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Cost Burden of Illness for Hepatitis C Patients with Employer-Sponsored Health Insurance

AMY W. PORET, S.M., RONALD J. OZMINKOWSKI, Ph.D., RON GOETZEL, Ph.D., JAIME E. PEW, S.M., and JEAN BALENT, B.S.

ABSTRACT

The disease burden of hepatitis C virus (HCV) is expected to more than double in the next two decades. Currently, there is very little information about the costs of HCV treatment for employers who pay for treatment and health plans that cover HCV patients. This study reports the medical costs of HCV for workers with health insurance. A retrospective claims data design was used for this study. A sample of HCV patients with health insurance was drawn from the inpatient, outpatient, and enrollment files of the MEDSTAT Group's MarketScan family of databases for 1993–1998. Patients were grouped into cohorts and studied for up to 2 years before and after HCV diagnosis. Sample size varies according to length of follow-up, peaking at 3,077 patients enrolled for at least 6 months. In the first year following HCV diagnosis, average payments for HCV patients ($10,925) were almost six times as high as payments for all patients in the MarketScan database ($1,186). Doctors are encouraged to test high-risk patients to find HCV patients earlier in the course of their disease and to better manage their care in order to avoid unnecessary illness and expenses for this disease.

INTRODUCTION

HEPATITIS C VIRUS (HCV), a viral infection leading to inflammation of the small bile ducts of the liver,[1] was first identified in 1989, and the first assay was developed in 1992.[2] According to the Centers for Disease Control and Prevention (CDC), HCV is the most common chronic blood-borne infection in the United States,[3] with current prevalence estimates of approximately 2.7–4 million people infected.[4–7] HCV may account for 40% of all chronic liver disease, 20–30% of all liver transplants, and 8,000–10,000 deaths annually.[7–9] Since 1991, 28,000–36,000 new cases of HCV have been uncovered each year,[7] the majority of which occur in people younger than 50 years of age.[10]

Although HCV infection can have serious long-term consequences, its clinical course is generally indolent and often takes years from exposure to the clinical expression of symptoms.[4,11] Typically, 20% of HCV-positive patients develop cirrhosis at 20 years after exposure. The risk of developing liver cancer is estimated at 1–5% at 20 years after exposure.[7] However, once cirrhosis develops, the risk of liver cancer increases 1–4% per year.[7] Most HCV-related deaths occur in patients who acquired the disease 20–40 years earlier, which indicates that people may have been exposed through contaminated blood transfusions prior to 1992. Therefore, the large cohort of HCV-positive people infected between 1960 and 1992 will lead to an expected rise in the death rate

The MEDSTAT Group, Ann Arbor, Michigan.

of 25,000 to 30,000 deaths over the next two decades.[7] Consequently, the burden of disease and death rate associated with HCV is expected to more than double over the next two decades as this large cohort of HCV-positive patients progress to cirrhosis, cancer, and liver failure.[7,10]

This study examines the cost burden associated with HCV and HCV-related comorbidities for patients with private health insurance. This group is of primary interest to employers who pay for health insurance and who stand to lose the productivity-related contributions of employees infected with the virus. It is also of primary interest to health plans that must cover the services needed to treat this condition.

The CDC has estimated the annual costs of HCV to be about $600 million,[12] but little is known about the progress of HCV patients over time and the associated cost burden. Through a retrospective, descriptive analysis using the MEDSTAT Group's MarketScan® databases, we estimate the cost of treating private-pay, fee-for-service HCV patients. We follow HCV patients to characterize their health experience, hospitalizations, and health care expenditures before and after their diagnosis with HCV. The results of this study should shed new light on the expenses related to the management of HCV and whether improved screening and treatment of HCV may be a wise financial investment.

MATERIALS AND METHODS

Data source

Data for this study were drawn from the MEDSTAT Group's MarketScan private pay fee-for-service databases. The MarketScan databases contain claim-level information about the inpatient and outpatient health care services used by patients covered in over 150 noncapitated benefit plans offered by large, primarily Fortune 500, employers. The number of covered lives varied by year over our 1993–1998 study; in 1997, the last full year from which HCV patients were selected, MarketScan databases included data for about 2.5 million continuously enrolled covered lives; these included active employees, early retirees, COBRA continuees, and their dependents.

Analytic file construction

The following diagnosis codes were used to find HCV patients in the MarketScan® database for 1993–1998: an ICD-9 diagnosis of HCV (070.51) or a variation, HCV including hepatic coma (070.41), carrier status (V02.54), chronic HCV (070.54), or HCV with hepatic coma (070.44). (Note: No patients in this study were found with a diagnosis of carrier status, V02.54.) To be included in the sample, individuals had to be continuously enrolled in their health plan for a minimum of 6 months following their first-observed HCV diagnosis, and they were followed for as long as the data allowed before and after that date. The first observed occurrence of HCV (referred to as the "index date") was between July 1, 1993 and June 30, 1998 for each sample member, thereby allowing for at least 6 months of investigation before and after the index diagnosis date.

Once the sample of HCV patients was selected, patients were grouped into cohorts based on time since the first-observed diagnosis. In total, eight sample cohort groups were created, each accounting for 6-month increments of time before and after the index date. These cohorts included all of the patients with experience: (1) 19–24 months before the index date; (2) 13 –18 months before the index date; (3) 7–12 months before the index date; (4) 0–6 months before the index date; (5) 0–6 months after the index date; (6) 7–12 months after the index date; (7) 13–18 months after the index date; and (8) 19–24 months after the index date. These groups were not mutually exclusive, and some patients could be followed longer than others. For example, some (but not all) of the patients followed for 6–12 months before the index date could also be followed for 13–18 months before the index date.

After finding HCV-diagnosed patients who met the inclusion criteria, patients were excluded if they were diagnosed with conditions that are contraindicated for HCV treatment. Specifically, patients with depression, current infertility treatment, active chemical dependency, severe renal impairment, hemoglobinaphathies (thalassemia, sickle-cell anemia), and a history of significant or unstable cardiac disease were excluded, as were pregnant women.

Next, variables were constructed to measure the demographic and clinical characteristics of HCV patients. The demographic variables were derived directly from the patient eligibility files (e.g., age, gender, relationship to employee), while the clinical characteristics were based on the patients' ICD-9 codes in the claims data. Over the study period, patients' primary diagnoses from inpatient and outpatient claims were counted. These codes were then grouped into major diagnostic categories (MDCs) developed by Fetter et al.[13] to characterize the major body systems affected by disease.

There are 25 possible MDCs; together these account for the 15,000 or so possible ICD-9 diagnosis codes. Most MDCs relate to a particular organ or body system (e.g., MDC 2 = diseases and disorders of the eye; MDC 7 = diseases and disorders of the hepatobiliary system and pancreas), but some span multiple body systems (e.g., MDC 25 = HIV infections). The average number of MDCs per patient was calculated for each 6-month interval, as a way of noting the extent of the health problems faced by HCV patients. The average number of physician visits per 6 months was also calculated. The MDCs and physician encounters served as crude indicators of the extent of patients' illnesses and the need for outpatient care.

Next, HCV comorbidities were identified and compared over time to enhance the description of disease severity. Comorbidities were identified on the basis of ICD-9 codes. The distribution of comorbidities in the 12 months before the index HCV diagnosis was compared to the distribution of comorbidities occurring during the 12 months following the index event, using a chi-squared test of independence. The analysis of comorbidities was also used to determine whether there were any HCV treatment-specific reductions in comorbidities observed posttreatment, and whether there were certain diagnoses that predicted the onset of HCV. Finally, we estimated the proportion of patients who developed complications related to HCV (e.g., liver disease) following their diagnosis.

Expenditure data were analyzed in 6-month intervals. Expenditures included claims dollars paid by the insurance plan and copayments and deductibles paid by HCV patients. All expenditure data were converted to year-2000 dollars using an index based on the Bureau of Labor Statistics' Gross Domestic Product Implicit Price Deflator.[14] Total payments were calculated as the sum of inpatient and outpatient payments. The primary diagnosis on the claim was used to classify payments into one of three categories: (1) payments for services when HCV was the primary diagnosis; (2) payments for services when an HCV-related diagnosis (but not HCV itself) was primary (see Appendix 1 for a list of HCV-related diagnoses); or (3) payments for services when another diagnosis was primary and HCV was secondary. These groupings of payments were used to explain the cost-drivers for HCV treatment (i.e., which category of claims accounted for most of the expenditures related to HCV care).

Expenditures were calculated on a per-capita basis. Per capita payments were derived by dividing expenditures for HCV patients by the number of patients in the entire sample, regardless of whether any inpatient or outpatient services were used. Per capita expenditures are often considered useful by health plan actuaries and others, because all categories of care are viewed across the same denominator of patients, allowing clear estimation of the share of treatment dollars going toward inpatient vs. outpatient care.

To compare the difference between patients with HCV and all patients in the MarketScan database, mean HCV inpatient, outpatient, and total expenditures were contrasted to mean expenditures in each category for the entire MarketScan database in 1997 (the last full year of experience). The MarketScan data provide a reference point for health care expenditures incurred by a large patient population in a noncapitated health insurance environment. The HCV-MarketScan comparison therefore provides a useful way of viewing the relative importance of HCV, at least in dollar terms.

RESULTS

Demographic and clinical characteristics of HCV patients

A total of 3,077 patients were found for this study. Demographic characteristics at the time of the index HCV diagnosis are presented in

Table 1. More than half (58%) of the sample was male and the average age was 45 years old. The greatest proportion (32%) of patients ($n = 977$) was first observed with HCV in 1997. Sixty-four percent of the patients were primary beneficiaries (i.e., employees as opposed to dependants or spouses). Wage information was not available for the entire sample; about 29% were known to be hourly workers, and about 25% were salaried. Wage information for the rest was either unknown or unavailable because not all patients were employed. About 25% of the sample members were unionized employees. The greatest concentration of sample members were associated with major policy holders from the durable goods manufacturing industry (31%), and about 22% more were associated with workers in government jobs.

As one moved away from the index date, the size of the sample decreased, as noted in Table 2 (which also presents expenditure results that will be described later). The sample declined over time as individual workers changed em-

Table 1. Demographic and Clinical Characteristics of HCV patients at Index Diagnosis Date ($n = 3,077$)

Variable	*Number*	*Percent or SD*
Gender		
Female	1,282	41.66%
Male	1,795	58.34%
Age (mean and SD), years	45.01	10.17
Year of initial hepatitis C diagnosis		
1993	122	3.96%
1994	355	11.54%
1995	411	13.36%
1996	650	21.12%
1997	977	31.75%
1998	562	18.26%
Insurance plan type		
Indemnity	1,124	36.53%
POS/EPO	289	9.39%
PPO	1,420	46.15%
Unknown	244	7.93%
Region		
Northeast	384	12.48%
North Central	733	23.82%
South	1,164	37.83%
West	621	20.18%
Unknown	175	5.69%
Employee relationship		
Employee	1,983	64.45%
Spouse	991	32.21%
Dependant	103	3.35%
Employment information		
Hourly	888	28.86%
Salaried	759	24.67%
Unknown wage type	1,430	46.47%
Unionized	777	25.25%
Industry of employment of major policy holder		
Oil and gas extraction, mining	107	3.48%
Manufacturing, durable goods	954	31.00%
Manufacturing, nondurable goods	246	7.99%
Transportation, communications, utilities	283	9.20%
Retail trade	33	1.07%
Finance, insurance, real estate	290	9.42%
Services	311	10.11%
Government	678	22.03%
Unknown	175	5.69%

Source: 1993–1998 MarketScan® Data; The MEDSTAT Group.

Table 2. Expenditures by 6-Month Increments for HCV Patients

	Prior to hepatitis C diagnosis								*Time of index hepatitis C diagnosis*	*Following hepatitis C diagnosis*							
	24–19 months (n = 944)		*18–13 months (n = 1,218)*		*12–7 months (n = 2,359)*		*6–0 months (n = 2,789)*			*0–6 months (n = 3,077)*		*7–12 months (n = 2,052)*		*13–18 months (n = 1,087)*		*19–24 months (n = 670)*	
Mean per-person expenditures	*Mean $*	*Median $*	*Mean $*	*Median $*	*Mean $*	*Median $*	*Mean $*	*Median $*		*Mean $*	*Median $*	*Mean $*	*Median $*	*Mean $*	*Median $*	*Mean $*	*Median $*
Total medical costs when	2,850.42	565.10	3,515.07	561.43	2,931.71	679.17	4,594.04	1,130.72		6,290.00	1,913.41	4,635.48	900.24	5,386.41	813.65	3,938.72	771.52
Hep-C is primary diagnosis	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		822.64	192.73	209.23	0.00	333.99	0.00	277.09	0.00
Hep-C related costs	165.53	0.00	424.41	0.00	370.90	0.00	540.75	0.00		918.48	0.00	1,000.85	0.00	741.44	0.00	551.00	0.00
Other medical costs	2,684.89	513.75	3,091.28	532.56	2,560.81	627.46	4,053.29	1,031.87		4,548.96	1,090.96	3,425.40	694.36	4,310.98	628.47	3,110.80	633.06
Total patient costs when	1,169.99	0.00	1,750.28	0.00	1,057.46	0.00	1,990.45	0.00		2,961.13	0.00	2,350.13	0.00	3,200.56	0.00	1,806.78	0.00
Hep-C is primary diagnosis	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		246.42	0.00	31.79	0.00	160.87	0.00	150.32	0.00
Hep-C related costs	39.53	0.00	319.94	0.00	233.21	0.00	276.65	0.00		559.05	0.00	804.12	0.00	587.89	0.00	261.88	0.00
Other medical costs	1,130.45	0.00	1,430.34	0.00	824.25	0.00	1,713.79	0.00		2,155.67	0.00	1,514.23	0.00	2,451.79	0.00	1,394.59	0.00
Total outpatient costs when	1,680.43	536.33	1,764.79	548.87	1,874.25	654.56	2,603.59	1,063.16		3,328.87	1,685.68	2,285.34	855.49	2,185.85	780.35	2,131.93	721.42
Hep-C is primary diagnosis	0.00	0.00	0.00	0.00	0.00	0.00	—	—		576.22	173.05	177.44	0.00	173.12	0.00	126.77	0.00
Hep-C related costs	126.00	0.00	104.47	0.00	137.70	0.00	264.44	0.00		359.43	0.00	196.73	0.00	153.55	0.00	289.12	0.00
Other medical costs	1,554.44	502.40	1,660.93	518.79	1,736.56	613.49	2,339.49	966.57		2,393.30	949.87	1,911.17	656.22	1,859.19	595.82	1,716.22	596.61

Costs are reported in year 2000 dollar equivalents.
Source: 1994–1998 MarketScan® Data; The MEDSTAT Group.

ployers or were no longer covered by their employer's health insurance for reasons unrelated to their health. In addition, patients exited the database as they moved further away in time from their index date, perhaps because they became too ill to work and eventually lost their insurance coverage or died. It is also possible that some patients responded to treatment and therefore incurred no future health care claims. The number of patients in these categories is unknown.

Health indicators

Some basic proxies for health status were established by counting the number of ICD-9 diagnoses at the three-digit level, the number of MDC groupings represented by the diagnoses on the patients' claims, and the number of physician visits. The assumption underlying this approach is that the more illnesses identified through various ICD-9 codes and the more body systems affected by the patient's diseases, the "sicker" the patient and more complex his/her disease pattern is to treat. As shown in Table 3, the number of ICD-9 codes, MDCs, and physician visits increased over time from 24 months before the index diagnosis (5.76, 2.98, and 2.90, respectively), to peak within 6 months postdiagnosis (at 8.67, 4.12, and 5.01, respectively). These numbers then decreased over time to 6.85 ICD-9 codes, 3.45 MDCs, and 3.45 physician visits, respectively, at 24 months after the index diagnosis. Although decreasing over time after the index HCV diagnosis, the levels at 24 months postdiagnosis were higher than the levels at 24 months preindex diagnosis.

These crude health status proxies suggest that HCV patients were most ill during the 6 months immediately after the index HCV diagnosis. If HCV diagnosis tends to occur after the onset of disease, these trends might indicate that diagnosis tends to be made relatively late in the course of illness. More information on the pattern of diagnoses and comorbidities is provided below.

Comorbidities associated with HCV

For the comorbidity analysis, we examined all additional diagnoses for the twelve months before and after HCV diagnosis. As shown in Table 4, before the HCV diagnosis, the five diagnoses occurring with the greatest frequency were: other noncongenital liver disorders (34%), abdomen and pelvis symptoms (27%), chronic liver disease and cirrhosis (26%), special investigations and exams—a general term that may indicate the search for problems like HCV (26%), and respiratory and other chest symptoms (21%). The percentages refer to how many individuals in our sample had at least one diagnosis for the above conditions during the 12 months preceding HCV diagnosis. During the 12 months following HCV diagnosis, significantly more patients were diagnosed with other non-congenital liver disorders (42%, $p < 0.001$) and chronic liver disease and cirrhosis (37%, $p < 0.001$). As noted in Table 4, all 10 most frequent comorbidities experienced by HCV patients were significantly more prevalent among HCV patients than among patients in the 1997 MarketScan database.

Expenditure results

Table 2 presents the average expenditures for HCV patients in 6-month increments preceding and following their diagnosis of HCV. As shown, average per capita expenditures rose steadily from $2,850 in the 19–24 months before the index HCV diagnosis to $4,594 in the 6 months immediately preceding the index date. For the 24-month period before an HCV diagnosis was observed, total annual per capita expenditures for HCV patients averaged $6,945. Trends in median expenditures were similar, but medians for inpatient care were often zero, since most patients were not hospitalized.

Following the index diagnosis, total per capita expenditures averaged $6,290 in the first 6 months past the index date. Thereafter, expenditures steadily declined, averaging $3,939 for the 19–24-month period following HCV diagnosis. For the entire 24 months following the index HCV diagnosis, total annual per capita expenditures for HCV patients averaged $10,110. Expenditures were roughly evenly divided between inpatient and outpatient services before the index diagnosis, but after the index HCV diagnosis inpatient expenditures increased as a proportion of total expenditures.

Table 3. Health Proxies: Mean Number of Major Diagnostic Categories, ICD-9 Codes, and Physician Office Visits

	19–24 months before index HCV diagnosis	*13–18 months before index HCV diagnosis*	*7–12 months before index HCV diagnosis*	*0–6 months before index HCV diagnosis*	*0–6 months after index HCV diagnosis*	*7–12 months after index HCV diagnosis*	*13–18 months after index HCV diagnosis*	*19–24 months after index HCV diagnosis*
Unique no. of ICD-9 codes at three-digit level	5.76	6.10	6.24	7.74	8.67	7.11	7.02	6.85
Major diagnostic categories	2.98	3.08	3.18	3.93	4.12	3.56	3.48	3.45
Doctor's office visits	2.90	3.00	3.40	4.09	5.01	3.89	3.65	3.45

Source: 1993–1998 MarketScan® Data; The MEDSTAT Group.

Table 4. 1993–1998 Patient Counts: HCV Patients with Comorbid Conditions and at Least 12 Months of Data before Index HCV Diagnosis

	HCV patients										
	Preperiod data (n = 2,359)			*Postdiagnosis data (n = 2,052)*				*Marketscan total 1997 data (n = 2,530,280)*			
ICD-9 code description	*Rank*	*Frequency*	*Percent*	*Rank*	*Frequency*	*Percent*	p *values*	*Frequency*	*Percent*	p *value vs. preperiod*	p *value vs. postperiod*
573 Other disorders of the liver	1	811	34%	1	855	42%	<.0001	14,139	0.6%	<0.001	<0.001
789 Other symptoms involving abdomen/pelvis	2	631	27%	4	543	26%	0.8377	209,255	8.3%	<0.001	<0.001
571 Chronic liver disease and cirrhosis	3	616	26%	2	762	37%	<.0001	6,563	0.3%	<0.001	<0.001
v72 Special investigations and examinations, including routine exam of a specific system	4	604	26%	3	573	28%	0.0879	447,428	17.7%	<0.001	<0.001
786 Symptoms involving respiratory system and other chest symptoms	5	497	21%	6	389	19%	0.0832	288,810	11.4%	<0.001	<0.001
780 General symptoms	6	478	20%	5	408	20%	0.7632	257,768	10.2%	0.076	0.022
401 Essential hypertension	7	428	18%	7	365	18%	0.7832	282,572	11.2%	<0.001	<0.001
794 Nonspecific abnormal results of function	8	403	17%	8	310	15%	0.0779	25,885	1.0%	<0.001	<0.001
790 Nonspecific findings on examination of blood	9	397	17%	9	320	16%	0.2697	46,049	1.8%	<0.001	<0.001
724 Other and NOS disorders of back	10	310	13%	10	289	14%	0.3783	181,946	7.2%	0.006	0.052

Source: 1994–1998 MarketScan® Data; The MEDSTAT Group.

Comparison to MarketScan norms

In comparison to MarketScan norms, total per capita payments for HCV patients in the first year following HCV diagnosis were almost six times as high as payments for all MarketScan patients in 1997 ($10,925 vs. $1,886). Inpatient costs for HCV patients were almost eight times as high ($5,312 vs. $676), and outpatient costs were almost 4.5 times as high as the overall MarketScan average ($5,614 vs. $1,210).

Examining "other medical costs"

Most of the expenditures for HCV patients were associated with claims for medical conditions other than HCV or its most common, related comorbidities. This was not surprising to us, since similar patterns have been found for other diseases, such as asthma and diabetes[15] and depression.[16] Moreover, one might suspect that treating such problems among an HCV population would be more difficult than treating the same problems among patients who do not have HCV, but addressing this issue was beyond the scope of our descriptive study.

To understand why the "other" cost category is the largest cost driver, we went back to the data to find the most prevalent and costly diagnoses for problems other than HCV that were first-listed on patients' medical claims incurred during the 12 months after the index HCV diagnosis. Not surprisingly, the list of "other" diagnoses we found was very similar to the list of comorbid conditions reported in Table 4. (The lists are not identical, because Table 4 pertains to all diagnoses, not just to the subset of diagnoses whose other, non-HCV, conditions were first-listed on the claims.)

Specifically, the top five most frequent, first-listed, non-HCV diagnoses in the 12-month period after the index HCV diagnosis was made included: hepatitis not otherwise specified (ICD-9 code 573.3, $n = 635$ patients), chronic hepatitis not otherwise specified (ICD-9 code 571.40, $n = 374$ patients), laboratory examinations (ICD-9 code v72.6, $n = 260$), abnormal liver function studies (ICD-9 code 794.8, $n = 241$ patients), and essential hypertension not otherwise specified (ICD-9 code 401.9, $n = 202$).

It is interesting that most of these conditions are for liver problems that can easily be confused with HCV. In fact, seven of the top 10 most prevalent conditions were liver-related, as were nine of the top 30. (Details are available upon request.) Given the difficulties involved in making an HCV diagnosis and the fact the HCV can lead to other serious complications, this pattern seems reasonable, and it may strengthen the case for HCV screening among patients with these problems, as noted later.

DISCUSSION

Employers and health plans are faced with a wide range of diseases affecting their workforce and plan members. Increasingly, treatment decisions require reliable financial data regarding the cost burden of these diseases, so intelligent choices can be made concerning alternative treatment options. One health condition that is becoming more common and costly to treat is HCV, whose prevalence now exceeds that of HIV infection.

It should be noted that HCV patients undergo a variety of diagnostic and therapeutic procedures that may include liver biopsy, treatment with interferon-based medication, treatment of the complications of liver failure, and liver transplantation. Some diagnosed with HCV may receive little or just palliative care. In our analysis, all patients with a diagnosis of HCV were examined regardless of treatment choice. Although liver transplantation is relatively uncommon among HCV patients, it is worth noting that HCV is now the most prevalent indication for liver transplantation in the United States.[17]

We estimated the cost burden of HCV to employers and attempted to understand the demographic, treatment, and cost profile of those who suffer from the disease. We found that the cost burden of HCV patients with health insurance is substantial, peaking during the 6 months immediately following the first-observed HCV diagnosis. Coupled with a decreasing sample size as one moves away from the index date, this cost pattern could be due to the selection of patients relatively late in

their course of illness, with some patients dying and other leaving employment as time moves on. Alternatively, the cost pattern could be due to some early success with treatment, negating the need for more expensive care later on.

Overall, for the 24-month period preceding HCV diagnosis, HCV patients cost employers an average of $6,945 per year. For the 24-month period following diagnosis, their average annual cost was $10,110. Much (but not most) of the expense appears to be associated with the consequences of HCV (i.e., liver disease and cirrhosis), suggesting that earlier testing and treatment might be able to pre-empt some of these illnesses and associated expenditures.

Once the HCV cost burden is better understood, employers and health plans might be interested in the available screening, testing, and treatment options and the cost-effectiveness of these options. Screening for HCV can be done via enzyme-linked immunoassay test for the HCV antibody, but this is not completely reliable, so it should be coupled with surveys designed to collect information on behavioral risk factors for the disease or the likely occurrence of occupational exposure to HCV.[18] Confirmation of the presence of HCV may involve several procedures, but usually focuses on the presence of HCV RNA in serum and a recent, known exposure to the virus, or seroconversion to positivity for antibodies to HCV.[19] Treatments for managing hepatitis include clinical monitoring of enzyme levels, interferon and combination therapy treatments, and finally liver transplantation. Additionally, many patients need medical management of HCV comorbidities.

Treatment with interferon alone costs approximately $2,150 for a 6-month course, while the combination with ribavirin raises the costs to approximately $8,600 for an average course of combination treatment.[20,21] Typical courses of treatment run either 6 or 12 months and, if successful, result in normalizing enzyme levels by eradicating the virus, improving liver histology, and ameliorating patients' clinical symptoms. This occurs in approximately 15% of patients on interferon monotherapy and approximately 43% of patients treated with Rebetron combination therapy.[22] Recently, a new treatment for HCV (peginterferon alfa-2b) has been approved by the Food and Drug Administration. It has increased efficacy and an improved dosing profile in comparison to available treatment options.[23]

The cost-effectiveness of HCV treatment will depend upon the treatment modality chosen, and on the likelihood of incurring problems like cirrhosis of the liver or the need for a liver transplant (among others), in the presence and absence of treatment. Recent pharmacoeconomic studies demonstrate the cost-effectiveness of interferon treatment, but not all studies reach the same conclusion. A computer simulation cohort model study by Wong concluded that interferon treatment is cost-saving and reduces lifetime medical expenditures. Savings were derived from reductions in lifetime medical costs averaging $6,300–$6,900 for each patient treated with interferon.[24] A cost-effectiveness analysis using clinical trial data and published studies of HCV patients who were treatment-naive found that, over an average lifetime, immediate antiviral therapy was cost-effective compared with biopsy management, producing a net savings of $7,000 relative to no antiviral therapy.[25] Overall, these researchers emphasize that treatment of HCV in its earlier stages is more likely to lead to higher costsavings and longer life expectancy.

A different conclusion about the cost-effectiveness of HCV treatment was reached by Batra,[26] who found that HCV screening and drug treatment for those who test positive for HCV is more costly than treating patients with liver transplantation. Thus, for the relatively few HCV patients who would require a liver transplant, the socially optimal approach would be to wait for this need to occur and then provide the transplant. Setting aside any other objections that might be raised with this approach, it is worth noting that Batra's study was performed in Great Britain, where the cost of liver transplantation is only about one-sixth to one-eighth the average cost in the United States. Adjusting for this alone would be enough to reverse his conclusions.

In addition to conducting cost-effectiveness analyses, several researchers have explored the impact of chronic or recurrent HCV on quality of life, functional status, and depression. Several studies have shown that treatment with interferon increases life expectancy and improves quality of life.[7] A meta-analysis of five prospec-

tive trials further supports these findings.[25] Wong et al.[27] examined the cost-effectiveness of retreatment with combination therapy versus interferon alone for patients who relapsed after initial interferon treatment. They found that Rebetron combination therapy prolonged life expectancy while increasing costs modestly in comparison to monotherapy.

Our focus has been on medical expenditures borne by the patient and the payer, and this leads to two important limitations. First, no information was available on the productivity impact of HCV, so the cost burden we estimated is conservative. It does not count days lost from work due to absenteeism or short-term disability program use, nor does it account for lapses in productivity while at work that may be caused by HCV. The latter is referred to as "presenteeism" in the health and productivity management literature.[28]

Second, since HCV may take 20–30 years to cause cirrhosis and other liver problems, and since the virus can be silent for long periods before any symptoms emerge, we have probably undercounted its prevalence. Whether we have also undercounted its cost burden depends upon whether any health care use prior to diagnosis for those we missed was due to HCV. We suspect the dollars have been undercounted as well, but there is no way to check for this with administrative claims data.

Another limitation might arise from the way we selected patients for this study. We focused on those who may be eligible for treatment (i.e., those with no known contraindications to treatment). We did this because the focus of this study is on the cost burden to those who pay for care—primarily patients and insurance plans or employers, and because doctors and health plans might consider testing for HCV primarily among those who could benefit from treatment. (Testing those with contraindications for treatment might seem like a waste of resources, unless there is net benefit in the knowledge that one has a disease that cannot be treated.) An unstated assumption that readers might make is that all patients without contraindications would be treated once diagnosed, but the literature suggests that many patients decline treatment for HCV.[26] We attempted to avoid this problem by counting dollars for health care received by HCV patients, regardless of whether HCV was the "primary" or first-listed diagnosis on the medical claim. Thus, treatment for other conditions that may be complicated by the presence of HCV was counted in this study.

Next, we should note that pharmaceutical expenditures were excluded from the study, because pharmaceutical claims were not available for most patients and few pharmaceutical interventions were available in the early 1990s, when some of our patients were found. Nevertheless, treatment for HCV is expensive, and the cost-burden of illness has been understated for the first year following diagnosis, when HCV drug treatment would be offered.

CONCLUSION

Our analysis has demonstrated a noteworthy cost burden associated with HCV. We found that the average medical expenditures associated with having an HCV diagnosis peak early after the first-observed diagnosis, but that diagnosis may come relatively late in the disease, leading to high costs. More specifically, inpatient and outpatient costs averaged over $10,000 per year in the first two years following diagnosis.

Armed with these data, employers and health plans can better justify effective prevention and treatment efforts directed at HCV. Koff[29] argues that disease management programs for hepatitis C should be developed and should focus on reducing unhealthy high-risk behavior by educating the uninfected, promoting healthier behavior such as the avoidance of alcohol in those infected, screening those at high risk with early confirmation of diagnosis, and then initiating appropriate and effective treatment regimens. We support this notion. With regard to screening, we agree that patients with known HCV-related comorbidities such as cirrhosis or chronic liver disease should be tested, in an effort to find HCV earlier and preclude some of the illness and expenditures associated with it. However, screening and testing must be voluntary and confidential, directly involving only the patient and the doctor. Health plans or employers may pay for these services, but the system for payment must still promote confidentiality while pro-

viding incentives for proper treatment (or no treatment, as the patients' best interests require).

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REFERENCES

1. Barlow Pugh M, ed. Steadman's medical dictionary, 27th ed. Baltimore, MD: Lippincott, Williams, and Wilkins, 2000.
2. The Hepatitis Information Network. Chronic hepatitis C [On-line]. Available: www.hepnet.com/hepc/sherman.
3. Centers for Disease Control. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR. 1998;47:RR-19.
4. Alter HJ, Conry-Cantilena C, Melpolder J, et al. Hepatitis C in asymptomatic blood donors. Hepatology 1997;26:29S–33S.
5. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000;284:450–456.
6. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alfa-2b or in combination with Ribavirin for the treatment of relapse of chronic hepatitis C. N Engl J Med 1998;339:1493–1499.
7. Wong JB. Epidemiology and treatment of hepatitis C. Presented at Leadership for an Emerging Health Care Crisis: National Economic Summit on Hepatitis C.
8. Wong J, Bennett W, Knoff R, Pauker S. Pretreatment evaluation of chronic hepatitis C. JAMA 1998;280: 2088–2093.
9. Bodenheimer HC, Lindsay KL, GL Davis, et al. Tolerance and efficacy of oral Ribavirin treatment of chronic hepatitis C: a multicenter trial. Hepatology 1997;26:473–477.
10. Alter MJ, D Kruszon-Moran, OV Nainan, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341: 556–562.
11. Seeff LB. Natural history of hepatitis C. Hepatology 1997;26:21S–28S.
12. Centers for Disease Control and Prevention. Recommendations for Prevention and Control of Hepatitis-C virus (HCV) Infection and HCV-Related Chronic Disease. Morbidity and Mortality Weekly Report 1998;47(No. RR-19):1–54.
13. Fetter RB, Shin Y, Freeman JL, Averill RF, Thompson JD. Case mix definition by diagnosis-related groups. Med Care 1980;18:iii, 1–53.
14. Getzen TE. Medical care price indexes: theory, construction, and empirical analysis of the U.S. series 1927–1990. Adv Health Econ Health Serv Res 1992;13:83–128.
15. Ozminkowski RJ, Wang S, Marder WD, Azzolini J, Schutt D. Cost implications for the use of inhaled antiinflammatory medications in the treatment of asthma. Pharmacoecon 2000;18:253–264.
16. Croghan TW, Obenchain RL, Crown WH. What does depression treatment really cost? Health Affairs 1998;17:198–208.
17. Detre KM, Belle SH, Lombardero M. Liver transplantation for chronic viral hepatitis. Viral Hepatitis Rev 1996;2:219–228.
18. Upfal M, Naylor P, Mutchnick MM. Hepatitis C screening and prevalence among urban public safety workers. J Occup Environ Med 2001;43:402–411.
19. Hoofnagle JH. Therapy for acute hepatitis C [Editorial]. N Engl J Med 2001;345:1495–1497.
20. Hwang M. Do you have hepatitis C? JAMA 1998; 28:2188.
21. Malone DC. Cost-effectiveness analysis of interferon alpha-2b with ribavirin for chronic hepatitis C infection. Formulary 2000;35:681.
22. Barbaro G, Di Lorenzo G, Soldini M, et al. Evaluation of long-term efficacy of interferon alpha-2b and ribavirin in combination in naive patients with chronic hepatitis C: an Italian multicenter experience. J Hepatol 2000;33:448–455.
23. Fried MW, Shiffman ML, Reddy RK, et al. Pegylated (40 kDa) interferon alpha-2a (PEGASYS) in combination with ribavirin: efficacy and safety results from a phase III randomized, actively-controlled, multicenter study. Gastroenterology 2001;120:A–55.
24. Wong JB. Cost-effectiveness of treatments for chronic hepatitis C. Am J Med 1999;107:74S–78S.
25. Wong JB, Raymond SK. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effective analysis. Ann Intern Med 2000;133:665–675.
26. Batra N. Hepatitis C screening and treatment versus liver transplantation. Dis Manage Health Outcomes 2001;9:371–384.
27. Wong JB, Davis GL, Pauker SG. Cost effectiveness of ribavirin/interferon alfa-2b after interferon relapse in chronic hepatitis C. Am J Med 2000;108:366–373.
28. Goetzel RZ, Ozminkowski RJ. Disease management as a part of total health and productivity management. Dis Manag Health Outcomes 2000;8:121–128.
29. Koff RS. Disease management programs for hepatitis C: a team approach to setting goals. Dis Manag Health Outcomes 2001;9:431–439.

Address reprint requests to:
Ronald J. Ozminkowski, Ph.D.
The MEDSTAT Group
777 East Eisenhower Pkwy., 803R
Ann Arbor, MI 48108

E-mail: ron.ozminkowski@medstat.com

APPENDIX 1: HCV-RELATED DIAGNOSES

155.0	Primary malignant neoplasm of liver (hepatocellular carcinoma)
245.2	Autoimmune thyroiditis
273.2	Cryoglobulinemia
277.1	Porphyria cutanea tarda
284.8	Aplastic anemia, other specified type
284.9	Aplastic anemia, unspecified
370.07	Mooren's (corneal) ulcer
446.0	Polyarteritis nodosa
456.20	Esophageal varices in diseases NED with hemorrhage
516.3	Pulmonary fibrosis (Hamman-Rich syndrome)
570	Acute and subacute necrosis of liver
571.5	Cirrhosis of liver without mention of alcohol
571.8	Other chronic nonalcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol
572.0	Abscess of liver
572.1	Portal pyemia
572.2	Hepatic coma
572.3	Portal hypertension
572.4	Kidney failure associated with liver disease
572.8	Other sequelae of chronic liver disease (e.g., hemorrhage, fulminant)
573.0	Chronic passive congestion of liver
573.4	Hepatic infarction
573.8	Other specified disorders of liver (e.g., hemorrhage)
573.9	Unspecified disorder of liver
580.81	Acute glomerulonephritis in diseases NEC (e.g., hepatitis)
581.1	Nephrotic syndrome with lesion of membranous glomerulonephritis
581.2	Nephrotic syndrome with lesion of membranoproliferative glomerulonephritis
582.1	Chronic glomerulonephritis with lesion of membranous glomerulonephritis
582.2	Chronic glomerulonephritis with lesion of proliferative glomerulonephritis
583.1	Nephritis NEC with lesion of membranous glomerulonephritis
583.2	Nephritis NEC with lesion of membranoproliferative glomerulonephritis
584.x	Acute renal (kidney) failure
585	Chronic renal failure
586	Unspecified renal failure
697.0	Lichen planus
701.0	Circumscribed scleroderma
710.2	Sjogren's syndrome
780.79	Malaise, fatigue
782.3	Edema
782.4	Jaundice
783.0	Anorexia
789.0x	Abdominal pain
789.5	Ascites
V02.62	Viral hepatitis C carrier