Digestive Diseases and Sciences (2022) 67:1994–2004
https://doi.org/10.1007/s10620-021-07075-2

REVIEW

Hepatic Encephalopathy-Related Hospitalizations in Cirrhosis: Transition of Care and Closing the Revolving Door

Catherine T. Frenette[1] · Cynthia Levy[2] · Sammy Saab[3]

Received: 11 March 2021 / Accepted: 24 May 2021 / Published online: 24 June 2021

Abstract

Cirrhosis is associated with substantial morbidity and mortality. Development of complications of cirrhosis, including hepatic encephalopathy (HE), portends poorer outcomes. HE is associated with hospital readmission, impaired patient and caregiver quality of life, risk of falls, and mortality. Guidelines recommend lactulose as first-line therapy for HE and rifaximin in combination with lactulose for reducing the risk of HE recurrence. Improving post-discharge outcomes, including readmissions, is an important aspect in the management of patients with HE. Approaches focused on improving management and prevention of HE, including properly titrating lactulose dosing, overcoming medication-related nonadherence, and incorporating rifaximin as therapy to reduce the risk of recurrence, as well as incorporating supportive care initiatives, may ease the transition from hospital to home. Strategies to decrease readmission rates include using hospital navigators, who can offer patient/caregiver education, post-discharge planning, and medication review; and involving pharmacists in post-discharge planning. Similarly, telemedicine offers providers the opportunity to monitor patients with HE remotely and improves outcomes. Providers offering transitional care management may be reimbursed when establishing contact with patients within 2 days post-discharge and conducting an outpatient visit within 7 days or 14 days. Several approaches have been shown to improve outcomes broadly in patients post-discharge and may also be effective for improving outcomes specifically in patients hospitalized with cirrhosis and HE, thus closing the revolving door on rehospitalizations in this population.

Keywords Hepatic encephalopathy · Liver cirrhosis · Hospitalization · Patient readmission · Rifaximin · Lactulose

Background

Cirrhosis is associated with a number of etiologic factors, including viral infections (e.g., hepatitis B and C), alcohol use, and nonalcoholic steatohepatitis [1]. Cirrhosis has been estimated to affect 0.3% of the US adult population and was the eleventh most common cause of mortality in the USA in 2017 [2, 3]. In 2014, liver disease was associated with 251,790 US hospitalizations, a 25% increase from 2005 [4]. In 2019, the overall economic costs of all hospital readmissions, which were, in part, considered preventable, were estimated at US$21 billion to US$22 billion [5]. While not broken down by disease state in that publication, it is likely patients with liver disease were included in that estimate.

Readmission rates in patients with liver disease have been high and have varied among studies (Table 1) [4, 6–10]. Indeed, pooled data from 7 independent studies published between 2001 and 2015 indicated that the 30-day readmission rate for patients with cirrhosis was 25.8% (95% confidence interval [CI], 23.8–28.0%; range 6.3–37%) [11]. In 2015, data from the all-payer US Nationwide Readmissions Database reported that the 30-day readmission rate for patients with liver disease was 15.0% [4].

The transition from the compensated to the decompensated state of cirrhosis is characterized by development of complications, including hepatic encephalopathy [HE], ascites, and variceal bleeding [12, 13]. Development of cirrhosis-related complications has been associated with significantly lower survival rates compared with rates for

✉ Sammy Saab
SSaab@mednet.ucla.edu

[1] Division of Organ Transplantation, Scripps Green Hospital, La Jolla, CA, USA

[2] Division of Digestive Health and Liver Diseases, University of Miami, Miami, FL, USA

[3] David Geffen School of Medicine, Department of Medicine, University of California At Los Angeles, UCLA Medical Center, Los Angeles, CA, USA

Table 1 Readmission rates in patients with liver disease

Study	Readmission rates
Volk et al. [6] (2006–2009; $n=402$ pts)	37% of pts readmitted within 1 mo (median time to first admission, 67 d)
Koola et al. [7] US VA (2006–2013; $n=179{,}298$ index hospitalizations)	30-day readmission rate: 23%
Rosenblatt et al. [8] Inpatient databases (2009–2013; 3 US states); pts with Medicare coverage whose index hospitalization was related to CHF, MI, or pneumonia ($n=797{,}432$ pts)	Pts with comorbid cirrhosis ($n=8964$) vs. no cirrhosis ($n=788{,}468$) 30-day readmission rate: 29.3% vs. 23.8%; $P<0.001$ 90-day readmission rate: 48.0% vs. 39.2%; $P<0.001$ In pts with cirrhosis, odds of: 30-day readmission: OR, 1.13; 95% CI, 1.08–1.19; $P<0.001$ 90-day readmission: OR, 1.09; 95% CI, 1.04–1.14; $P<0.001$
Tapper et al. [9] 5 US states (2011; $n=119{,}722$ index hospitalizations)	30-day readmission rate: 12.9% 90-day readmission rate: 21.2%
Shaheen et al. [10] US Nationwide Readmissions Database (2014; $n=58{,}954$ pts)	90-day readmission rate: 25.3%
Peery et al. [4] US Nationwide Readmissions Database (2015; $n=139{,}971$ index hospitalizations)	30-day readmission rate: 15.0%

CHF congestive heart failure, *CI* confidence interval, *MI* myocardial infarction, *mo* month, *OR* odds ratio, *pts* patients, *VA* Veterans Administration

patients with compensated cirrhosis (> 12 years vs. ~ 2 years, respectively) [13]. An EU single-center, retrospective study reported that HE was the cause of hospitalization for approximately one-third (35.1%) of admissions among 177 patients with decompensated cirrhosis (2008–2014; 427 hospitalizations); among 250 rehospitalizations, the 30-day readmission rate was 31.2% [14]. Patient mortality risk was greatest ≤ 30 days post-discharge (range, 9.4% [2004] to 10.1% [2013]).

Interviews with patients newly diagnosed with cirrhosis and their caregivers have provided insight into the negative impacts of a cirrhosis diagnosis [15]. Not surprisingly, the time of cirrhosis diagnosis has been described as an emotionally distressing period for both patients and caregivers [15]. Caregivers have reported burnout associated with disruptions to daily life resulting from unanticipated hospitalizations and patients' increasing dependence [15]. The impact of cirrhosis on employment has been felt both by patients and caregivers, with patients working less, if at all; the resulting decrease in income, compounded with increasing healthcare costs, has posed economic challenges for patients [15, 16]. The aim of this narrative review is to provide an overview of the impact of HE on patients with cirrhosis, including hospitalizations and risk for HE recurrence and readmission, and to discuss clinically relevant opportunities for improving patient outcomes, including steps for mitigating hospital readmissions in this patient population.

Hepatic Encephalopathy

Overt HE is a neurologic complication of cirrhosis that is distinguished by a wide range of symptoms, from lethargy, personality changes, confusion, and inappropriate or odd behavior to coma in the most severely affected patients [17]. A pattern of hospitalization and subsequent readmission is common in patients with cirrhosis, particularly in those with HE (Fig. 1) [11]. In a US single-center, retrospective study (2011–2013) of 222 patients with decompensated cirrhosis, more than half (59.4%) were readmitted within a median 54 days, with HE cited most often as the cause for readmission (35.5%) [18]. The presence of HE at the time of the index hospitalization was a significant predictor of shorter time to readmission and a significant predictor of readmission ≤ 30 days [18]. Similarly, the presence of HE increased the odds of 30-day readmission in patients with cirrhosis from 3 US states included in the Hospital Readmissions Reduction Program (HRRP) between 2009 and 2013 [8]. Finally, in a single center study (2008–2014), HE was cited as the cause for almost half of the 250 readmissions (45.4%) [14]. Repeat hospitalizations can place substantial financial burden on healthcare systems. For example, larger hospitals and teaching and safety-net hospitals treating Medicare patients in the HRRP, which were more likely to treat a sicker and more socioeconomically disadvantaged population, had higher readmission rates than smaller hospitals and non-teaching and nonsafety-net hospitals and were

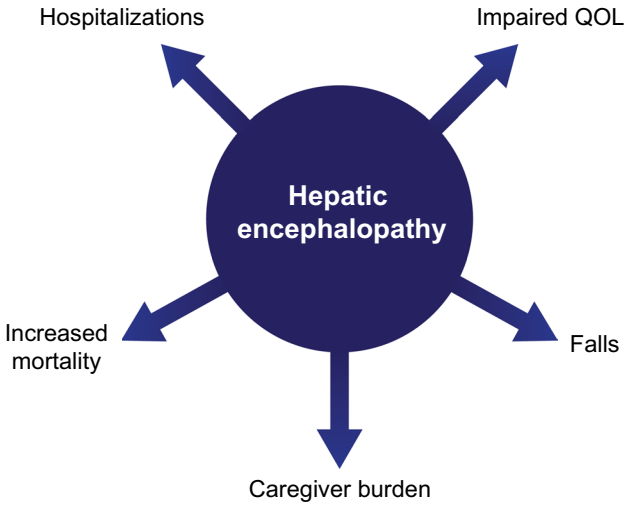

Fig. 1 Effects of hepatic encephalopathy. QOL = quality of life

more likely to be penalized by receiving a cut in Medicare reimbursement [19]. According to data from the US National (Nationwide) Inpatient Sample, HE-related hospitalizations increased significantly from 75,475 in 2009 to 106,915 in 2013 [20]. However, there was a significant decrease in the mean length of hospitalization (7.6 days vs. 7.1 days, respectively) and inpatient mortality (11.9% vs. 10.2%) during this time [20].

The burden of hospitalizations on caregivers cannot be overlooked, as a study showed that caregivers of patients with more than 2 hospitalizations due to complications of liver disease within a year were more likely to experience caregiver burden (Zarit Burden Interview score > 21) than other caregivers [21]. Beyond the burden of hospitalizations, overt HE negatively affects patient and caregiver quality of life (QOL; Fig. 1) [21–24]. A significant association has been shown between impaired patient QOL and history of overt HE in patients with decompensated cirrhosis [22]. Caregivers of patients with advanced liver disease have demonstrated significantly lower mental health scores compared with the general population, including in the areas of emotional health, mental health, social functioning, and vitality [21]. Patient history of HE has been identified as a significant predictor of increased caregiver burden [21]. Psychological effects of HE also have been shown to be an important component of diminished QOL in patients with HE and their caregivers [24]. Caregivers of patients with overt HE have reported feeling overwhelmed at the first onset of symptoms; feeling "tied down" due to increased household responsibilities and the need to evaluate the patient for symptoms of overt HE; and experiencing communication issues with healthcare providers [23].

A significantly higher rate of falls has been observed in patients with cirrhosis and cognitive impairment, such as that seen with HE, compared with those without cognitive issues (40.4% vs. 6.2%, respectively) [25]. This is important, as cirrhosis has been shown to be a predictor of peripheral fractures [26]. Data from the US Nationwide Emergency Department Sample (2009–2012) indicated that patients with cirrhosis who presented to the emergency department (ED) with falls had greater odds of severe injury compared with patients without cirrhosis, including intracranial hemorrhage and pelvic fractures [27]. The presence of HE was significantly associated with severe fall-related injuries in patients with cirrhosis [27], and HE was shown to increase the risk of hip fracture in patients aged > 50 years [28]. Thus, it is apparent that the presence of HE in patients with cirrhosis is associated with hospital readmissions, increased mortality, impaired QOL, and greater fall risk.

Management of HE

Guidelines from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend therapies for HE, including the nonabsorbable disaccharide lactulose and the nonsystemic antibiotic rifaximin [17]. Lactulose is endorsed as first-line therapy for overt HE, with rifaximin as add-on therapy for reducing the risk of overt HE recurrence [17]. Lactulose dosing is typically 25 mL every 1–2 h, usually administered orally, until ≥ 2 loose or soft stools per day occur, with subsequent dosing titration to maintain 2–3 bowel movements per day [17]. Rifaximin 550 mg is administered twice daily [29].

AASLD/EASL guidelines stress that identifying and controlling precipitating factors (e.g., electrolyte imbalance, gastrointestinal bleeding, infection) is key for treating HE (Table 2) [17, 30]. Precipitating factors for HE observed in patients with cirrhosis included acute kidney failure, constipation, dehydration, and infections (e.g., spontaneous bacterial peritonitis, urinary tract infection) [30]. In a case–control study, infections significantly increased the risk of developing HE in patients with cirrhosis (adjusted odds ratio [OR], 3.04; 95% CI, 2.44–3.78; $P < 0.0001$) [31]. Further, patients with cirrhosis and a history of 1–3 infections were more likely to develop HE compared with those without a history of infections (adjusted OR, 2.68; 95% CI, 2.13–3.37; $P < 0.001$) [31].

Certain medications can also precipitate HE in patients with cirrhosis [30]. Lactulose is effective when used properly, but paradoxically, lactulose use also can be a precipitating factor for HE [30]. Failure to properly titrate lactulose may result in diarrhea, which can lead to dehydration, and, in turn, precipitate HE [30]. In addition, study results showed that approximately half of 145 patients hospitalized with HE were nonadherent to lactulose recommendations [30]. Use of opioid analgesics and

Table 2 Precipitants of hepatic encephalopathy [30]

Acute renal failure
Constipation
Dehydration
Electrolyte imbalances (e.g., hypokalemia [potassium < 3.5 mmol/L]; hyponatremia [sodium < 130 mEq/L])
GI bleeding
High-protein diet
Infections (e.g., abdominal infection, bacteremia, cellulitis, respiratory infection, SBP, UTI)
Lactulose nonadherence
Large-volume paracentesis
Medications (e.g., benzodiazepines, opioids)
Acute portal vein thrombosis
Spontaneous portosystemic shunts
TIPS
Unknown/unidentified factors

GI gastrointestinal, *SBP* spontaneous bacterial peritonitis, *TIPS* transjugular intrahepatic portosystemic shunt, *UTI* urinary tract infection

Data from Pantham G, et al. *Dig Dis Sci*. 2017;62:2166–2173 [30]

benzodiazepines was identified as an HE precipitant in 20.1% of 149 patients in the retrospective part of the study and 26.6% of 45 patients in the prospective part [30]. Surprisingly, a single-center retrospective study of 217 hospitalized patients with cirrhosis reported that more than half (54.4%) received opioid analgesics during hospitalization, and 51.2% of 118 patients with HE prior to admission received opioid analgesics during hospitalization [32]. It has been suggested that patients with cirrhosis not be prescribed opioid analgesics, given their nature as a potential precipitant of HE [30].

Reducing Risk of HE-Related Hospitalizations in Patients with Cirrhosis

Improving post-discharge outcomes, including reducing the risk of rehospitalization in patients with cirrhosis who previously had been hospitalized for HE, is an important part of the treatment paradigm for HE. A variety of approaches to minimize readmissions and improve quality of care for patients with HE (e.g., therapy-related approaches, supportive care; Fig. 2) should be considered by health care providers. In a single-center study of patients with cirrhosis, 36 of 165 (21.8%) readmissions occurring within 1 month were considered preventable [6]. Preventing readmissions is important, given that rehospitalization (for any cause) was associated with increased mortality in a population of 2133 Medicare beneficiaries ≥ 65 years of age [33]. The mortality

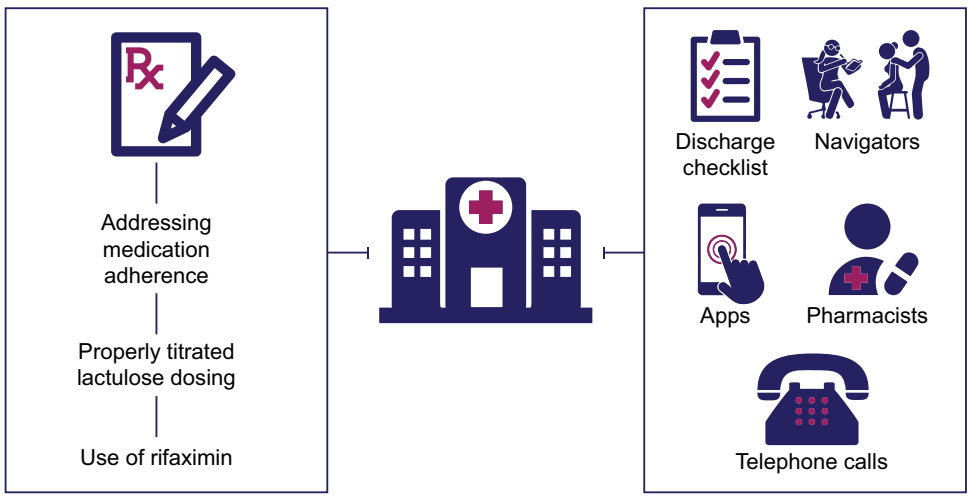

Fig. 2 Approaches for improving outcomes post-discharge in patients with cirrhosis hospitalized for hepatic encephalopathy

rate at 1 year was significantly greater in patients with a hospital readmission ≤ 30 days post-discharge compared with patients not readmitted during this timeframe (38.7% vs. 12.1%, respectively; $P < 0.001$) [33].

Treatment-Related Approaches

Treatment Adherence

In 2 surveys of patients with cirrhosis, one with 50 patients and one with 100 patients, more than half of patients (54% and 58%, respectively) indicated they were not fully adherent to the medications they were prescribed [34, 35]. A retrospective study in patients with HE reported that medication adherence 6 months after an HE-related ED visit or HE-related hospitalization ranged from 48 to 77%, depending on the type of medication [36]. Adherence to therapy is important, given that medications can help prevent precipitating factors for HE (e.g., constipation, infections) [36]. However, data from the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) indicated that medications were implicated in 32% of HE episodes in hospitalized patients with cirrhosis [37]. In that study, a larger percentage of patients with medication as the HE precipitant were hospitalized because of HE compared with those hospitalized due to other precipitating factors [37].

Data, though not specific for a cirrhosis population, suggest medication costs may play a role in nonadherence [35, 38, 39]. In 2004, of the estimated 4.4% of Medicare beneficiaries who failed to fill ≥ 1 prescription, 55% cited economic costs as a reason [38]. This may, in part, be due to Medicare beneficiaries incurring responsibility for any medication costs as they enter the coverage gap, or "donut hole" [40]. US survey data indicated that 6.8% of adults ≥ 65 years of age reported cost-related medication nonadherence (e.g., skipping or decreasing medication doses, failing to fill prescriptions) [39]. A lack of insurance coverage significantly increased the odds of cost-related medication nonadherence (adjusted OR, 3.80; 95% CI, 1.36–10.65); conversely, respondents with a higher income (i.e., income/poverty ratio ≥ 4.0) were significantly less likely to report cost-related medication nonadherence (adjusted OR, 0.43; 95% CI, 0.24–0.77) [39]. Specific to patients with cirrhosis, survey data have supported that medication costs can be a factor for low adherence [35].

Lactulose

As highlighted earlier, inappropriate use of lactulose can play a role in HE recurrence. NACSELD data have underscored the role of lactulose nonadherence as a precipitant of HE, accounting for 20% of medication-related HE hospitalizations reported [37]. Lactulose nonadherence can be attributed to several factors, including adverse effects of treatment (e.g., diarrhea, abdominal pain, nausea), adverse events related to overuse (e.g., dehydration, hyponatremia, which are HE precipitating factors), and lack of awareness of the importance of ongoing dose titration to maintain 2–3 bowel movements daily [41]. Indeed, in one study, HE recurrence due to lactulose nonadherence was reported in more than one-third of patients (39/103 [39.7%]), with 82.0% of nonadherent patients failing to regularly fill the prescription; nonadherence was linked to improperly titrating lactulose because of unpredictable diarrhea (69.2%), bloating (46.2%), and abdominal pain (41.0%) [42]. Caregiver interviews have indicated that educating patients and caregivers on proper use of lactulose during hospitalization and/or at discharge would be helpful, given that the length of time between discharge and first outpatient visit with a hepatologist can be weeks to months [15].

Rifaximin

A phase 3, randomized, double-blind, placebo-controlled, multinational study demonstrated that a lower percentage of patients with a history of recurrent overt HE experienced breakthrough HE during 6 months of treatment with rifaximin 550 mg twice daily (31/140 patients [22.1%]) compared with placebo (73/159 patients [45.9%]) [43]. Of note, 91% of patients in each arm received concomitant lactulose [43]. Rifaximin treatment also decreased the relative risk of breakthrough overt HE by 58% compared with placebo during 6 months of treatment (hazard ratio [HR], 0.42; 95% CI, 0.28–0.64; $P < 0.001$) [43]. An open-label maintenance study that included patients who had participated in the aforementioned study showed that rifaximin 550 mg twice daily provided long-term benefit for patients with a history of overt HE [44]. HE-related hospitalizations per person-years of exposure (PYE) were lower in patients treated with rifaximin compared with placebo (0.21 vs. 0.72 events/PYE) [44]. All-cause hospitalizations per PYE also were lower with rifaximin versus placebo (0.45 vs. 1.30 events/PYE, respectively) [44]. In an EU study, the mean duration of each hospitalization decreased significantly (> 35%) in 158 patients over 1 year following initiation of rifaximin treatment compared with the 1-year period prior to treatment (8.6 vs. 13.5 days, respectively; $P = 0.017$) [45]. Overall, the total mean hospital length of stay decreased by > 50% during 1 year of rifaximin treatment compared with the year prior to treatment (11.5 vs. 24.4 days; $P < 0.001$) [45].

While US economic cost data regarding the long-term benefits of rifaximin use for the prevention of HE recurrence are limited, 2014 data from a cost-effectiveness model estimated costs of $20,287 and $26,672 per patient in life-years (LY) and quality-adjusted life-years (QALY) gained, respectively, for rifaximin for the prevention of HE recurrence [46].

A cost-effectiveness analysis published in 2020 showed that rifaximin plus lactulose was cost-effective at a willingness-to-pay threshold of $50,000 per QALY/LY [47].

Nutrition Optimization

Patients with cirrhosis and HE have specific nutritional requirements given their tendency to malnutrition and sarcopenia, especially as their liver disease worsens [48]. Achieving an adequate daily caloric intake (i.e., 30–35 kcal/kg body weight) will decrease the likelihood of muscle wasting. In addition to consuming adequate calories, patients should be encouraged to consume 1.2 to 1.5 g protein per kilogram body weight daily to maintain lean body mass. Further, caloric intake should be spread out over several small meals or snacks during the course of the day, rather than concentrated into a few larger meals [48, 49]. Micronutrient supplementation may be required for some patients, as correction of vitamin deficiencies and electrolyte imbalances is important [48]. Thus, screening for, and management of, malnutrition and sarcopenia in patients with cirrhosis may improve outcomes [50].

Utility of Closing Splenorenal Shunts

Spontaneous portosystemic shunts, including splenorenal shunts, are common in patients with recurrent HE [51]. Splenorenal shunts have been associated with worsening liver function and increased mortality in patients with cirrhosis [52]. A retrospective study of patients with recurrent HE reported that embolization of spontaneous portosystemic shunts, including splenorenal shunts, effectively prevented recurrence of HE in 22 of 37 patients (59.4%) within 100 days ($P < 0.001$ compared with before embolization); 18 (48.6%) patients experienced no HE recurrence during the follow-up period (i.e., mean 697 days; $P < 0.001$ compared with before embolization) [53]. A second retrospective study supported embolization of spontaneous portosystemic shunts, including splenorenal shunts, for preventing HE recurrence for up to 2 years compared with standard medical therapy ($n = 17$ patients in each group; 39.9% vs. 79.9%, respectively; $P = 0.02$) [54]. The 2-year survival rate was improved numerically with embolization versus standard medical therapy, but the difference was not statistically significant (64.7% vs. 53.4%; $P = 0.98$) [54]. Thus, closing splenorenal shunts may be beneficial for preventing HE recurrence [53, 54].

Fecal Microbial Transplantation

Fecal microbial transplantation (FMT) directly targets the gastrointestinal (GI) microbial composition of patients with HE by administration of donor fecal matter into the GI tract (e.g., enema, oral capsules) [55]. In an open-label, randomized clinical trial, patients with recurrent HE receiving rifaximin plus lactulose ($n = 10$) undergoing FMT by enema using the same fecal donor experienced significant improvement from baseline in HE-related cognitive test scores at 20 days post-treatment ($P \leq 0.01$), while patients assigned to standard of care treatment ($n = 10$) had no significant improvement in cognition from baseline [56]. Further, no HE episodes occurred in patients undergoing FMT through day 150, compared with 6 HE episodes in the standard of care group ($P = 0.03$). Results of a phase 1, randomized, placebo-controlled trial of patients with recurrent HE receiving rifaximin plus lactulose ($N = 20$) found FMT (using the same donor as in the previous study) administered orally as a single dose of 15 capsules improved cognitive test scores, for 1 measure, from baseline after 5 months, while no significant changes from baseline were observed in the placebo group [57]. Analysis of both of these trials indicated that antibiotic resistance gene expression was decreased from baseline following FMT, which may have utility in patients with cirrhosis who are increasingly diagnosed with multidrug resistance [58]. However, clinical trials involving larger numbers of patients are warranted.

Supportive Care

Supportive care needs during the transition from hospital to home have been highlighted through interviews with patients and caregivers [15]. Newly diagnosed patients with cirrhosis and their caregivers have indicated that receipt of a discharge checklist, provider-recommended online resources, mental health support, caregiver support/training, and financial navigation tools may facilitate improvements in disease management (Table 3) [15].

Hospital Navigators and Post-discharge Follow-Up

Although not evaluated specifically in a cirrhosis population, use of patient navigators has been shown to significantly improve patient outcomes post-discharge. In a matched-cohort study that included 7841 hospitalizations, use of patient navigators significantly decreased the length of hospitalization compared with the use of care teams that did not include patient navigators (6.2 vs. 7.5 days, respectively; $P < 0.001$) [59]. Transitional care management was designed to ease the transition from hospital to home for discharged patients [60]. Components of transitional care management include review of discharge information with the patient, patient/caregiver education, assistance with post-discharge follow-up appointments, and medication review [61].

One study in 1973 patients showed that among patients over 60 years of age, use of hospital-based workers to help in navigation from inpatient to outpatient significantly

Table 3 Supportive care resources for patients with cirrhosis and their caregivers [15]

Resource	Information desired
Discharge checklist	Symptoms to be aware of When/whom to call after the onset of specific symptoms
Online resources	
https://liverfoundation.org/*	HCP-recommended resources
https://www.niddk.nih.gov/health-information/liver-disease*	Basic disease-state information
Mental health support	Recommendations for mental health professionals or support resources for patients and caregivers
Caregiver support/training	Education on liver disease and its progression Education on what is expected of caregivers
Financial navigation	Resources for financial assistance

*Accessed January 13, 2021

HCP health care provider

Data from Ufere NN, Donlan J, Indriolo T, et al. *Dig Dis Sci*. 2020;10.1007/s10620-020-06617-4

lowered 30-day readmission rates compared with the use of standard discharge protocols (adjusted absolute decrease, 4.1%; 95% CI, −8.0% to −0.2%) [62]. In a single-center study ($N=7038$ hospitalizations), use of nurse transition care coordinators, with duties that included symptom screening, patient education, post-discharge planning, and telephone follow-up, was significantly more effective than usual care (i.e., performed by treating providers; no discharge telephone call) for reducing the odds of 30-day readmission (OR, 0.51; 95% CI, 0.39–0.67) and 90-day readmission (OR, 0.59; 95% CI, 0.48–0.72) [63]. Further, cost savings with nurse transition care coordinators compared with usual care were $3969 per patient at 30 days and $5684 at 90 days [63]. A prospective study of patients discharged from 2 hospitals ($N=25,628$) reported that not receiving post-discharge follow-up telephone calls made by nurses, which included discussions related to post-discharge medications, symptoms and disease management, and follow-up appointments, increased the likelihood of 30-day readmission compared with patients who received the intervention (adjusted OR, 1.27; 95% CI, 1.12–1.44) [64].

Adequately educating patients with cirrhosis and their caregivers about HE should be a part of discharge, as providing only limited education has been shown to contribute to readmissions [15]. A pilot study ($N=39$) showed that HE-related hospitalizations were significantly reduced in patients receiving brief (≤15 min), targeted outpatient education (i.e., focused on the pathophysiology of HE, maintenance of bowel movements, treatment of HE) facilitated by nurses compared with patients not receiving this intervention (HR, 0.14; 95% CI, 0.02–0.77; $P=0.02$) [65]. Another study showed that almost one-quarter (24.1%) of patients ($N=460$; with chronic conditions) enrolled in a Medicare Advantage program who were identified as nonadherent to treatment and unresponsive to telephone calls became adherent following receipt of a mailed reminder to refill their maintenance prescription(s) [66].

Telemedicine

Telemedicine can facilitate monitoring and care of patients with cirrhosis and HE from afar [67]. In a pilot study of 40 patients with HE and their caregivers, the Patient Buddy™ smartphone app (Creative IT, Inc.; Falls Church, VA, USA), which monitors medication adherence, sodium intake, body weight, orientation, and cognition, provided alerts related to altered mental status and prevented 8 potential HE-related hospitalizations within 30 days post-discharge [68]. A study of patients with cirrhosis participating in a telehealth program showed that no HE- or fluid overload-related readmissions occurred within 90 days among the 19 patients in the telehealth group, while 33.8% of 143 patients in the control group experienced such readmissions ($P=0.02$) [69]. Of note, results from a survey ($N=102$) showed that acceptance of technology correlated with patient perception of its usefulness ($r=0.77$; 95% CI, 0.67–0.84) and ease of use ($r=0.65$; 95% CI, 0.52–0.75), as well as patient level of computer-related anxiety ($r=-0.54$; 95% CI, −0.66 to −0.38) [70].

Hospital Pharmacists

Involving pharmacists in the hospital discharge process has been shown to have beneficial effects on outcomes, including readmissions. A single-center quality-improvement initiative targeting hospitalized Medicare beneficiaries assessed involvement of pharmacists in medication management during hospitalization and post-discharge and showed that 30-day readmissions were significantly

Fig. 3 Checklist for providers of patients with cirrhosis discharged from the hospital. *CPT* current procedural terminology

lower with this involvement compared with standard care (30/305 [9.8%] vs. 110/538 [20.4%] admissions, respectively; $P < 0.001$) [71]. In this study, 93 of 457 (20.4%) recommendations from pharmacists were related to medication access (e.g., prior authorization, obtaining non-preferred therapies, facilitating lower copayments) [71]. Data from an observational registry study indicated that incorporation of telemedicine and pharmacists in outpatient management of patients with cirrhosis and HE receiving rifaximin improved adherence and outcomes after 6 months compared with published data from a pivotal, phase 3 study of rifaximin [43]: rifaximin nonadherence (6.4% vs. 15.8%, respectively; $P = 0.0006$); HE-related hospitalizations (2.7% vs. 13.6%; $P < 0.0001$); and worsening of HE or mortality (15.6% vs. 26.4%; $P < 0.0001$) [72]. Further, in a survey study, patients participating in a pharmacist-led transition of care initiative (i.e., discharge education, medication reconciliation, and follow-up telephone call; $n = 414$) indicated greater satisfaction compared with patients in a control group ($n = 1314$; discharge education only [$n = 368$], follow-up telephone call only [$n = 184$], or no education or telephone call [$n = 762$]) [73]. In this study, a significantly lower percentage of patients receiving a follow-up telephone call experienced a 30-day readmission compared with patients receiving no telephone follow-up (12.4% vs. 17.3%, respectively; $P = 0.007$) [73]. Thus, it is apparent that incorporating supportive care measures in the discharge process is beneficial and may help reduce the risk of readmission in patients with cirrhosis and HE.

Table 4 Transition of care management codes [75]

CPT Code	wRVU	Complexity of medical decision making	Timing of communication with patient or caregiver	Additional information*
99495	2.11	Moderate	≤2 business d of discharge: contact by phone, email, or in-person ≤14 d of discharge: face-to-face visit	Medication reconciliation and management should happen no later than face-to-face visit CPT codes can be used following care from: Inpatient hospital setting (i.e., acute hospital, rehabilitation hospital, long-term acute hospital) Partial hospitalization Observation status in a hospital Skilled nursing facility CPT codes cannot be used with G0181 (home health care plan oversight) or G0182 (hospice care plan oversight) Billing at end of 30-d post-discharge period Payable only once per patient in 30 d after discharge (if patient is readmitted, CPT codes cannot be billed again) Only 1 provider can bill per patient Important to establish at the time of discharge the primary provider who will be providing and billing for transition of care services Codes apply to new or established patients
99496	3.05	High	≤2 business d of discharge: contact by phone, email, or in-person ≤7 d of discharge: face-to-face visit	

*Applies to CPT Codes 99495 and 99496

CPT current procedural terminology, *wRVU* work relative value unit

Reimbursement

In the US, health care providers can bill for transitional care management when establishing contact (i.e., "in person" visits, email, telephone call) with the patient within 2 days of discharge and for outpatient visits occurring within 7 days using Current Procedural Terminology (CPT) code 99496 or within 14 days using CPT code 99495 days (Fig. 3; Table 4) [60, 61, 74, 75]. Data analyzed from the Centers for Medicare and Medicaid Service's Hospital Compare tool indicated that discharge instructions, nurse communication, and physician communication all significantly decreased 30-day readmission rates compared with situations in which these interventions did not occur ($P < 0.0001$ for all) [76].

Conclusions

Hospitalizations due to liver disease are increasing in the USA, and HE is a major cause of hospitalizations and hospital readmissions. A multipronged management strategy is important for reducing the risk of HE recurrence and HE-related hospitalizations. This includes identifying and controlling precipitating factors, prescribing HE preventative medication at hospital discharge, supplying patient and caregiver education, and improving medication adherence. Lactulose alone and with rifaximin is recommended in hepatology guidelines for reducing the risk of HE recurrence. Not unexpectedly, patients and caregivers have a vested interest in implementation of supportive care initiatives. Utilization of hospital navigators and pharmacists, follow-up telephone calls and letters, and telemedicine tools have been shown to improve post-discharge outcomes. Combining treatment-related approaches with supportive care measures in transition of care may be beneficial to patients with cirrhosis and HE, effectively closing the revolving door on rehospitalizations.

Acknowledgments Technical editorial and medical writing assistance was provided, under direction of the authors, by Mary Beth Moncrief, PhD, and Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Salix Pharmaceuticals, Bridgewater, NJ.

Declarations

Conflict of interest CTF reports serving on the speakers' bureau for Salix Pharmaceuticals. CL reports having no conflicts to disclose. SS reports serving on the speakers' bureau for Salix Pharmaceuticals.

References

1. Ge PS, Runyon BA. Treatment of patients with cirrhosis. *N Engl J Med.* 2016;375:767–777.
2. Scaglione S, Kliethermes S, Cao G et al. The epidemiology of cirrhosis in the United States: a population-based study. *J Clin Gastroenterol.* 2015;49:690–696.
3. Kochanek KD, Murphy SL, Xu J, Arias E. Deaths: final data for 2017. *Natl Vital Stat Rep.* 2019;68:1–77.
4. Peery AF, Crockett SD, Murphy CC et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. *Gastroenterology.* 2019;156:254–272.
5. Shrank WH, Rogstad TL, Parekh N. Waste in the US health care system: estimated costs and potential for savings. *JAMA.* 2019;322:1501–1509.
6. Volk ML, Tocco RS, Bazick J, Rakoski MO, Lok AS. Hospital readmissions among patients with decompensated cirrhosis. *Am J Gastroenterol.* 2012;107:247–252.
7. Koola JD, Ho SB, Cao A et al. Predicting 30-day hospital readmission risk in a national cohort of patients with cirrhosis. *Dig Dis Sci.* 2020;65:1003–1031.
8. Rosenblatt R, Cohen-Mekelburg S, Shen N et al. Cirrhosis as a comorbidity in conditions subject to the Hospital Readmissions Reduction Program. *Am J Gastroenterol.* 2019;114:1488–1495.
9. Tapper EB, Halbert B, Mellinger J. Rates of and reasons for hospital readmissions in patients with cirrhosis: a multistate population-based cohort study. *Clin Gastroenterol Hepatol.* 2016;14:1181–1188.
10. Shaheen AA, Nguyen HH, Congly SE, Kaplan GG, Swain MG. Nationwide estimates and risk factors of hospital readmission in patients with cirrhosis in the United States. *Liver Int.* 2019;39:878–884.
11. Tapper EB. Building effective quality improvement programs for liver disease: a systematic review of quality improvement initiatives. *Clin Gastroenterol Hepatol.* 2016;14:1256–1265.
12. Ginés P, Quintero E, Arroyo V et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology.* 1987;7:122–128.
13. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol.* 2006;44:217–231.
14. Gaspar R, Rodrigues S, Silva M et al. Predictive models of mortality and hospital readmission of patients with decompensated liver cirrhosis. *Dig Liver Dis.* 2019;51:1423–1429.
15. Ufere NN, Donlan J, Indriolo T, et al. Burdensome transitions of care for patients with end-stage liver disease and their caregivers [published online ahead of print September 22, 2020]. *Dig Dis Sci.* 2020;https://doi.org/10.1007/s10620-020-06617-4.
16. Bajaj JS, Wade JB, Gibson DP et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am J Gastroenterol.* 2011;106:1646–1653.
17. Vilstrup H, Amodio P, Bajaj J et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the

European Association for the Study of the Liver. *Hepatology.* 2014;60:715–735.
18. Seraj SM, Campbell EJ, Argyropoulos SK, Wegermann K, Chung RT, Richter JM. Hospital readmissions in decompensated cirrhotics: factors pointing toward a prevention strategy. *World J Gastroenterol.* 2017;23:6868–6876.
19. Joynt KE, Jha AK. Characteristics of hospitals receiving penalties under the Hospital Readmissions Reduction Program. *JAMA.* 2013;309:342–343.
20. Trieu H, Patel A, Wells C, Saab S, Lee EW. Disparities in mortality and health care utilization for 460,851 hospitalized patients with cirrhosis and hepatic encephalopathy [published online ahead of print September 14, 2020]. *Dig Dis Sci.* 2020;https://doi.org/10.1007/s10620-020-06582-y.
21. Nguyen DL, Chao D, Ma G, Morgan T. Quality of life and factors predictive of burden among primary caregivers of chronic liver disease patients. *Ann Gastroenterol.* 2015;28:124–129.
22. Labenz C, Toenges G, Schattenberg JM et al. Health-related quality of life in patients with compensated and decompensated liver cirrhosis. *Eur J Intern Med.* 2019;70:54–59.
23. Künzler-Heule P, Beckmann S, Mahrer-Imhof R, Semela D, Händler-Schuster D. Being an informal caregiver for a relative with liver cirrhosis and overt hepatic encephalopathy: a phenomenological study. *J Clin Nurs.* 2016;25:2559–2568.
24. Fabrellas N, Moreira R, Carol M et al. Psychological burden of hepatic encephalopathy on patients and caregivers. *Clin Transl Gastroenterol.* 2020;11:e00159.
25. Soriano G, Román E, Córdoba J et al. Cognitive dysfunction in cirrhosis is associated with falls: a prospective study. *Hepatology.* 2012;55:1922–1930.
26. Diamond T, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S. Osteoporosis and skeletal fractures in chronic liver disease. *Gut.* 1990;31:82–87.
27. Ezaz G, Murphy SL, Mellinger J, Tapper EB. Increased morbidity and mortality associated with falls among patients with cirrhosis. *Am J Med.* 2018;131:645–650.
28. Yeh K-T, Yu T-C, Lee R-P et al. Hepatic encephalopathy increases the risk of hip fracture: a nationwide cohort study. *BMC Musculoskeletal Disorders.* 2020;21:779.
29. Xifaxan® (rifaximin) tablets, for oral use [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2020.
30. Pantham G, Post A, Venkat D, Einstadter D, Mullen KD. A new look at precipitants of overt hepatic encephalopathy in cirrhosis. *Dig Dis Sci.* 2017;62:2166–2173.
31. Yuan LT, Chuah SK, Yang SC et al. Multiple bacterial infections increase the risk of hepatic encephalopathy in patients with cirrhosis. *PLoS One.* 2018;13:e0197127.
32. Moon AM, Jiang Y, Rogal SS, Becker J, Barritt AS 4th. In inpatients with cirrhosis opioid use is common and associated with length of stay and persistent use post-discharge. *PLoS One.* 2020;15:e0229497.
33. Lum HD, Studenski SA, Degenholtz HB, Hardy SE. Early hospital readmission is a predictor of one-year mortality in community-dwelling older Medicare beneficiaries. *J Gen Intern Med.* 2012;27:1467–1474.
34. Hayward KL, Valery PC, Cottrell WN et al. Prevalence of medication discrepancies in patients with cirrhosis: a pilot study. *BMC Gastroenterol.* 2016;16:114.
35. Hayward KL, Valery PC, Martin JH et al. Medication beliefs predict medication adherence in ambulatory patients with decompensated cirrhosis. *World J Gastroenterol.* 2017;23:7321–7331.
36. Vadhariya A, Chen H, Serna O, Zamil H, Abughosh SM. A retrospective study of drug utilization and hospital readmissions among Medicare patients with hepatic encephalopathy. *Medicine (Baltimore).* 2020;99:e19603.
37. Bajaj JS, O'Leary JG, Tandon P et al. Targets to improve quality of care for patients with hepatic encephalopathy: data from a multicentre cohort. *Aliment Pharmacol Ther.* 2019;49:1518–1527.
38. Kennedy J, Tuleu I, Mackay K. Unfilled prescriptions of Medicare beneficiaries: prevalence, reasons, and types of medicines prescribed. *J Manag Care Spec Pharm.* 2020;26:935–942.
39. Chung GC, Marottoli RA, Cooney LM Jr, Rhee TG. Cost-related medication nonadherence among older adults: findings from a nationally representative sample. *J Am Geriatr Soc.* 2019;67:2463–2473.
40. Unuigbe A. The Medicare Part D coverage gap, prescription use, and expenditures. *Med Care Res Rev.* 2020;77:442–450.
41. Suraweera D, Sundaram V, Saab S. Evaluation and management of hepatic encephalopathy: current status and future directions. *Gut Liver.* 2016;10:509–519.
42. Bajaj JS, Sanyal AJ, Bell D, Gilles H, Heuman DM. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. *Aliment Pharmacol Ther.* 2010;31:1012–1017.
43. Bass NM, Mullen KD, Sanyal A et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362:1071–1081.
44. Mullen KD, Sanyal AJ, Bass NM et al. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. *Clin Gastroenterol Hepatol.* 2014;12:1390–1397.
45. Orr JG, Currie CJ, Berni E et al. The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-α. *Liver Int.* 2016;36:1295–1303.
46. Bozkaya D, Barrett AC, Migliaccio-Walle K. Cost-effectiveness of rifaximin treatment in patients with hepatic encephalopathy [abstract 382]. *Hepatology* 2014;60:389A-390A.
47. Jesudian AB, Ahmad M, Bozkaya D, Migliaccio-Walle K. Cost-effectiveness of rifaximin treatment in patients with hepatic encephalopathy. *J Manag Care Spec Pharm.* 2020;26:750–757.
48. Shaw J, Tate V, Hanson J, Bajaj JS. What diet should I recommend my patient with hepatic encephalopathy? *Curr Hepatol Rep.* 2020;19:13–22.
49. Bischoff SC, Bernal W, Dasarathy S et al. ESPEN practical guideline: Clinical nutrition in liver disease. *Clin Nutr.* 2020;39:3533–3562.
50. Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis. *PLoS One.* 2017;12:e0186990.
51. Riggio O, Efrati C, Catalano C et al. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case-control study. *Hepatology.* 2005;42:1158–1165.
52. Yi F, Guo X, Wang L, et al. Impact of spontaneous splenorenal shunt on liver volume and long-term survival of liver cirrhosis. *J Gastroenterol Hepatol.* 2021;36:1694–1702.
53. Laleman W, Simon-Talero M, Maleux G et al. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy. *Hepatology.* 2013;57:2448–2457.
54. An J, Kim KW, Han S, Lee J, Lim YS. Improvement in survival associated with embolisation of spontaneous portosystemic shunt in patients with recurrent hepatic encephalopathy. *Aliment Pharmacol Ther.* 2014;39:1418–1426.
55. Hassouneh R, Bajaj JS. Gut microbiota modulation and fecal transplantation: an overview on innovative strategies for hepatic encephalopathy treatment. *J Clin Med.* 2021;10:330.
56. Bajaj JS, Kassam Z, Fagan A et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. *Hepatology.* 2017;66:1727–1738.
57. Bajaj JS, Salzman NH, Acharya C et al. Fecal microbial transplant capsules are safe in hepatic encephalopathy: a phase 1, randomized, placebo-controlled trial. *Hepatology.* 2019;70:1690–1703.

58. Bajaj JS, Shamsaddini A, Fagan A et al. Fecal microbiota transplant in cirrhosis reduces gut microbial antibiotic resistance genes: analysis of two trials. *Hepatol Commun.* 2021;5:258–271.
59. Kwan JL, Morgan MW, Stewart TE, Bell CM. Impact of an innovative inpatient patient navigator program on length of stay and 30-day readmission. *J Hosp Med.* 2015;10:799–803.
60. Agarwal SD, Barnett ML, Souza J, Landon BE. Medicare's care management codes might not support primary care as expected. *Health Aff (Millwood).* 2020;39:828–836.
61. Kangovi S, Grande D. Transitional care management reimbursement to reduce COPD readmission. *Chest.* 2014;145:149–155.
62. Balaban RB, Galbraith AA, Burns ME, Vialle-Valentin CE, Larochelle MR, Ross-Degnan D. A patient navigator intervention to reduce hospital readmissions among high-risk safety-net patients: a randomized controlled trial. *J Gen Intern Med.* 2015;30:907–915.
63. Kripalani S, Chen G, Ciampa P et al. A transition care coordinator model reduces hospital readmissions and costs. *Contemp Clin Trials.* 2019;81:55–61.
64. Hoyer EH, Brotman DJ, Apfel A et al. Improving outcomes after hospitalization: a prospective observational multicenter evaluation of care coordination strategies for reducing 30-day readmissions to Maryland hospitals. *J Gen Intern Med.* 2018;33:621–627.
65. Garrido M, Turco M, Formentin C et al. An educational tool for the prophylaxis of hepatic encephalopathy. *BMJ Open Gastroenterol.* 2017;4:e000161.
66. Mann A, Esse TW, Serna O, Castel LD, Abughosh SM. Effectiveness of mailed letters to improve medication adherence among Medicare Advantage Plan participants with chronic conditions. *Patient Prefer Adherence.* 2019;13:37–46.
67. Stotts MJ, Grischkan JA, Khungar V. Improving cirrhosis care: the potential for telemedicine and mobile health technologies. *World J Gastroenterol.* 2019;25:3849–3856.
68. Ganapathy D, Acharya C, Lachar J et al. The Patient Buddy app can potentially prevent hepatic encephalopathy-related readmissions. *Liver Int.* 2017;37:1843–1851.
69. Khungar V, Serper M, Peyton D et al. Use of an innovative telehealth platform to reduce readmissions and enable patient-centered care in cirrhotic patients [abstract 170]. *Hepatology* 2017;66:94A-95A.
70. Louissaint J, Lok AS, Fortune BE, Tapper EB. Acceptance and use of a smartphone application in cirrhosis. *Liver Int.* 2020;40:1556–1563.
71. Shull MT, Braitman LE, Stites SD, DeLuca A, Hauser D. Effects of a pharmacist-driven intervention program on hospital readmissions. *Am J Health Syst Pharm.* 2018;75:e221–e230.
72. Wells J, Rodas F, Loo N et al. Health outcomes in patients with hepatic encephalopathy managed through telemedicine and a specialized pharmacy team [abstract S0988]. *Am J Gastroenterol* 2020;115:S503–S504.
73. March KL, Peters MJ, Finch CK, et al. Pharmacist transition-of-care services improve patient satisfaction and decrease hospital readmissions [published online ahead of print September 18, 2020]. *J Pharm Pract*. 2020;https://doi.org/10.1177/0897190020958264.
74. Davis J, Savoy M, Bittner-Fagan H. Improving patient safety: care transitions. *FP Essent.* 2017;463:16–20.
75. What practices need to know about transition care management codes. Available at: https://www.acponline.org/practice-resources/business-resources/coding/what-practices-need-to-know-about-transition-care-management-codes#:~:text=CPT%20Code%2099495%20covers%20communication,the%20visit%20is%20not%20specified. Accessed April 20, 2021.
76. Mitchell JP. Association of provider communication and discharge instructions on lower readmissions. *J Healthc Qual.* 2015;37:33–40.