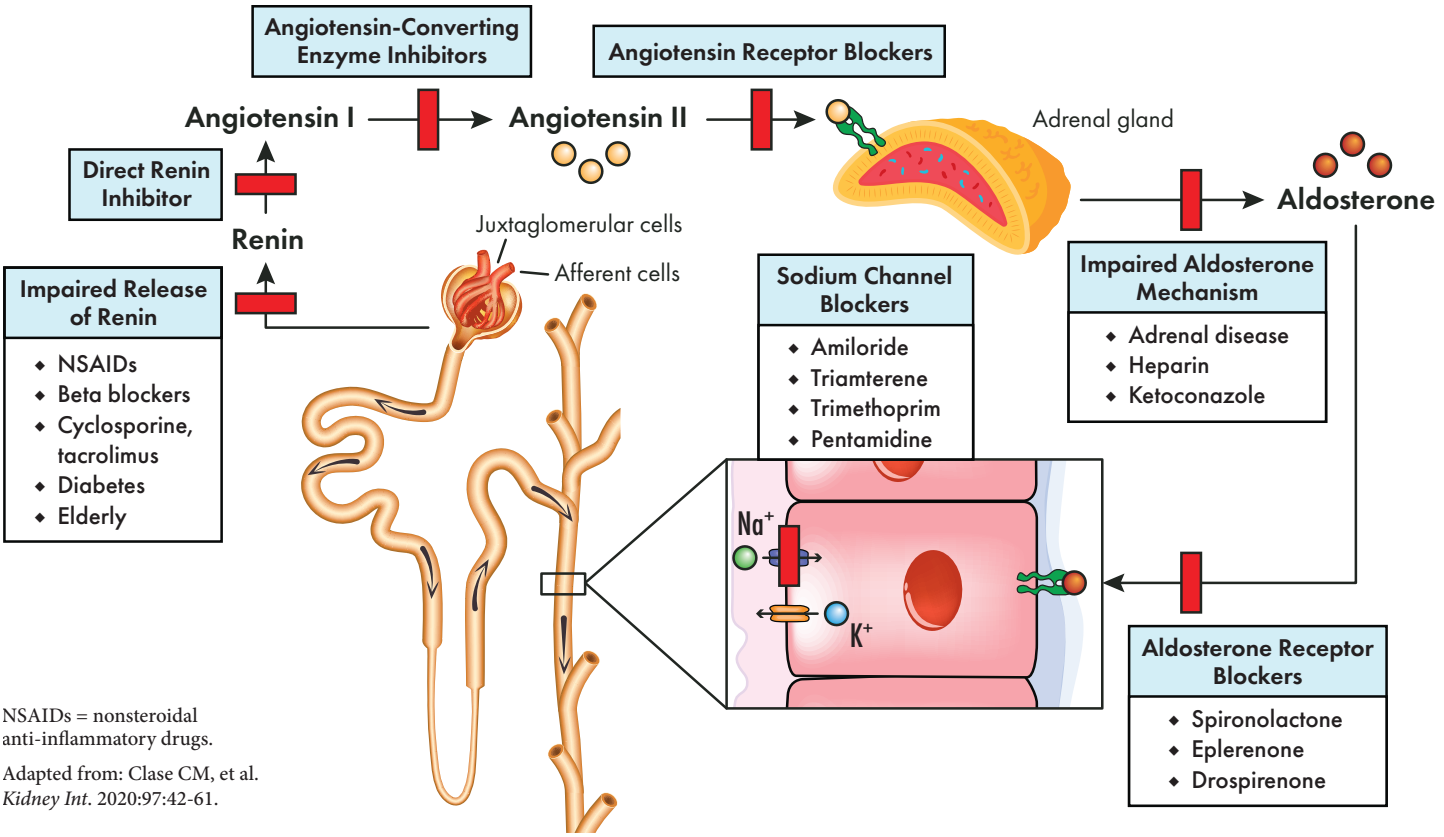
Potassium, the most abundant cation in the body, is needed by all cells for proper functioning.[8-10] Healthy potassium homeostasis (normokalemia) requires a precise ratio of intracellular to extracellular potassium; 98% of exchangeable potassium is in the intracellular compartment, whereas 2% of total body potassium is in the extracellular fluid.[8-10] Cellular level homeostasis is a regulated exchange of sodium and potassium: the enzyme sodium-potassium adenosine triphosphatase pumps sodium out of cells while pumping potassium into cells.[11] The kidneys, the primary organ responsible for potassium homeostasis, protect the body against potassium imbalance by excreting 90% of potassium taken in through food each day.[12]

Normokalemia lies within a very narrow extracellular fluid range (3.5 to 5.3 mEq/L), thus a large deviation from these values is not compatible with life. In fact, even a small shift in the potassium intra- and extra-cellular ratio can upset this delicate balance, resulting in hypokalemia or hyperkalemia. Numerous factors can contribute to hyperkalemia, including (1) mechanical issues (eg, a release of potassium during phlebotomy due to fist-clenching or incorrect tourniquet application); (2) a potassium cellular shift or redistribution (due to mineral acidosis, hypertonicity, insulin deficiency, the use of β-blockers or α-adrenergics, tissue injury, or strenuous exercise); (3) excess potassium intake through food or supplements; and (4) decreased renal excretion of potassium.[8,9] Diseases and drugs that can impair renal potassium secretion and increase the risk of hyperkalemia are shown in Figure 1.

Diagnosis and Monitoring of Hyperkalemia

Identifying hyperkalemia can be difficult because patients are often asymptomatic and potassium levels are dynamic.[9] Pseudohyperkalemia (a measurement artifact due to mechanical release of potassium from cells during phlebotomy or specimen processing) should be considered and ruled out first.[8,9] Hyperkalemia should be suspected in all patients with diabetes mellitus, HF, and/or CKD, especially in those who are receiving RAAS inhibitors (ie, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists).[2,9,10] Recommended in-hospital monitoring includes the frequent measurement of potassium levels after hyperkalemia has

Figure 1. Diseases and Drugs That Can Impair Renal Potassium and Increase Risk of Hyperkalemia



NSAIDs = nonsteroidal anti-inflammatory drugs.

Adapted from: Clase CM, et al. *Kidney Int.* 2020:97:42-61.

been diagnosed and treatment initiated.[9] Continuous electrocardiogram (ECG) monitoring is recommended for in-hospital patients with severe hyperkalemia;[9] however, the procedure is not sensitive enough to be used as a diagnostic tool, as there is often little correlation between potassium levels and ECG results.[7,13] Data from a study investigating long-term potassium monitoring in post-discharge patients with HF showed that (1) single baseline assessment is insufficient because it neglects dynamic changes in potassium over time and that (2) long-term monitoring and potassium normalization can reduce hyperkalemia-related mortality.[14]

Treatment of Hyperkalemia

The treatment of hyperkalemia is based on signs and symptoms, rate and severity of the increase in plasma potassium concentration, and the underlying etiology.[10] Emergent treatment is indicated in patients who experience changes on ECG and/or a rapid increase in plasma potassium (as in rhabdomyolysis, tumor lysis syndrome, or crush injury). In the nonemergent setting, pseudohyperkalemia should be ruled out, especially in the absence of risk factors.[9,10] See Table 1.

The Impact of Hyperkalemia on RAAS Inhibitor Dose

Evidence-based treatment guidelines recommend the use of RAAS inhibitors titrated up to moderate to high doses in patients with HF or CKD, as well as in patients with diabetes mellitus who have hypertension and/or renal insufficiency;[15-18] however, the use of these drugs may be limited by their potential to cause hyperkalemia.[19] In fact, a retrospective analysis of more than 200,000 patients with ≥2 serum potassium readings assessing the impact of hyperkalemia on RAAS inhibitor usage showed that (1) only 19% to 26% of patients were prescribed the maximum dose; (2) the dose was down-titrated after 16% to 21% of hyperkalemia events; (3) RAAS inhibitors were discontinued after 22% to 27% of hyperkalemia events; and (4) outcomes were worse in patients who received submaximum RAAS inhibitor doses or who discontinued RAAS inhibitors than in patients who received maximum doses.[19]

Steps that can be taken to reduce the risk of hyperkalemia when using RAAS inhibitors[9]:

- Evaluate renal function to determine the overall risk of hyperkalemia
- Discontinue agents that can impair renal potassium excretion, including NSAIDs and herbal supplements
- Reduce potassium in diet and avoid potassium-containing salt substitutes
- Use effective and appropriate diuretic therapy
- Correct metabolic acidosis if present
- Initiate low RAAS inhibitor doses and check potassium within 1 week

Table 1. Hyperkalemia Treatment Algorithms[10]

Treatment Type	Algorithm
Emergent Treatment	◆ Stabilize the myocardial cell membrane by administering calcium gluconate ◆ Move potassium into the cells by administering insulin, followed by glucose ◆ Remove potassium from the body by hemodialysis (for oliguria or ESRD), diuretics (for hypervolemia), or sodium bicarbonate (for metabolic acidosis) ◆ Consider potassium-binding drugs
Nonemergent Treatment	◆ Conduct dietary counseling and instruct patients to reduce foods high in potassium (eg, avocados and citrus juices) and to avoid salt substitutes ◆ If possible, discontinue drugs that interfere with kidney potassium secretion ◆ Inquire about the use of over-the-counter NSAIDs and herbal preparations ◆ Ensure effective diuretic therapy ◆ Treat metabolic acidosis with oral $NaHCO_2$ ◆ Consider potassium-binding drugs to facilitate recommended doses of RAAS inhibitors

ESRD = end-stage renal disease.

Potassium Binders for Chronic Hyperkalemia

Three potassium binders—patiromer, sodium zirconium cyclosilicate (SZC), and sodium polystyrene sulfonate (SPS)—are approved for the treatment of patients with hyperkalemia.[20-23] Patiromer and SZC—approved by the Food and Drug Administration (FDA) in 2015 and 2018, respectively—can prevent hyperkalemic episodes while allowing RAAS inhibitor therapy to continue at optimal doses; these nonabsorbable agents are available in a powder formulation that can be mixed with water. Both agents increase potassium excretion through the colon: patiromer exchanges potassium for calcium in the colon, and SZC selectively binds potassium ions and exchanges them for sodium and hydrogen throughout the entire intestine.[20,21] SPS, approved by the FDA in 1958, is an older nonabsorbable agent that increases potassium excretion through the colon; it is available in a powder formulation for suspension (oral or rectal use).[22]

Key Clinical Trials Evaluating Patiromer

Patiromer has been evaluated in several phase 2 and phase 3 clinical trials. For example, in the 4-week phase 2 PEARL-HF trial in 105 patients with chronic HF, CKD, or prior hyperkalemia, treatment with patiromer was shown to significantly reduce serum potassium levels versus placebo, with a difference between groups of -0.45 mEq/L ($P < .001$).[24] Data from the 52-week phase 2 AMETHYST-DN trial, which was conducted in 306 patients with diabetic CKD and hyperkalemia who received RAAS inhibitors, showed that treatment with patiromer was associated with statistically significant mean reductions in serum potassium levels for the entire study period in those with mild and moderate hyperkalemia ($P < .001$).[25] The phase 3 OPAL-HK trial, which included a 4-week initial treatment phase (N = 219) and an 8-week withdrawal phase (N = 107), was conducted in patients with CKD and hyperkalemia who were receiving RAAS inhibitors.[26] In the initial treatment phase, the mean change in serum potassium was -1.01 ± 0.03 mmol/L ($P < .001$); at week 4, 76% of patients had reached the target potassium level. In the withdrawal phase, hyperkalemia recurrence occurred in 15% of patients receiving patiromer compared with 60% of those receiving placebo through week 8 ($P < .001$).

Key Clinical Trials Evaluating SZC

SZC has been evaluated in several phase 3 trials, including the HARMONIZE trial and the HARMONIZE Open-Label Extension trial. HARMONIZE, which included a 48-hour open-label phase and a 28-day randomized phase, was conducted in patients with diabetes mellitus, HF, or CKD with hyperkalemia, most of whom were receiving RAAS inhibitors.[27] In the open-label phase, treatment with SZC was shown to reduce potassium levels within 48 hours; 98% of patients achieved normokalemia (median time, 2.2 hours). In the randomized phase, normokalemia between 80% and 94% was maintained across all SZC dosing groups compared with 46% in the placebo group ($P < .001$). In the HARMONIZE Open-Label Extension trial, which included 123 patients from the HARMONIZE trial, a mean serum potassium level of ≤5.1 mmol/L was achieved by 88.3% of patients, and a mean serum potassium level of ≤5.5 mmol/L was achieved by 100% of patients; most patients maintained normokalemia for up to 11 months.[28]

Other phase 3 trials evaluating SZC include ZS-003, ZS-005, and DIALIZE. In the ZS-003 trial, which was conducted in 753 patients with diabetes mellitus, HF, or CKD with and without hyperkalemia, treatment with SZC versus placebo was associated with a significant reduction in potassium levels at 48 hours across all dosing groups, with normokalemia maintained during a 12-day maintenance

period.[29] The ZS-005 trial, which included a correction phase and a maintenance phase, was conducted in patients with diabetes mellitus, HF, CKD who had hyperkalemia, hypertension, and other comorbidities; most of the patients were receiving RAAS inhibitors.[30] In the correction phase (N = 751), the duration of which was up to 72 hours, 99% of patients achieved normokalemia. In the 12-month maintenance phase (N = 746), a mean serum potassium level of ≤5.1 mmol/L was achieved by 88% of patients, and a mean serum potassium level of ≤5.5 mmol/L was achieved by 99% of patients; furthermore, 74% of patients receiving RAAS inhibitors were able to maintain the start dose. In the 8-week phase 3b DIALIZE trial in 196 patients with end-stage renal disease who were on hemodialysis 3 times per week and had predialysis hyperkalemia, the primary endpoint (ie, maintenance of predialysis serum potassium level of 4.0 to 5.0 mmol/L during at least three of four hemodialysis treatments after the interdialytic interval and no need for urgent rescue therapy to reduce serum potassium) was achieved by 41.2% versus 1.0% of patients receiving SZC and placebo, respectively (P < .001).[31]

Multidisciplinary Interventions in Hospitalized Patients With Hyperkalemia

In hospitalized patients with hyperkalemia, a multidisciplinary rapid response team intervention is important to facilitate a rapid diagnosis, a timely correction of laboratory test results, and appropriate management.[32] Multidisciplinary interventions, which provide integrated, collaborative care involving specialists, primary care providers, and midlevel practitioners, can quickly identify patients who are not truly hyperkalemic (and thus do not require treatment), optimize the recognition of hyperkalemia in high-risk patients who are prone to it, and enhance treatment efficacy and outcomes.[32-33]

Hospital Discharge Instructions

At hospital discharge, the patient should understand what hyperkalemia is, why he or she is at risk for hyperkalemia, the symptoms of hyperkalemia, what foods and supplements should be avoided to reduce the risk, and why it is important to take all medications as prescribed.[34]

Hyperkalemia occurs most often within the first month after hospital discharge,[35] thus measurement of potassium is recommended at every lab assessment.[15] Lab assessment and clinical follow-up is advised within 1 week after discharge.[36] RAAS inhibitors should be started and monitored (when indicated) before discharge, and patients should be counseled to continue the dose exactly as prescribed.[36] If RAAS inhibitors have been discontinued in hospital, restart before discharge and continue upward titration to full dose in the outpatient setting; use a potassium binder to optimize RAAS inhibitor therapy.[1] Referral to a dietician for dietary counseling should also be considered.[23]

Conclusions

Hyperkalemia is a common and potentially deadly electrolyte imbalance that most often occurs in patients with advanced CKD and HF. Potassium homeostasis is a delicate balance within a very narrow range, thus it is important to diagnose hyperkalemia in a timely manner and monitor potassium levels frequently. Although RAAS inhibitors are one of many potential causes of hyperkalemia, multiple studies show worse cardiovascular outcomes when treatment is reduced or discontinued. Appropriate steps should be taken to mitigate against hyperkalemia and optimize RAAS inhibitor treatment using multiple strategies and potassium binders.

References

1. Rosano GMC, Tamargo J, Kjeldsen P, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother*. 2018;4:180-188.
2. Betts KA, Woolley M, Mu F, McDonald E, Tang W, Wu EQ. The prevalence of hyperkalemia in the United States. *Curr Med Res Opin*. 2018;34:971-978.
3. Tromp J, van der Meer P. Hyperkalaemia: aetiology, epidemiology, and clinical significance. *Eur Hear J*. 2019;21:A6-A11.
4. Kim T, Rhee CM, Streja E, et al. Racial and ethnic differences in mortality associated with serum potassium in a large hemodialysis cohort. *Am J Nephrol*. 2017;45:509-521.
5. Khanagavi J, Gupta T, Aronow WS, et al. Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes. *Arch Med Sci*. 2014;10:251-257.
6. Littmann L, Gibbs MA. Electrocardiographic manifestations of severe hyperkalemia. *J Electrocardiol*. 2018;51:814-817.
7. De Nicola L, Di Lullo L, Paoletti E, Cupisti A, Bianchi S. Chronic hyperkalemia in non-dialysis CKD: controversial issues in nephrology practice. *J Nephrol*. 2018;31:653-664.
8. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ*. 2016;40:480-490.
9. Palmer BF, Clegg DJ. Diagnosis and treatment of hyperkalemia. *Cleveland Clin J Med*. 2017;84:934-942.
10. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: core curriculum 2019. *Am J Kidney Dis*. 2019;74:682-695.
11. Gumz ML, Rabinowitz L, Wingo CS. An integrated view of potassium homeostasis. *N Engl J Med*. 2015;373:60-72.
12. Epstein M, Lifschitz MD. Potassium homeostasis and dyskalemias: the respective roles of renal, extrarenal, and gut sensors in potassium handling. *Kidney Int Suppl*. 2016;6:7-15.
13. Montford JR, Linas S. How dangerous is hyperkalemia? *J Am Soc Nephrol*. 2017;28:3155-3165.
14. Núñez J, Bayés-Genís A, Zannad F, et al. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. *Circulation*. 2018;137:1320-1330.
15. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810-1852.
16. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012;14:803-869.
17. National Institute for Health and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management. July 23, 2014. Accessed September 30, 2020. https://www.nice.org.uk/guidance/cg182/resources/chronic-kidney-disease-in-adults-assessment-and-management-pdf-35109809343205
18. American Diabetes Association. Standards of medical care in diabetes – 2015 abridged for primary care providers. *Clin Diabetes*. 2015;33:97-111.

19. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care*. 2015;21:S209-S223.
20. Patiromer (Veltassa) [prescribing information]. Redwood City, CA: Relypsa, Inc. May 2018.
21. Sodium zirconium cyclosilicate (Lokelma) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. April 2020.
22. Sodium polystyrene sulfonate (Kayexalate) [prescribing information]. St. Michael, Barbados: Concordia Pharmaceutical Inc. July 2017.
23. Pitt B, Bakris GL. New potassium binders for the treatment of hyperkalemia. Current data and opportunities for the future. *Hypertension*. 2015;66:731-738.
24. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF trial. *Eur Heart J*. 2011;32:820-828.
25. Bakris GL, Pitt B, Weir MR, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease. The AMETHYST-DN randomized clinical trial. *JAMA*. 2015;314:151-161.
26. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;373:211-221.
27. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia. The HARMONIZE randomized clinical trial. *JAMA*. 2014;312:2223-2233.
28. Roger SD, Spinowitz BS, Lerma EV, et al. Efficacy and safety of sodium zirconium cyclosilicate for treatment of hyperkalemia: an 11-month open-label extension of HARMONIZE. *Am J Nephrol*. 2019;50:473-480.
29. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015;372:222-231.
30. Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia. A 12-month phase 3 study. *Clin J Am Soc Nephrol*. 2019;14:798-809.
31. Fishbane S, Ford M, Fukagawa M, et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. *J Am Soc Nephrol*. 2019;30:1723-1733.
32. Rayan N, Baird R, Masica M. Rapid response team interventions for severe hyperkalemia: evaluation of a patient safety initiative. *Hosp Pract*. 2011;39:161-169.
33. Lema GF, Tesema HG, Fentie DY, Arefayne NR. Evidence-based perioperative management of patients with high serum potassium level in resource-limited areas: a systematic review. *Int J Surg Open*. 2019;21:21-29.
34. National Kidney Foundation (NKF). Educate your patients about hyperkalemia and kidney disease. 2016. Accessed September 30, 2020. https://www.kidney.org/sites/default/files/02-10-7271_ABG_Hyperkalemia_Card_P11b.pdf
35. Saito Y, Yamamoto H, Nakajima H, Takahashi O, Komatsu Y. Incidence of and risk factors for newly diagnosed hyperkalemia after hospital discharge in non-dialysis-dependent CKD patients treated with RAS inhibitors. *PLoS One*. 2017;12:e0184402.
36. Allen LA, Shetterly SM, Peterson PN, et al. Guideline concordance of testing for hyperkalemia and kidney dysfunction during initiation of mineralocorticoid receptor antagonist therapy in patients with heart failure. *Circ Heart Fail*. 2014;7:43-50.

Optimizing Transitions From Hospital to Home: Best Practices for Reducing Readmissions in Heart Failure

Introduction

Heart failure (HF) is a clinical syndrome caused by structural or functional impairment of ventricular filling or ejection of blood from the heart.[1,2] In the United States, HF affects more than 6.2 million people aged ≥20 years, and estimates suggest that more than 8 million people aged ≥18 years will be affected by 2030.[3] Data from several large studies show that the lifetime risk of developing HF is 20% to 29% in black males, 24% to 46% in black females, 30% to 42% in white males, and 32% to 39% in white females.[3] At all ages, the lifetime risk of HF has been shown to be greater in individuals with relatively higher blood pressure and body mass index levels.[3]

Despite advances in the treatment of HF and several related risk factors, HF remains a serious disorder associated with substantial morbidity and mortality.[4] In 2015, more than 2.6 million physician office visits were assigned a primary diagnosis of HF,[3,5] and 481,000 emergency department visits were attributable to HF.[3,6] The average annual incidence of hospitalization for acute decompensated HF has been shown to be 11.6 per 1000 individuals aged ≥55 years, with age-adjusted annual rates being highest in black men (15.7 per 1000) and lowest in white women (9.9 per 1000).[7]

Hospital readmission rates for HF have also been shown to be higher than those associated with other common conditions. For example, recent data from the Centers for Medicare and Medicaid Services (CMS) show that 22% of Medicare recipients hospitalized initially for HF are readmitted within 30 days, compared with 17.0% of those initially hospitalized for myocardial infarction and 16.9% of those initially hospitalized for pneumonia.[8,9] In a large population-based observational study, case fatality rates after hospitalization for HF were found to be 10.4%, 22.0%, and 42.3% at 30 days, 1 year, and 5 years, respectively.[3,10] Notably, HF is listed as a contributing factor on 1 in 8 death certificates in the US.[3]

The economic burden associated with HF is substantial. In 2012, the total cost of HF was estimated to be $30.7 billion, of which more than two-thirds represented direct medical costs.[3,11] By 2030, the total cost of HF is expected to reach $69.8 billion, which amounts to about $244 for every adult in the US.[3,11]

Heart Failure Symptomatology and Classification

The major clinical manifestations of HF are dyspnea, fatigue, and fluid retention; however, patient presentation is variable and includes a wide range of signs and symptoms.[1,2,12] The classification of HF is based on the measurement of left ventricular ejection fraction (EF) as follows[2,13]:

- EF ≤40% indicates HF with reduced ejection fraction (HFrEF); it is also referred to as systolic HF
- EF between 41% and 49% indicates HF with mid-range ejection fraction (HFmrEF)
- EF ≥50% indicates HF with preserved ejection fraction (HFpEF); it is also referred to as diastolic HF
- EF >40% after previous HFrEF indicates HF with recovered ejection fraction (HFrecEF)

It is important to note that HFrEF is the only HF type for which effective therapies have been identified.[2]

Two classification systems are used to describe HF progression and severity of symptoms. The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) system, which focuses on the development and progression of HF, is divided into four stages, A, B, C, and D.[2] The New York Heart Association (NYHA) functional classification system emphasizes symptoms within the context of exercise capacity and ranges from I to IV.[2] The two classification systems complement each other and are used together to help determine the most appropriate guideline-directed medical therapy (GDMT) for patients with HF.[2] See Table 1.

Heart Failure Diagnosis

Patients with suspected HF in a nonacute setting should be assessed based on clinical history, presenting symptoms, physical exam, and resting electrocardiogram (ECG); if more than one finding is abnormal, measurement of plasma natriuretic peptides (NPs) is advised.[12] Patients with elevated plasma NPs (ie, NT-proBNP ≥125 pg/mL or BNP

Table 1. ACCF/AHA Heart Failure Staging System and NYHA Functional Classification[2,14,15]

ACCF/AHA HF Stage		NYHA Functional Classification	
A	At high risk of HF, but without structural heart disease or HF symptoms	None	
B	Structural heart disease, but without HF signs/symptoms	I	No limitation of physical activity
C	Structural heart disease with previous or current HF symptoms	I	No limitation of physical activity
		II	Slight limitation of physical activity
		III	Marked limitation of physical activity
		IV	Unable to engage in any physical activity without HF symptoms (or symptoms of HF at rest)
D	Refractory HF; specialized interventions needed	IV	Unable to engage in any physical activity without HF symptoms (or symptoms of HF at rest)

≥35 pg/mL) should undergo echocardiography.[12] If HF is confirmed based on all available data, the etiology should be determined, stage and functional class should be assessed, and treatment should be initiated.

Heart Failure Treatment

Evidence-based guidelines suggest that patients in stages B-D of any functional class HF should be treated with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) in combination with a β-blocker.[16] Patients with a current or recent history of fluid retention should not be prescribed a β-blocker without a diuretic.[16] An aldosterone antagonist should be considered in patients with class II-IV HF who have normal potassium levels and renal function.[16] Isosorbide dinitrate/hydralazine is indicated in African American patients with class III-IV HF who are already on an ACE inhibitor or ARB and in patients in any functional class who are unable to take ACE inhibitors or ARBs due to renal insufficiency, hyperkalemia, or adverse events (AEs).[2,17,18]

Assessing renal function is a critical step in the selection of GDMT, as it will elucidate whether a patient can tolerate an ACE inhibitor, ARB, or aldosterone antagonist; the level of diuresis needed; and what type of diuretic to prescribe.

Several agents have indications to reduce the risk of hospitalization and/or cardiovascular death in patients with HF. Sacubitril/valsartan (a tablet consisting of the neprilysin inhibitor sacubitril and the ARB valsartan) is indicated for the treatment of patients with chronic HF (NYHA class II-IV) and reduced EF to reduce the risk of hospitalization and cardiovascular death due to HF, as well as for the treatment of pediatric patients aged ≥1 year with symptomatic HF and systemic left ventricular systolic dysfunction.[19] Sacubitril/valsartan is usually administered in conjunction with other HF therapies in place of an ACE inhibitor or other ARB.[19] Ivabradine (a hyperpolarization-activated cyclic nucleotide-gated channel blocker) is indicated for the treatment of adults with stable symptomatic chronic HFrEF to reduce the risk of hospitalization for worsening HF and for the treatment of stable symptomatic HF due to dilated cardiomyopathy in pediatric patients aged ≥6 months.[20] The sodium-glucose transport 2 (SGLT2) inhibitor dapagliflozin is indicated (1) to reduce the risk of hospitalization for HF in adults with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors and (2) to reduce the risk of cardiovascular death and hospitalization for HF in adults with HFrEF (NYHA class II-IV).[21] Of note, dapagliflozin versus placebo has been shown to reduce HF hospitalization or cardiovascular death regardless of diabetes status in patients with chronic kidney disease.[22] Canagliflozin, another SGLT2 inhibitor, is indicated to reduce the risk of end-stage renal disease, doubling of serum creatinine, cardiovascular death, and hospitalization for HF in adults with type 2 diabetes and diabetic nephropathy with albuminuria.[23]

Aggressive blood pressure control in patients with HF has been shown to be associated with significantly fewer hospitalizations compared with less aggressive blood pressure control;[24] optimal blood pressure in patients with HF is 130/80 mm Hg.[2]

Most patients with HF have stage C functional class III disease. Table 2 has been presented here to show GDMT recommendations for patients with stage C HFrEF.

Efficacy and Safety Data from Key Clinical Trials Evaluating Newer Heart Failure Agents

Several clinical trials have evaluated the efficacy and safety of ivabradine, sacubitril/valsartan, and dapagliflozin. In the SHIFT trial, which was conducted in 6558 patients with symptomatic HFrEF, ivabradine reduced the risk of cardiovascular death and hospitalization for worsening HF by 18% versus placebo (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.75 to 0.90; P < .0001); however, several AEs were significantly more common in the former than latter treatment arm, including symptomatic bradycardia (5% vs

Table 2. Treatment of Stage C HFrEF[2]

COR	LOE	Recommendation
I	ACEi: A ARB: A ARNI: B-R	The clinical trial strategy of **inhibition of the RAAS with ACEis, ARBs, or ARNIs in conjunction with evidence-based β-blockers and aldosterone antagonists in selected patients is recommended for patients with chronic HFrEF** to reduce morbidity and mortality.
I	ACEi: A	The **use of ACEis is beneficial for patients with prior or current symptoms of chronic HFrEF** to reduce morbidity and mortality.
I	ARB: A	The use of **ARBs to reduce morbidity and mortality is recommended in patients** with prior or current symptoms of chronic HFrEF **who are intolerant to ACEis** because of cough or angioedema.
I	ARNI: B-R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, **replacement by an ARNI is recommended to further reduce morbidity and mortality**.
III: Harm	B-R	**ARNI should not be administered concomitantly with ACEis** or within 36 hours of the last dose of an ACEi.
III: Harm	C-EO	**ARNI should not be administered to patients with a history of angioedema.**
IIa	Iva: B-R	**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT**, including a β-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.

ACEi = ACE inhibitor; COR = Classification of Recommendation; Iva = ivabradine; LOE = Level of Evidence

1%, respectively; P < .0001), asymptomatic bradycardia (6% vs 1%, respectively; P < .0001), and visual symptoms (3% vs 1%, respectively; P < .0001).[25] Data from the PARADIGM-HF trial, which included 8442 patients with HFrEF, showed that death from cardiovascular causes or hospitalization for HF occurred in 21.8% of patients receiving sacubitril/valsartan versus 26.5% of patients receiving enalapril (HR, 0.80; 95% CI, 0.73 to 0.87; P < .001); symptomatic hypotension was more common with sacubitril/valsartan than with enalapril (14.0% vs 9.2%, respectively), but the rate of angioedema was similar in the two treatment arms.[26] Notably, PARADIGM-HF was stopped early due to the overwhelming benefit of sacubitril/valsartan compared with enalapril.

The PANORAMA-HF trial evaluated the efficacy and safety of sacubitril/valsartan versus enalapril in pediatric patients aged 1 to <18 years with HF due to systemic left ventricular systolic dysfunction.[27] At 12 weeks, sacubitril/valsartan demonstrated greater reductions from baseline in NT-proBNP compared with enalapril (44% vs 33%, respectively). Improvement in cardiovascular outcomes in pediatric patients was inferred based on data from the PARADIGM-HF trial in adults; the safety and tolerability of sacubitril/valsartan in pediatric patients were similar to that in adults.

In the TRANSITION trial, which evaluated the initiation of sacubitril/valsartan before hospital discharge versus after hospital discharge (in outpatient settings) in 1002 patients with HFrEF, the target drug dose was achieved within 10 weeks by 45.4% versus 50.7% of patients, respectively (risk ratio [RR], 0.90; 95% CI, 0.79 to 1.02), after 10 weeks of treatment; discontinuation due to AEs occurred in 7.3% versus 4.9% of patients, respectively (RR, 1.49; 95% CI, 0.90 to 2.46).[28] In the DAPA-HF trial, which evaluated dapagliflozin versus placebo in 4744 patients with HFrEF regardless of diabetes status, death from cardiovascular causes or worsening HF (hospitalization or an urgent visit requiring intravenous therapy for HF) occurred in 16.3% versus 21.2% of patients, respectively (HR, 0.74; 95% CI, 0.65 to 0.85; P < .001); furthermore, the findings were similar in patients with and without diabetes.[29] The occurrence of AEs related to volume depletion, renal dysfunction, and hypoglycemia did not differ between the two treatment arms.

Recently, the investigational agent vericiguat (a novel oral soluble guanylate cyclase stimulator) was compared with placebo in the VICTORIA trial, which included 5050 patients with chronic high-risk HF who had recently been hospitalized or had received intravenous diuretic therapy.[30] At median follow-up of 10.8 months, the composite of death from any cause or hospitalization for HF occurred in 37.9% of patients treated with vericiguat versus 40.9% of those treated with placebo (HR, 0.90; 95% CI, 0.83 to 0.98; P = .02). Symptomatic hypotension occurred in 9.1% of patients treated with vericiguat versus 7.9% of those treated with placebo (P = .12), and syncope occurred in 4.0% and 3.5% of patients, respectively (P = .30). In July 2020, the US Food and Drug Administration granted vericiguat a priority review status.[31]

Transitions of Care in Heart Failure Management

The pathway to improve outcomes after hospitalization for HF follows a clinical course that begins with admission, continues through the process of decongestion and transition to oral therapies before the day of discharge, and connects through the first postdischarge follow-up visit.[32] Effective transitions of care involve a multidisciplinary program focused on structured follow-up with patient education, optimization of medical treatment, psychosocial support, and increased access to care; see Table 3.[12]

Table 3. Components of Effective Transition Programs[12]

ESC Guideline Recommendations	
Components	Optimized medical and device management
	Adequate **patient education**, with special emphasis on adherence and self-care
	Patient involvement in symptom monitoring and flexible diuretic use
	Follow-up after discharge (regular clinic and/or home-based visits; possible telephone support or remote monitoring)
	Increased access to healthcare (through in-person follow-up and by telephone contact; possibly through remote monitoring)
	Facilitated access to care during episodes of decompensation
	Assessment of (and appropriate intervention in response to) an unexplained change in weight, nutritional status, functional status, quality of life, or laboratory findings
	Access to advanced treatment options
	Provision of **psychosocial support** to patients, family, and/or caregivers

Numerous barriers to effective transitions of care have been identified, including issues with (1) medication management (eg, unclear instructions, cost); (2) follow-up appointments (eg, lack of transportation; failure of healthcare provider to follow GDMT); (3) healthcare provider communication (eg, insufficient patient education, poor handoffs); and (4) the management of nonmedication signs and symptoms (eg, nonadherence to diet, activity, exercise, and fluid management).[33] Telemedicine and nurse-led interventions may be used to overcome these barriers and have been shown to improve cardiovascular outcomes in patients with HF.[34]

The goal of HF management is to provide "a seamless system of care that embraces both the community and hospital throughout the heath care journey."[12] To that end, the implementation of structured support programs has been shown to reduce hospital readmissions and confer other benefits in patients with HF. For example, in a randomized trial in 127 patients with HFrEF, the use of a nurse-led intervention program versus standard care was associated with significant improvements in perceived quality of life (Minnesota Living with Heart Failure Questionnaire ± SD: 10.9 ± 14.75 vs 2.29 ± 14; P = .04) and a reduction in hospital readmissions (18% vs 35%, respectively; P = .04).[35] A meta-analysis of 30 randomized controlled trials that included 10,193 patients with HF found that (1) structured telephone support versus usual care reduced the odds of hospitalizations (odds ratio [OR], 0.69) and mortality (OR, 0.80) due to HF; (2) telemonitoring versus usual postdischarge care reduced the odds of mortality (OR, 0.53) and hospitalizations related to HF (OR, 0.64); and (3) interventions involving electrocardiogram monitoring versus usual care reduced the odds of hospitalization due to HF (OR, 0.71).[34]

The Expanding Role of Telemedicine in the COVID-19 Era

Healthcare delivery for patients with HF has been disrupted in the wake of COVID-19.[36] Since the early days of the pandemic, health systems have in large part transitioned to noncontact care for ambulatory patients with HF to maintain the well-being of healthcare workers and to reduce the spread of COVID-19.[36] In early March 2020, CMS expanded access to telehealth services in the Coronavirus Preparedness and Response Supplemental Appropriations Act to help mitigate pandemic-related challenges.[37] Additionally, Section 1135 of the Social Security Act was used to waive certain CMS requirements, thereby allowing Medicare to pay for telehealth services provided in inpatient, outpatient, and home settings by a variety of providers.[36,38] The European Society of Cardiology 2020 guidelines for managing patients with cardiovascular disease during the pandemic recommend utilizing telemedicine "whenever possible to provide medical advice and follow-up of stable HF patients."[39]

The use of virtual healthcare provides a convenient and effective alternative to in-person visits by facilitating face-to-face communications between patients with HF and their healthcare providers.[36] Through virtual visits, clinicians are able to monitor vital signs using home medical devices; perform limited physical examinations; gain knowledge of relevant domestic circumstances; visualize pill containers to reconcile medication usage; and interact with caregivers.[36]

Data from a study evaluating the use of telemedicine to manage patients with HF during the COVID-19 outbreak in Italy showed that no patient using this service contracted COVID-19.[40] Furthermore, patients with access to telemedicine during the pandemic versus patients without access to telemedicine in 2019 were less likely to be hospitalized for HF, with no significant difference in mortality.[40] The study findings confirm that telemedicine is a valuable tool in the management of HF and show its feasibility during the COVID-19 pandemic.[40]

Conclusions

HF is a serious disorder associated with substantial morbidity and mortality. Notably, HF is listed as a contributing factor

on 1 in 8 death certificates in the US. Initial treatment for HF includes the use of ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists; diuretics are used to relieve the signs and symptoms of congestion. Several new agents, including sacubitril/valsartan, ivabradine, dapagliflozin, and canagliflozin, are available for use in patients with HF to reduce the risk of hospitalization and/or cardiovascular death. Effective transitions of care should include structured follow-up with patient education, optimization of medical treatment, psychosocial support, and improved access to care. Telemedicine is a useful approach and has been shown to improve outcomes in patients with HF.

References

1. Jessup M, Brozena S. Heart failure. *N Engl J Med*. 2003;348:2007-2018.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240-e327.
3. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. *Circulation*. 2019;139:e56-e66.
4. Ni H, Xu J. Recent trends in heart failure-related mortality: United States, 2000 – 2014. *NCHS Data Brief*. 2015;231:1-8.
5. Centers for Disease Control and Prevention. National ambulatory medical care survey: 2015 state and national summary tables. Accessed September 30, 2020. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf
6. Centers for Disease Control and Prevention. National hospital ambulatory medical care survey: 2015 emergency department summary tables. Accessed September 30, 2020. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf
7. Chang PP, Chambless LE, Shahar E, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol*. 2014;113:504-510.
8. Kilgore M, Patel HK, Kielhorn A, Maya JF, Sharma P. Economic burden of hospitalizations of Medicare beneficiaries with heart failure. *Risk Manag Healthcare Policy*. 2017;10:63-70.
9. Data.Medicare.gov. Complications and deaths – national. Accessed September 30, 2020. https://data.medicare.gov/Hospital-Compare/Complications-and-Deaths-National/qqw3-t4ie
10. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101:1016-1022.
11. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6:606-619.
12. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J Fail*. 2016;18:891-975.
13. Bhambhani V, Kizer JR, Lima JAC, et al. Predictors and outcomes of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2018;20:651-659.
14. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;119:e391-e479.
15. The Criteria Committee of New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels, 9th ed. Boston, MA: Little & Brown; 1994.
16. Yancy CW, Januzzi JL, Allen LA, et al. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction. A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2018;71:201-230.
17. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2016;134:e282-e293.
18. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Card Fail*. 2017;23:628-651.
19. Sacubitril/valsartan (Entresto) [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation. October 2019.
20. Ivabradine (Corlanor) [prescribing information]. Thousand Oaks, California: Amgen Inc. April 2019.
21. Dapagliflozin (Farxiga) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. October 2019.
22. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436-1446.
23. Canaglifozin (Invokana) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. January 2020.
24. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: from mechanisms to therapies. *Eur Heart J*. 2018;39:2780-2792.
25. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. *Lancet*. 2010;376:875-885.
26. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
27. Novartis. Novartis Entresto receives FDA approval for pediatric heart failure, helping to address critical unmet need for treatment options. October 1, 2019. Accessed September 30, 2020. https://www.novartis.us/news/media-releases/novartis-entresto-receives-fda-approval-pediatric-heart-failure-helping-address
28. Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilized heart failure patients in hospital or early after discharge: primary results of the randomized TRANSITION study. *Eur J Heart Fail*. 2019;21:998-1007.
29. McMurray JJV, Solomon S, Inzycchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;38:1995-2008.
30. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382:1883-1893.
31. Business wire [press release]. FDA grants priority review to Merck's new drug application for vericiguat. July 16, 2020. https://www.businesswire.com/news/home/20200716005203/en/FDA-Grants-Priority%20Review-to-Merck%E2%80%99s-New-Drug-Application-for-Vericiguat.%20Accessed%20September%2030,%202020
32. Hollenberg SM, Stevenson LW, Ahmad T, et al. 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure. *J Am Coll Cardiol*. 2019;74:1966-2011.
33. Albert NM, Barnason S, Deswal A, et al. Transitions of care in heart failure. A scientific statement from the American Heart Association. *Circ Heart Fail*. 2015;8:384-409.
34. Kotb A, Cameron C, Hsieh S, Wells G. Comparative effectiveness of different forms of telemedicine for individuals with heart failure (HF): a systematic review and network meta-analysis. *PLoS One*. 2015;10:e0118681.
35. Ortiz-Bautista C, Morán-Fernández L, Díaz-García M, et al. Evaluation of a nurse-led intervention program in heart failure: a randomized trial. *Med Clin (Barc)*. 2019;152:431-437.
36. DeFilippis EM, Reza N, Donald E, Givertz MM, Lindenfeld J, Jessup M. Considerations for heart failure care during the COVID-19 pandemic. *JACC Heart Fail*. 2020;8(8):681-691.
37. Congress.gov. H.R.6074 – Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020. Accessed October 20, 2020. https://www.congress.gov/bill/116th-congress/house-bill/6074
38. CMS.gov. Coronavirus waivers & flexibilities. October 16, 2020. Accessed October 21, 2020. https://www.cms.gov/about-cms/emergency-preparedness-response-operations/current-emergencies/coronavirus-waivers
39. European Society of Cardiology. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. June 10, 2020. Accessed October 20, 2020. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance
40. Salzano A, D'Assante R, Stagnaro FM, et al. Heart failure management during the COVID-19 outbreak in Italy: a telemedicine experience from a heart failure university tertiary referral centre. *Eur J Heart Fail*. 2020;22:1048-1050.

The Impact of COVID-19 on Hospital Medicine

Introduction

COVID-19 is a fast-spreading pandemic that has created substantial disruptions in the healthcare system.[1] Initially, the size and magnitude of COVID-19 was grossly underestimated, and preparations were inadequate. Practical considerations for managing a novel disease with many unknowns remain an enormous challenge.

Since the start of the pandemic, front-line hospital-based clinicians have adapted to care for an increased patient load under extremely stressful conditions. In 2015, the average bed occupancy rate in all US hospitals (federal, nonfederal, and community) was 65.5%.[2] In May 2019, the percent of inpatient beds occupied in the US was highly variable, ranging from 0% to 39.9% in South Dakota to ≥70% in Washington, Nevada, Maryland, Massachusetts, and Rhode Island.[3] At the same time, the percent of intensive care unit (ICU) beds occupied in the US was also highly variable, ranging from 20% to 39.9% in three states to ≥70% in eleven states; in most of the country, ICU beds had less than two-thirds occupancy.[3]

Staffing Shortage and the Staffing Domino Effect

In February 2020, the American Hospital Association (AHA) projected that 4.8 million hospitalizations would be associated with COVID-19, thereby increasing the clinical care demand on hospital staffing.[4] There are only 28,808 intensivists in the US, and about 48% of acute care hospitals have no intensivists; the model predicted that one million patients with COVID-19 would need ventilator support. Shortages may be compounded by the conventional practice of staffing the hospital at about 60% of patient census and adding staff, as needed, through float pools. Other staffing issues include the personal concerns and needs of hospital workers (eg, fear, family pressures) and the necessity of self-quarantining by hospital workers after becoming ill or caring for family members.

Concerns of Healthcare Professionals

In the early days of the pandemic, widespread reports of personal protective equipment (PPE) shortages, inadequate staffing, and suboptimal decontamination programs may have led to fear and anxiety among frontline healthcare workers caring for patients with COVID-19.[5-7] In March 2020, the AHA, American Medical Association (AMA), and American Nurses Association wrote a joint letter to Congressional leaders requesting staffing and financial support to: (1) obtain scarce supplies, including PPE; (2) update and train staff on the implementation of pandemic preparedness plans to respond to COVID-19; (3) increase infection control and triage training in all healthcare settings; (4) train for and implement expanded telemedicine and telehealth capabilities; and (5) cover the increased costs associated with higher staffing levels.[8]

The AMA has recently published a series of articles to provide guidance on the delivery of ethical medical care during the COVID-19 pandemic. In the first article, the AMA acknowledges that the responsibilities and obligations of healthcare personnel in a pandemic pose a "greater than usual risk to physicians' own safety, health or life."[7] Not surprisingly, the stress of caring for others during a time of urgent medical need may cause healthcare personnel to worry about their own health and the health of loved ones. Other stressors may include changes in sleep or eating patterns; difficulty sleeping or concentrating; worsening of chronic or mental health conditions; and increased substance use.[6]

Numerous articles published since the beginning of the COVID-19 outbreak have discussed the psychological effects of the pandemic on healthcare workers.[9] Eight listening sessions with 69 healthcare professionals held during the first week of the COVID-19 pandemic consistently identified several sources of anxiety that focused on access to appropriate PPE, exposure to COVID-19 in the workplace, risk of infecting family members, uncertainty of employer support, and lack of access to current information and communication.[10]

Public Health Emergency Preparedness

Public health emergency preparedness adapts to emerging threats and emergencies and constantly changes and

evolves.[11] The need for a public health emergency preparedness infrastructure became apparent after the 2001 World Trade Center and anthrax attacks. In response to 9/11, Congress funded the Public Health Emergency Preparedness (PHEP) program in 2002 to help build state and local public health emergency preparedness. Lessons learned from 9/11 helped to inform capability standards moving forward, as the country faced natural disasters (hurricanes, floods, wildfires), the 2009 influenza pandemic, the 2015 Ebola outbreak and the 2016 Zika virus outbreak.

The need for planning standards to accelerate and improve public health emergency management activities emerged in 2011, at which time the CDC published the Public Health Preparedness Capabilities: National Standards for State and Local Planning and introduced a new framework to guide the PHEP cooperative agreement. After 2011, public health and emergency management continued to work together to prepare for, respond to, and recover from new and emerging threats to the US.

In 2018, the CDC published updated capability standards (ie, Public Health Emergency and Preparedness and Response Capabilities) to advance state, local, tribal, and territorial preparedness based on current guidance and practices.[12] Drivers for the updates included (1) evolution of public health preparedness guidance and resources; (2) lessons learned from public health emergency response; (3) findings from internal CDC reviews and assessments; and (4) feedback from the public health preparedness practice community.[12] The six domains of preparedness include: community resilience, incident management, coordinating an effective response, information management, countermeasures and mitigation, surge management, and biosurveillance.[13]

Screening Patients for COVID-19

Screening patients before they enter a hospital reduces exposure for other patients and healthcare personnel, helps to prevent the spread of disease within the facility, and helps to ensure that PPE is used effectively. Numerous general screening measures have been implemented in the COVID-19 era (eg, advising to patients to check their temperature before leaving home, using face coverings regardless of symptoms, separating patients with and without symptoms in waiting areas, separating patients by ≥6 feet throughout the facility, and posting signs at facility entry points with instructions for patients).[14]

Extrapulmonary Complications of COVID-19

COVID-19 causes a wide range of pulmonary problems that can affect both the upper and lower respiratory tract;[15] however, the infection is not limited to the respiratory system.[16] Patients with COVID-19 may also experience extrapulmonary complications, some of which are thought to be due to a "cytokine storm."[16] Notably, widespread cytokine release can cause cellular, tissue, and organ damage.[15,16] At present, a broad spectrum of extrapulmonary complications (eg, cardiac, renal, hematologic, gastrointestinal, neurologic, mediastinal, and liver) has been observed in patients with COVID-19.[16]

Therapeutic Strategies and Vaccines

No therapeutics have yet been approved by the FDA for the treatment of COVID-19, but numerous antiviral agents are currently under investigation. In October 2020, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel (the Panel) published summary recommendations for the use of chloroquine with or without azithromycin, hydroxychloroquine with or without azithromycin, lopinavir/ritonavir and other HIV protease inhibitors, and remdesivir. The Panel acknowledged that treatment decisions for COVID-19 should be made by patients and their healthcare provider, as is the case for all other diseases.

The first clinical trial to evaluate an experimental treatment for COVID-19 found that the antiviral agent remdesivir accelerated recovery from advanced COVID-19.[17] In the placebo-controlled Adaptive COVID-19 Treatment Trial, which was conducted in 1063 hospitalized patients with a confirmed diagnosis of COVID-19, preliminary data showed that treatment with remdesivir was associated with a 31% faster time to recovery than was treatment with placebo (11 vs 15 days, respectively; $P < .001$).[17]

Several blood-derived products are also under evaluation for the treatment of COVID-19, but as of October 2020, data were insufficient for the Panel to recommend either for or against the use of COVID-19 convalescent plasma and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins.[18] In October 2020, the Panel recommended against the use of mesenchymal stem cells and non-SARS-CoV-2–specific intravenous immunoglobulins (IVIGs); however, the latter recommendation should not preclude the use of IVIGs if otherwise indicated for the treatment of complications that develop during the course of COVID-19.

Several vaccines are at various stages of development, with some of them now being tested in phase 3 clinical trials.

Concomitant Medication Use in Patients With COVID-19

In July 2020, the Panel published summary recommendations regarding the concomitant use of several common medications in patients with COVID-19.[18] In brief, the Panel recommended that patients receiving ACE inhibitors, ARBs, statins, or NSAIDs for underlying conditions should continue treatment as previously directed. Furthermore, oral corticosteroid therapy used prior to a COVID-19 diagnosis for an existing condition should also not be discontinued, nor should inhaled corticosteroids used for asthma and chronic obstructive pulmonary disease. The Panel also provided detailed recommendations on the use of corticosteroids in the management of COVID-19.

Testing for Severe Acute Respiratory Syndrome Coronavirus 2 Infection

In June 2020, the Panel published three summary recommendations pertaining to testing for SARS-CoV-2 infection.[18] The Panel recommended the use of a molecular or antigen test for SARS-CoV-2 to diagnose acute SARS-CoV-2 infection and recommends against the use of serologic testing as the sole basis for the diagnosis of acute SARS-CoV-2 and also to determine whether an individual is immune to SARS-CoV-2 infection. All three recommendations were designated as AIII, with "A" signifying a strong recommendation rating, and "III" signifying that the rating of evidence was expert opinion.

COVID-19 Antigen and Antibody Testing

Antigen tests, immunoassays used to detect the presence of a specific viral antigen, are relatively inexpensive and can be used at the point-of-care; the turnaround time is about 15 minutes.[19] Currently authorized antigen tests are performed on nasopharyngeal or nasal swab specimens that are placed directly into an extraction buffer or reagent. Antigen tests perform optimally when a patient is in the early stages of COVID-19 infection, the time at which the viral load is usually at its highest. In general, antigen tests for COVID-19 are less sensitive than are viral tests that detect nucleic acid using reverse transcriptase-polymerase chain reaction (RT-PCR).

Serologic antibody testing for COVID-19 can be useful in determining whether an individual was previously infected with the disease (even in the absence of symptoms) and in confirming the presence of current infection.[20,21] The first serologic antibody test for COVID-19 was approved by the FDA on April 1, 2020, and numerous serologic assays are now broadly available.[20] Current serologic assays, which employ a wide range of technologies, measure different classes of immunoglobulins and detect antibodies directed against the virus.[21]

The CDC has developed interim guidance on the use of antibody tests, the main points of which are as follows: (1) there is no identified advantage of one serologic assay (IgG, IgM and IgG, or total antibody) over another; (2) it is important to minimize false-positive results by selecting an assay with high specificity and by testing populations/individuals with increased likelihood of previous exposure to COVID-19; (3) an orthogonal testing algorithm can be used when the expected positive predictive value of a single test is low; (4) antibodies most commonly become detectable 1 to 3 weeks after symptom onset, suggesting that the degree of infectiousness may be greatly reduced and that the individual has developed some degree of immunity from future infection; and (5) additional data are needed before modifying public health recommendations based on serological testing.[20] Information on the clinical utility and performance of serologic testing in patients with COVID-19 is rapidly evolving.[21]

The Care of Critically Ill Patients With COVID-19

Severe COVID-19 may be associated with acute respiratory distress syndrome, septic shock, cardiac dysfunction, increased levels of multiple inflammatory cytokines that induce a cytokine storm, and/or exacerbation of existing comorbidities.[18] The effective management of critically ill patients with COVID-19 therefore requires treating not only the medical condition that led to admission to the ICU, but also treating comorbidities and nosocomial complications. In October 2020, the Panel published summary recommendations for the care of critically ill patients with COVID-19 pertaining to infection control, hemodynamic support, ventilatory support, acute kidney injury and renal replacement therapy, and pharmacologic interventions.

Changes to Telemedicine Due to COVID-19

Many restrictions on the use of telemedicine have been lifted by CMS and the federal government in response to COVID-19.[22] In particular, Medicare has greatly expanded access to telehealth to its beneficiaries. Effective March 1, 2020 and throughout the national public health emergency, Medicare has agreed to pay physicians for telehealth services at the same rate as in-office visits for all diagnoses. Furthermore, CMS allows Medicare Advantage or other organizations that submit diagnoses for risk-adjusted payment to include diagnoses from telehealth visits. Telehealth-specific technology is not necessary—ie, physicians can use any two-way audiovisual device, but should not use public-facing communication services.

Social Distancing and Its Impact on Community Medicine

Limiting close face-to-face contact with other people is the best way to reduce the spread of COVID-19.[23] Social distancing (also called "physical distancing") means keeping a safe distance from people outside of one's household. The CDC has offered guidance on social distancing in the community, which includes staying ≥6 feet away from others; wearing a cloth face covering over the nose and mouth while in public; working from home, if possible; limiting the use of public transportation, if possible; avoiding large gatherings outside of the household; and considering distance learning.[23] Of note, cloth face coverings should not be placed on children aged <2 years; individuals who have trouble breathing; or individuals who are unconscious, incapacitated, or otherwise unable to remove the mask without assistance.[23]

The ramifications of social distancing on community medicine is far-reaching and may include (1) negative effects on mental health and well-being; (2) concerns of expectant parents and negative effects of separating partners, mothers, and infants; (3) cancellation of doctor's appointments, prenatal examinations, and elective surgeries; and (4) missed vaccinations, which could potentially lead to other outbreaks (eg, UNICEF estimates that up to 117 million children could miss vaccinations due to the pandemic).[24,25]

Social Distancing in the Hospital

Social distancing in the hospital is critical to ensure the health and well-being of hospital-based clinicians during the pandemic and to prevent nosocomial transmission. Social distancing strategies that could be implemented in the hospital setting include transitioning in-person conferences, meetings, and rounds to virtual events; using phone sign outs; reorganizing clinical workrooms; and locating additional call rooms, reallocating space for call rooms, or other solutions.[26]

Conclusions

COVID-19 has been a fast-spreading pandemic that has created substantial disruptions to the US healthcare system. In particular, front-line hospital-based clinicians have adapted to care for an increased patient load under extremely stressful conditions. Public health preparedness is constantly changing, and COVID-19 will inform future policies and processes. The future of hospital medicine may include increases in virtual care delivery, telehealth, and permanent physical distancing protocols.

Unanswered Questions about COVID-19

- What does the future hold regarding childhood manifestations of COVID-19?
- When will the world return to "normal"?
- How will virtual healthcare evolve over time?
- Will COVID-19 re-emerge?
- What is the process for the re-engagement of non-COVID-19 patients who have avoided necessary medical care?

References

1. Jain NK, Tirupathi R, Palabindala V. COVID-19: managing resource crunch and ethical challenges. The Hospitalist. April 14, 2020. Accessed September 30, 2020. https://www.the-hospitalist.org/hospitalist/article/220724/coronavirus-updates/covid-19-managing-resource-crunch-and-ethical

2. American Hospital Association. Annual survey of hospitals. Hospital statistics, 2015, 2016, and 2017 editions. Chicago, IL.

3. Centers for Disease Control and Prevention. Current hospital capacity estimates – snapshot. July 14, 2020. Accessed September 30, 2020. https://www.cdc.gov/nhsn/covid19/report-patient-impact.html

4. Daly R. Hospitals face staffing 'domino effect' from the coronavirus outbreak adviser says. March 17, 2020. Accessed September 30, 2020. https://www.hfma.org/topics/news/2020/03/hospitals-face-staffing--domino-effect--from-the-coronavirus-out.html

5. National Nurses United. NNU COVID-19 survey results. Updated July 27, 2020. Accessed September 30, 2020. https://act.nationalnursesunited.org/page/-/files/graphics/0720_Covid19_Survey3_Results_Flyer_REV.pdf

6. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). May 5, 2020. Accessed September 30, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/mental-health-healthcare.html

7. American Medical Association. AMA code of medical ethics: guidance in a pandemic. April 14, 2020. Accessed September 30, 2020. https://www.ama-assn.org/delivering-care/ethics/ama-code-medical-ethics-guidance-pandemic

8. American Hospital Association. Letter to Congress. March 16, 2020. Accessed September 30, 2020. https://www.aha.org/system/files/media/file/2020/03/aha-ama-ana-to-congress-re-economic-stimulus-package-3-16-2020.pdf

9. Callaway E, Cyranoski D, Mallapaty S, Stoye E, Tollefson J. The coronavirus pandemic in five powerful charts. *Nature*. 2020;579:482-483. doi:10.1038/d41586-020-00758-2

10. Shanafelt T, Ripp J, Trockel M. Understanding and addressing sources of anxiety among health care professionals during the COVID-19 pandemic. April 7, 2020. Accessed September 30, 2020. https://jamanetwork.com/journals/jama/fullarticle/2764380

11. Centers for Disease Control and Prevention. Threats change: public health adapts. Accessed September 30, 2020. https://www.cdc.gov/cpr/readiness/00_docs/2018_Capabilities_PublicHealthAdapts_Factsheet_P4.pdf

12. Centers for Disease Control and Prevention. Center for Preparedness and Response. Keeping the US prepared and ready to respond to public health threats. September 10, 2020. Accessed September 30, 2020. https://www.cdc.gov/cpr/index.htm

13. Centers for Disease Control and Prevention. Six domains of preparedness. Accessed September 30, 2020. https://www.cdc.gov/cpr/readiness/00_docs/PHEP__SixDomainsOfPrep.pdf

14. Centers for Disease Control and Prevention. Screening and triage at intake. April 14, 2020. Accessed September 30, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis/screening.html

15. Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55:105924.

16. Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: radiologic and clinical overview. *Clin Imaging*. 2020;66:35-41.

17. National Institutes of Health. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. April 29, 2020. Accessed September 30, 2020. https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

18. National Institutes of Health. COVID-19 treatment guidelines. October 2020. Accessed October 13, 2020. https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

19. Centers for Disease Control and Prevention. Interim guidance for rapid antigen testing for SARS-CoV-2. September 4, 2020. Accessed September 30, 2020. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html#table2

20. Centers for Disease Control and Prevention. Interim guidelines for COVID-19 antibody testing. August 1, 2020. Accessed September 30, 2020. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html

21. Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: serologic testing. August 18, 2020. Accessed September 30, 2020. https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/

22. American Medical Association. CARES Act: AMA COVID-19 pandemic telehealth fact sheet. April 27, 2020. Accessed September 30, 2020. https://www.ama-assn.org/delivering-care/public-health/cares-act-ama-covid-19-pandemic-telehealth-fact-sheet

23. Centers for Disease Control and Prevention. Social distancing. July 15, 2020. Accessed September 30, 2020. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/social-distancing.html

24, Galea S, Merchant RM, Lurie N. The mental health consequences of COVID-19 and physical distancing. The need for prevention and early intervention. *JAMA Intern Med*. April 10, 2020. Accessed September 30, 2020. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2764404

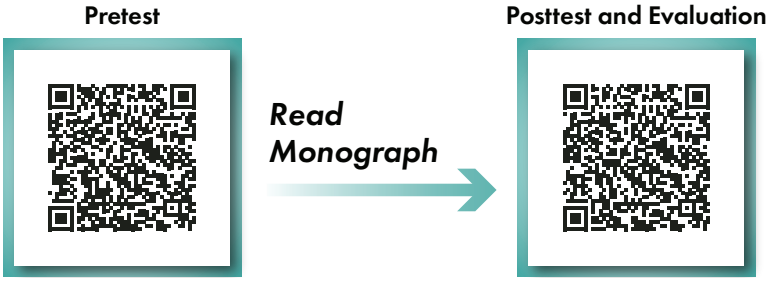
25. Cohut M. How the pandemic has affected primary healthcare around the world. *Medical News Today*. May 15, 2020. Accessed September 30, 2020. https://www.medicalnewstoday.com/articles/how-the-pandemic-has-affected-primary-healthcare-around-the-world

26. Arora VM, Chivu M, Schram A, Meltzer D. Implementing physical distancing in the hospital: a key strategy to prevent nosocomial transmission of COVID-19. *J Hosp Med*. 2020;155:290-291.

Instructions to Receive Credit

During the period of December 30, 2020 through December 30, 2021, participants must read the CME/CE information and learning objectives, complete the pretest, study the educational activity, complete the posttest and evaluation form. A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better.

The pretest and posttest along with the evaluation can be accessed online at **www.integrityce.com/hms-supplement** or by scanning the QR codes below.



Pharmacists must check the CPE monitor for their credits within 60 days of the activity.

About Integrity CE

Integrity Continuing Education, founded in 2006, is a full-service, ACCME-accredited provider of continuing medical education for healthcare professionals. Our mission is to develop and implement cutting-edge CME/CE initiatives featuring evidence-based scientific content of the highest integrity. The overall goal of our CME program is to provide today's busy healthcare providers with high quality CME activities that can effect change in clinical practice by improving competence, performance, and ultimately, patient outcomes. The Integrity CE leadership team possesses over 35 years of experience in the medical education industry.

www.integrityce.com

106 Apple Street
Suite 300
Tinton Falls, NJ 07724