Cole et al. Int Arch Nurs Health Care 2016, 2:057
Volume 2 | Issue 5
ISSN: 2469-5823

International Archives of
Nursing and Health Care

Review Article: Open Access

Acute Care Nursing Considerations in the Era of Direct-Acting Hepatitis C Antivirals

Jennifer L Cole* and Jennifer E Stark

Veterans Health care System of the Ozarks, Fayetteville, USA

***Corresponding author:** *Jennifer L Cole, Pharm D, BCPS, BCCCP, Veterans Health Care System of the Ozarks, 1100 North College Avenue, Fayetteville, AR 72703, USA, Tel: 479-444-4020, E-mail: Jennifer.cole@va.gov*

Abstract

Chronic hepatitis C virus (HCV) has a major impact on healthcare globally. Comorbidities are common in HCV-infected patients and as this population ages, acute care admissions are on the rise. With the introduction of the direct-acting antiviral (DAA) regimens, treatment for HCV has become better tolerated and more effective with shorter durations. Treatment rates for HCV are on the rise with the DAA agents, making it more likely to encounter patients on these medications during hospital admissions. There are limited data in the published literature regarding DAAs in the acute care setting and this remains an unmet need. This review focuses on important clinical considerations for the hospitalized patient prescribed DAA therapy.

Keywords

Hepatitis C infection, Direct-Acting antivirals, Inpatient care, Acute care

Introduction

Hepatitis C viral (HCV) infections are a major healthcare issue across the globe with an estimated 2.7-3.9 million cases of chronic hepatitis C infection in the United States alone [1]. Research indicates there are 3-4 million new infections each year globally [2] and the Centers for Disease Control (CDC) reported an increased, but stabilizing, prevalence in the United States from 2010 to 2014 [3]. In addition to the complications imposed by the development of cirrhosis, chronic HCV infection is the leading cause of hepatocellular cancer, the leading indication for liver transplantation, and recently surpassed HIV as a cause of death in the United States [4,5].

Although acute complications of viral hepatitis C can be severe, the major burden of the disease lies in the chronic condition. Because of the slow progression of HCV, diagnosis can be delayed for years. Research indicates that HCV detection in elderly patients is likely to increase and that these patients are more likely to have hepatic complications like cirrhosis and progressive liver disease [6]. Early detection is paramount to improved outcomes and limiting transmission. Subsequently, the CDC now recommends a one-time HCV screening for all individuals born between the years 1945 and 1965 in addition to testing those with known HCV risk factors [7]. Patients born during this time period are disproportionately affected, accounting for 75% of HCV infections.

Historically, HCV has been difficult to treat with interferon-α based therapy that was fraught with adverse events and high treatment failures as evidenced by low sustained virologic response (SVR) [8]. Since 2011, a new era of direct-acting antivirals (DAA) has revolutionized HCV treatment. These newer treatment combinations have demonstrated shorter treatment durations, improved tolerability and efficacy with SVR estimated at 90-100% [9]. Current DAAs fall within three classes: Protease Inhibitors (simeprevir, paritaprevir, and grazoprevir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, velpatasvir and elbasvir), and NS5B polymerase inhibitors (sofosbuvir and dasabuvir). Many of the DAA agents are combined into fixed dose combinations (ledipasvir/sofosbuvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir) or co-packaged product packs (e.g. paritaprevir/ritonavir/ombitasvir with or without dasabuvir). Ribavirin is an older antiviral agent, but it continues to be a component of some DAA treatment regimens (Table 1). The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) offer expert guidance for the treatment of adults with HCV [7].

Since these newer agents have reached the market, treatment rates for HCV have grown [10]. Additionally, research shows that hospital admissions rates for HCV patients is expected to rise in the coming years [11]. Given the aging HCV population coupled with newer, well tolerated treatment strategies, patients on DAA therapy with other comorbidities are more commonplace. Nurses in the hospital setting can expect to encounter these newer agents as part of their patients' existing drug therapy upon admission. There is a need for more publication on clinical experience in the acute care arena with DAA regimens. This review is a focus on some of the common clinical considerations when dealing with these patients.

Cost

One of the more noteworthy issues of the DAA regimens is the staggering cost of therapy. Treatment combinations have been reported to cost on average between $75,000-$94,500 for a 12-week treatment period [12]. Higher cure rates and ease of therapy have been coupled with higher treatment cost. Co-packaged preparations, such as Harvoni® and Viekira Pak™, have an average wholesale price (AWP) of $1,350 and $1,190 per day of therapy, respectively.

Historically, pharmaceutical companies have defended these prices by citing the high costs of research and development,

Citation: Cole JL, Stark JE (2016) Acute Care Nursing Considerations in the Era of Direct-Acting Hepatitis C Antivirals. Int Arch Nurs Health Care 2:057

Received: July 27, 2016: **Accepted:** September 27, 2016: **Published:** September 30, 2016

Copyright: © 2016 Cole JL, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ClinMed International Library

Table 1: Currently available DAA agents, common adverse events, renal and hepatic function considerations.

Drug	Brand Name	HCV genotype	Adverse Event Reported > 10%	Renal function limits	Hepatic function limits
Simeprevir	Olysio®	1 when combined with sofosbuvir	Photosensitivity, fatigue, headache, dizziness, insomnia, nausea, increased bilirubin, diarrhea, myalgia, dyspnea	None	Avoid in decompensated cirrhosis or Child-Pugh B or C
Sofosbuvir	Sovaldi®	1 when combined with ledipasvir, 3 when combined with daclatasvir	Fatigue, nausea, headache, insomnia, weakness	Not recommended for CrCl < 30 ml/min	None
Ledipasvir/Sofosbuvir	Harvoni®	1 and 4	Headache, fatigue, insomnia	Not recommended for CrCl < 30 ml/min	None
Ombitasvir/Paritaprevir Ritonavir/Dasabuvir	Viekira Pak™ Viekira XR™	1	Fatigue, headache, insomnia, rash, pruritis, diarrhea, nausea, anemia, increased bilirubin, increased ALT, weakness, muscle spasm, cough	None	Avoid in decompensated cirrhosis or Child-Pugh B or C
Daclatasvir	Daklinza™	3 when combined with sofosbuvir	Fatigue, nausea, headache, anemia	None	None
Ombitasvir/Paritaprevir Ritonavir	Technivie™	4	Fatigue, insomnia, rash, pruritis, nausea, increased ALT, anemia	None	Avoid in decompensated cirrhosis or Child-Pugh B or C
Elbasvir/Grazoprevir	Zepatier™	1 & 4	Fatigue, headache, nausea	None	Avoid in decompensated cirrhosis or Child-Pugh B or C
Sofosbuvir/Velpatasvir	Epclusa®	1,2,3,4,5 & 6	Headache, fatigue	Not recommended for CrCl < 30 ml/min	None

Data obtained from product package insert [27,33,34,46-51].

production, marketing, distribution, and, ultimately, the value of SVR. These unusually high drug costs contributed to a noticeable increase in overall spending on prescription drugs in the US in recent years and, understandably, raise concerns for healthcare facilities as well as third-party payers [13]. Simulated prediction models have shown DAA regimens to be cost effective from a societal perspective [14], however application to "real world" treatment scenarios are lacking [15,16].

In recent practice, some payers have prioritized patients for treatment by severity of liver disease. In these cases only patients with advanced cirrhosis or fibrosis are covered and patients with milder liver disease are not [17]. This practice of resource allocation is under debate, however, and some argue that treatment deferral is unethical and could ultimately raise overall costs [18].

Minimizing Therapy Interruptions

Chronic medications that are unrelated to the acute process are often times not continued at hospital admission, particularly in ICU admissions [19]. Non-adherence with antiviral treatment is associated with treatment failures [20]. Other variables that impact DAA treatment response include age, gender, HCV genotype and subtype, degree of liver fibrosis, previous treatment, certain comorbidities, such as HIV co-infection or renal failure, and the presence of resistance-associated variants (RAV) [21]. The presence of RAVs indicates a variance in the binding site of DAAs to the HCV target protein, leading to an altered antiviral response and increased risk of treatment failure.

The hepatitis C virus has a high rate of replication. Multiple antivirals are often employed in HCV treatment regimens in order to target different mechanisms [22]. It is therefore important to resume all agents of a given regimen to minimize selection pressure.

Unfortunately, little is known about the effects of altered physiology seen in critically ill patients on the DAA agents. The systemic inflammatory response often seen in critically ill patients can alter the absorption and distribution of medications. Additionally, metabolism and elimination of medications can be either increased or decreased in some scenarios [23]. Careful consideration regarding risks and benefits should be taken. DAA therapy should be resumed as soon as it is considered to be safe for the patient, ensuring that no component of the patient's HCV treatment regimen is causing the problems for which the patient is being admitted. Prolonged therapy interruptions should be discussed with the patient's infectious diseases or hepatology specialist.

Crushing Tablets

Many patients in the acute care setting may lose their ability to swallow whole medications due to either dysphagia or decreased levels of consciousness. In such cases, a feeding tube is often placed necessitating the consideration of crushing oral dosage forms of medications. Crushing tablets or opening capsules can alter drug delivery and in doing so create adverse events [24]. This is especially notable in sustained release formulations. Specific to antiviral therapy, there may be clinical concerns for subtherapeutic drug levels leading to resistance or increased drug exposure leading to toxicity [25,26].

None of the DAA agents are currently available in a parenteral or oral suspension formulation. Although there are no published data on the safety or efficacy of crushing tablets for administration, most of the currently available DAA agents are not enteric coated nor intended to be sustained release. Until further pharmacokinetic studies are available, the benefit of continuing DAA therapy in a crushed form appear to outweigh the risks.

One notable exception regarding tablet crushing is the recently approved extended-release formulation of Viekira XR™ [27]. This is a reformulated product of conventional Viekira™ that combines ingredients into three film-coated bilayer tablets that are to be taken once daily. The tablets include an extended-release layer of dasabuvir and an immediate-release layer of ombitasvir, paritaprevir, and ritonavir. The extended release tablets should not be crushed, chewed or split. The package labeling indicates Viekira XR™ tablets must be taken once daily with a meal and alcohol must be avoided within 4 hours of the daily dose. Although alcohol ingestion should not be an issue in the inpatient setting, it is not clear whether the alcohol found in many medication syrups and elixirs may also interact with Viekira XR™. This is important as alcohol impairs release of dasabuvir and could result in decreased dasabuvir serum levels [27].

The American Journal of Health-System Pharmacy has published a review of medication administration through feeding tubes [28]. Considerations for holding tube feeds around DAA administration may be necessary depending on absorption during fasting or fed states. Nurses and providers should consult with the pharmacy department in these situations.

Drug Interactions

Given the frequent comorbidities of HCV patients, polypharmacy is common. Drug-drug interactions are a significant risk in the DAA treatment population [29]. This can be especially problematic in hospitalized patients given new medications for acute illness. Many of the clinically significant drug interactions with the DAA agents are related to decreased drug levels resulting in increased risk of treatment failure. This can be due to increased metabolism of the DAA by the interacting agent or due to decreased absorption of the DAA. However, some drug interactions are concerning for severe toxicity due to either the DAA or the interacting drug. One recent example is the unexpected interaction between sofosbuvir and amiodarone that resulted in several cases of severe bradyarrhythmias requiring pacemaker placement and even death [30].

Three co-packaged product packs (Viekira™, Viekira XR™ and Technivie™) contain an additional agent, ritonavir. Ritonavir is not active against HCV, but is a potent inhibitor of CYP3A [31]. This interaction is intentionally used to augment serum drug concentrations of the co-packaged component paritaprevir. However, an unintended consequence is severe interactions with several non-HCV medications. A recent observational study noted a somewhat paradoxical finding of decreased dose response trends in patients previously stable on warfarin when DAA agents were added [32]. For this and other safety reasons, INR should be monitored closely in patients on both warfarin and DAA therapy.

A common practice in hospitalized patients is the use of proton pump inhibitors (PPI) and other acid-blocking agents. Ledipasvir and velpatasvir require an acidic environment for adequate absorption and each have different timing and fasting requirements with PPI therapy. The daily dose of PPIs should not exceed that equivalent to omeprazole 20 mg when co-prescribed with these agents [33,34]. Other less potent acid-blocking agents (histamine receptor blockers or antacids) can still decrease absorption of ledipasvir or velpatasvir resulting in increased risk of treatment failure. Each class of acid-blocking agent has different timing recommendations with ledipasvir or velpatasvir that must be adhered to. Ledipasvir must be taken at the same time as the PPI under fasting conditions to avoid significant decreased drug serum levels. According to package labeling, concomitant velpatasvir and PPI use should be avoided. If a PPI must be co-administered, the velpatasvir should be taken with food, and then the PPI should be administered exactly 4 hours later. When ledipasvir or velpatasvir are administered with histamine receptor blockers (e.g. famotidine, ranitidine), they can be given either at the same time or separated by 12 hours. When these agents are given with antacids, they should be separated by at least 4 hours before or after the antacid dose [33,34].

Mental health disorders are common among chronic hepatitis C patients [35]. Antipsychotics and antidepressants that may be co-prescribed with DAAs increase the risk of drug interactions. Drugs that are extensively metabolized through cytochrome P450 enzymes or affect P-glycoprotein transport may accumulate or cause significant changes in DAA plasma concentration [36]. Due to the potential for QTc prolongation, close ECG monitoring may be required in these situations.

Strong inducers of P-glycoprotein, such as rifampin and St. John's Wort should be avoided with many DAAs. Other medications commonly seen continued or initiated in the acute care setting that are particularly problematic in the cytochrome p450 pathways are lipid-lowering agents (e.g. simvastatin, atorvastatin, gemfibrozil) antiarrhythmics (e.g. amiodarone, diltiazem), and anticonvulsants (e.g. carbamazepine, phenytoin, valproic acid) [37]. Clinicians should seek out expert consultation prior to co-administration of these medications with DAA regimens. It is also imperative that clinicians recognize that many hospitals' electronic medical records may not identify drug interactions between currently prescribed medications due to errors or gaps in electronic interface.

Adverse Events

Although the newer DAA regimens are generally reported as being well tolerated, they are not without adverse events. Anemia, headache, fatigue, and GI disturbances were frequently seen during clinical trials and varied by agent. Insomnia, irritability, and pruritus were also commonly reported (Table 1).

Patients on regimens containing ribavirin are especially at risk for developing anemia, a common finding in acute care patients. Careful work up may be indicated to determine other causes of anemia, such as blood loss, iron deficiency, non-HCV drugs, or chronic disease. If ribavirin is determined to be the culprit, treatment strategies include reducing the dose, the addition of erythropoietin therapy, or red blood cell transfusions [38].

Hepatotoxicity is a less common but potentially severe adverse effect of DAA therapy, although this could be attributable to the underlying disease. Alterations in hepatic metabolism seen in advanced liver disease may lead to drug induced toxicity [39]. The protease inhibitors (simeprevir, paritaprevir, and grazoprevir) have the potential to be hepatotoxic. These medications are contraindicated in patients with decompensated cirrhosis or Child-Pugh class B or C. Hepatotoxicity risk is increased with the protease inhibitors when they are administered with other hepatotoxic agents. Liver function should be carefully evaluated during the acute care process. Physical exam findings such as new ascites and the development of dark amber urine should be immediately reported to the medical team.

Another common acute care consideration is the presence or development of acute kidney injury [40]. There are limited treatment options in patients with severe renal failure (CrCl < 30 ml/min). Options include Zepatier™, Viekira™, Viekira XR™ and Technivie™. Ribavirin has dosing recommendations for patients with renal impairment, but is typically not well tolerated in this population due to severe anemia and prolonged drug clearance. Sofosbuvir is a backbone in many different treatment regimens but it is not recommended for use in patients with CrCl < 30 ml/min (Table 1). Careful attention should be paid to the patient's renal function as DAA therapy may require interruption until renal failure resolves.

Perhaps more pertinent to nurses in the acute care setting is the development of unexpected adverse events. Clinicians should note the relatively limited clinical experience of the DAA agents globally. Adverse event rates are largely determined by those observed in clinical trials. Rarely seen side effects may take a much larger patient population to be recognized. Once a drug gains FDA approval, post marketing surveillance is needed to evaluate the effect of newer agents in a larger, non-study population. Vigilant reporting can lead to important changes in prescribing and safety labeling [41]. Clinicians are encouraged to report any suspected drug related adverse events to the FDA's safety reporting program MedWatch (www.fda.gov/safety/medwatch).

Hospital Policy

Acute care facilities should have a plan in place for handling these high cost, high priority medications. Some hospitals may need to make exceptions to existing "no home medications" policies. If the patient did not bring in their outpatient supply, every effort should be employed to retrieve and identify these prescriptions. Given the substantial cost of any "missing doses", facilities may consider handling these agents similar to narcotics for increased accountability. Hospitals with mobile dose tracking technology may benefit from a decrease in missing doses [42].

At the authors' facility the pharmacy processes both inpatient and outpatient prescriptions. Many patients are treated through the on-site Hepatitis C clinic. If these patients are admitted during their treatment course, the pharmacy department will generate an outpatient prescription fill and dispense these as inpatient unit dose medications until the patient is discharged. Any remaining meds can then be dispensed home when the patient leaves. For other

patients, attempts are made to contact family members to bring in any current DAA prescriptions. These are delivered to the pharmacy where they are identified, stored, packaged, and barcoded as a unit dose prescription for the designated patient. Unit doses are then hand delivered directly to the patient's nurse at the time of administration to avoid storage in medication rooms or automated dispensing machines.

Hospitals vary in their implementation of The Joint Commission on Accreditation of Healthcare Organizations patient safety goal of mediation reconciliation [43]. Nurses play a vital role in medication reconciliation as they are often the first clinicians to assess the patient and the last to communicate with them before discharge [44]. Asking the patient open-ended questions about what medications they take and how could reveal important information that may have been missed upon admission.

Conclusion

Chronic hepatitis C infection affects a large population and treatment rates with the new DAA medications are on the rise. With the recent rapid progression in understanding of hepatitis C replication and blocking key pathways, research in treatment strategies shows no signs of stopping. Future developments include pan-genotypic therapy with shorter treatment durations. There is further need for the development of ribavirin-free strategies, hard-to-treat cases, and treatment failures [45]. There is limited information in the medical literature on these agents in the acute care setting, however clinical experience is growing rapidly. There is a need for future research on the pharmacologic and pharmacokinetic effects on DAA agents seen in the critically ill population. Nurses and other clinicians are encouraged to check for updated information on safety, administration, and drug interactions when dealing with HCV patients on DAA therapy.

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, et al. (2006) The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 144: 705-714.
2. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST (2013) Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 57: 1333-1342.
3. Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis-United States, 2014.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP (2006) The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 45: 529-538.
5. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, et al. (2012) The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med 156: 271-278.
6. Davis GL, Alter MJ, El-Serag H (2010) Aging of hepatitis C virus infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression. Gastroenterology 138: 513-521.
7. AASLD/IDSA HCV Guidance Panel (2015) Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 62: 932-954.
8. Lee SS, Bain VG, Peltekian K, Krajden M, Yoshida EM, et al. (2006) Treating chronic hepatitis C with pegylated interferon alfa-2a (40 KD) and ribavirin in clinical practice. Aliment Pharmacol Ther 23: 397-408.
9. Liang TJ, Ghany MG (2014) Therapy of hepatitis C--back to the future. N Engl J Med 370: 2043-2047.
10. Yao X, Sangaralingham LR, Ross JS, Shah ND, Talwalkar JA (2016) Adoption of new agents and changes in treatment patterns for hepatitis C: 2010-2014. Am J Manag Care 22: e224-232.
11. Schanzer DL, Paquette D, Lix LM (2014) Historical trends and projected hospital admissions for chronic hepatitis C infection in Canada: a birth cohort analysis. CMAJ Open 2: E139-144.
12. Vernaz N, Girardin F, Goossens N (2016) Drug Pricing Evolution in Hepatitis C. PLoS One 11: e0157098.
13. McCarthy M (2015) New drug for hepatitis C contributes to 13% rise in spending on prescription drugs in US. BMJ 350: h2055.
14. Najafzadeh M, Andersson K, Shrank WH, Krumme AA, Matlin OS, et al. (2015) Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. Ann Intern Med 162: 407-419.
15. Le TK, Kalsekar A, Macaulay D (2015) Treatment patterns, health care resource utilization, and costs in US patients diagnosed with chronic hepatitis C infection who received telaprevir or boceprevir. J Manag Care Spec Pharm 21: 308-318.
16. Luhnen M, Waffenschmidt S, Gerber-Grote A, Hanke G (2016) Health Economic Evaluations of Sofosbuvir for Treatment of Chronic Hepatitis C: a Systematic Review. Appl Health Econ Health Policy 14: 527-543.
17. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, et al. (2015) Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States. Ann Intern Med 163: 215-223.
18. Craxì L, Sacchini D, Refolo P, Minacori R, Daloiso V, et al. (2016) Prioritization of high-cost new drugs for HCV: making sustainability ethical. Eur Rev Med Pharmacol Sci 20: 1044-1051.
19. Bell CM, Brener SS, Gunraj N, Huo C, Bierman AS, et al. (2011) Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. JAMA 306: 840-847.
20. Mocroft A, Phillips AN, Rockstroh J (2005) Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: increased incidence of stopping due to toxicity or patient/phsycian choice in patients with hepatitis C coinfection. AIDS Res Hum Retroviruses 21: 527-536.
21. Sarrazin C (2016) The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hepatol 64: 486-504.
22. Jazwinski AB, Muir AJ (2011) Direct-acting antiviral medications for chronic hepatitis C virus infection. Gastroenterol Hepatol (NY) 7: 154-162.
23. Zagli G, Tarantini F, Bonizzoli M, Di Filippo A, Peris A, et al. (2008) Altered pharmacology in the Intensive Care Unit patient. Fundam Clin Pharmacol 22: 493-501.
24. Cornish P (2005) "Avoid the crush": hazards of medication administration in patients with dysphagia or a feeding tube. CMAJ 172: 871-872.
25. Duggan JM, Akpanudo B, Shukla V (2015) Alternative antiretroviral therapy formulations for patients unable to swallow solid oral dosage forms. Am J Health Syst Pharm 72: 1555-1565.
26. Arenas Villafranca JJ, NeitoGuindo M, Romero Dominguez R (2013) Review of enteral drugs administration for viral diseases: HIV, HBV, and HCV. Farm Hosp 37: 412-418.
27. (2016) Viekira XR (ombitasvir/paritaprevir/ritonavir/dasabuvir) prescribing information. AbbVie, Inc, North Chicago IL.
28. Williams NT (2008) Medication administration through enteral feeding tubes. Am J Health Syst Pharm 65: 2347-2357.
29. Höner Zu Siederdissen C, Maasoumy B, Marra F, Deterding K, et al. (2016) Drug-Drug Interactions With Novel All Oral Interferon-Free Antiviral Agents in a Large Real-World Cohort. Clin Infect Dis 62: 561-567.
30. Food and Drug Administration. FDA hepatitis update - important safety information: Harvoni and Sovaldi. March 21, 2015.
31. (2015) Norvir (ritonavir) Tablets and oral solution [prescribing information], AbbVie, Inc, North Chicago, IL.
32. DeCarolis DD, Westanmo AD, Chen YC, Boese AL, Walquist MA, et al. (2016) Evaluation of a Potential Interaction Between New Regimens to Treat Hepatitis C and Warfarin. Ann Pharmacother.
33. (2016) Harvoni (ledipasvir/sofosbuvir) prescribing information, Gilead Sciences, Inc, Foster City, CA.
34. (2016) Epclusa (sofosbuvir/velpatasvir) prescribing information, Gilead Sciences, Inc, Foster City, CA.
35. Schaefer M, Capuron L, Freibe A (2012) Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. J Hepatol 57: 1379-1390.
36. Smolders EJ, de Kanter CT, de Knegt RJ, van der Valk M, Drenth JP, et al. (2016) Drug-Drug Interactions Between Direct-Acting Antivirals and Psychoactive Medications. Clin Pharmacokinet.
37. European Association for Study of Liver (2015) EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 63: 199-236.
38. Barritt AS (2013) Management of anemia in patients receiving triple therapy for hepatitis C. Gastroenterol Hepatol (N Y) 9: 314-316.
39. Dyson JK, Hutchinson J, Harrison L, Rotimi O, Tiniakos D, et al. (2016) Liver toxicity associated with sofosbuvir, an NS5A inhibitor and ribavirin use. J Hepatol 64: 234-238.
40. Case J, Khan S, Khalid R, Khan A (2013) Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract 2013: 479730.
41. Westerholm B (1987) The rationale for a post-marketing surveillance. Hum Reprod 2: 41-44.

42. Kelm M, Campbell U (2016) Impact of Mobile Dose-Tracking Technology on Medication Distribution at an Academic Medical Center. Hosp Pharm 51: 382-388.

43. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL (2012) Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med 172: 1057-1069.

44. Shah C, Ishmael N, Wright J (2015) How nurses contribute to medicines reconciliation. Nurs Manag (Harrow) 22: 18-22.

45. Petta S, Craxì A (2015) Current and future HCV therapy: do we still need other anti-HCV drugs? Liver Int 1: 4-10.

46. (2016) Olysio (simeprevir) [package insert], Janssen Therapeutics, Titusville, NJ.

47. Sovaldi (sofosbuvir) [prescribing information], Gilead Sciences, Foster City, CA.

48. (2016) Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir) [prescribing information], : AbbVie Inc, North Chicago, IL.

49. (2016) Daklinza (daclatasvir) [prescribing information], Bristol-Myers Squibb Co, Princeton, NJ.

50. (2016) Technivie (ombitasvir, paritaprevir, and ritonavir) [prescribing information], AbbVie, North Chicago, IL.

51. (2016) Zepatier (elbasvir and grazoprevir) [prescribing information], Merck Sharp & Dohme Corp, Whitehouse Station, NJ.