Hepatitis B Management Costs in France, Italy, Spain, and the United Kingdom

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Goals: To estimate the costs associated with the management of chronic hepatitis B (CHB) and its sequelae in France, Italy, Spain, and the United Kingdom from the perspective of the healthcare payer.

Background: The World Health Organization estimates that the disease sequelae related to hepatitis B account for 1 million deaths annually worldwide. Northern Europe is a low endemic area, while Mediterranean regions are classified as intermediate endemic areas. The introduction of vaccination programs in France, Italy, and Spain in recent years has lowered the hepatitis B incidence rates.

Study: The purpose of this study was to identify the medical management patterns of CHB patients in France, Italy, Spain, and the United Kingdom and estimate the economic burdens of CHB-related disease states for each country. A central questionnaire was used to collect data from specialist physicians in four countries, and responses were collated into management patterns for chronic active hepatitis, compensated and decompensated cirrhosis, and hepatocellular carcinoma.

Results: The average cost by disease state for each European country was found to increase across the identified disease states reflecting disease progression. Year-2001 average annual disease state costs per patient were estimated to be as follows: CHB, €1,093–€3,396; compensated cirrhosis, €1,134–€3,997; decompensated cirrhosis, €5,292–€8,842; hepatocellular carcinoma, €3,731–€9,352; and, from published sources, liver transplant surgery, €25,165–€84,568.

Conclusion: The cost of CHB is variable both within and between European countries. The association of disease progression with increased cost of disease management suggests that measures to prevent or delay its progression would be economically beneficial.

Key Words: hepatitis B, cost, disease state, treatment

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Chronic hepatitis B (CHB) infection is one of the major causes of morbidity and mortality worldwide. Globally, more than 2 billion people have been infected with hepatitis B virus (HBV), and of these, approximately 350 million progress to CHB infection.[1] The acute disease is generally asymptomatic and resolves without treatment. However, individuals who progress to a chronic infection are at risk for increased morbidity and mortality. CHB is the leading cause of cirrhosis and hepatocellular carcinoma, and 15% to 25% of CHB patients die because of these liver disease sequelae.[2] The World Health Organization estimates that CHB-related liver disease sequelae account for more than 1 million deaths annually, making it the third most deadly disease worldwide. Most hepatitis B infections in the developed world result from sexual activity, intravenous drug use, or occupational exposure among health workers.[1]

The prevalence of hepatitis B varies throughout the world. It is categorized into low, medium (2%–5%), and high (5%–10%) endemic areas based upon prevalence.[1] The Mediterranean regions of Europe (including Italy and Spain) are classified as intermediate endemicity while Northern Europe (including France and the United Kingdom) is classified as having a low endemicity. Within Italy, however, there is variation, with the more northern areas having lower prevalence rates.[3] In Spain, the prevalence in some regions is as low as 1.7%, but incidence is higher among people 15 to 24 years of age and those in urban populations of low socioeconomic level.[4] The United Kingdom has approximately 600 hepatitis B infections reported annually, with a 0.37% prevalence of chronic active hepatitis B who are at risk for progression to the more serious sequelae.[5,6] In France, the number of new hepatitis B cases is between 100,000 and 150,000 annually with approximately 1000 CHB-related deaths over a year.[7,8]

Immunization programs have targeted hepatitis B. Since 1995, France has had an immunization program for infants and children and an active program in prevention of hepatitis B infection, which is reflected in its low hepatitis B rate.[7,8] A vaccination program of newborn infants was initiated in Italy in 1992, which resulted in significant decreases in both acute and chronic hepatitis B.[9] Over the last 20 years, the Spanish regions have adopted vaccination programs among newborns and adolescents to the extent that approximately 85% of young people have now been vaccinated. The U.K. vaccination program focuses primarily on healthcare workers.

Public health interventions in France, Italy, and Spain have reduced the burden of CHB on their populations, but immigration from areas with higher endemnicity and individuals with immunodeficiency diseases make hepatitis B a continuing concern. This study focuses on CHB and its

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sequelae: compensated and decompensated cirrhosis, and hepatocellular carcinoma.

The course of hepatitis B infection is highly variable and depends on age of acquiring the infection. Acute hepatitis B is often asymptomatic, although between 15% and 25% of infections are associated with symptoms, of which jaundice is the most common reason for presenting to the healthcare system.[2] Most acute hepatitis B infections are self-limited and trigger an immune response that effectively turns off viral replications. Although these individuals retain quiescent HBV DNA, they are neither infectious to others nor at risk for complications of the infection. However, approximately 6% to 10% of infected adult patients continue to carry active replicating virus and become chronically infected.[1] Patients are defined as having CHB if they have hepatitis B surface antigen in their serum for longer than 6 months. These individuals are at risk for the long-term liver disease complications of CHB.

CHB can be managed with immune-modulating or antiviral drugs. Interferon-α, lamivudine, and adefovir are used in most European countries. New on the market are pegylated interferons, which are also starting to be used in some patients. The treatment goals for CHB are: 1) to stop or reverse the progression of liver disease, thereby preventing subsequent development of cirrhosis; 2) to prevent the development of hepatocellular carcinoma; and 3) to eliminate infectivity and transmission of hepatitis B to others.

Although the time to onset of CHB-induced cirrhosis varies, approximately 20% of those with chronic active hepatitis B for more than 5 years will eventually progress to cirrhosis.[10] Decompensated cirrhosis patients have additional complications of ascites, variceal hemorrhage, or encephalopathy.

Hepatocellular carcinoma frequently occurs in the background of underlying cirrhosis, which can complicate management options.[11] Potential treatments include total surgical resection, local embolization procedures, or liver transplantation. Complete surgical removal of the affected tissue offers the only potential cure.

The purpose of this study was to identify the medical management patterns of CHB patients in France, Italy, Spain, and the United Kingdom and to estimate the costs associated with their management from the perspective of the healthcare payer.

MATERIALS AND METHODS

Patient registries and databases were not available to estimate the resource utilization by CHB patients in these European countries, so a modified Delphi approach was used whereby physicians experienced in managing hepatitis B patients estimate the health care resource consumed.[12] A central questionnaire was prepared in collaboration with a hepatologist to obtain estimates of the usual management of patients already identified as having CHB. CHB liver disease was separated into the following states to gather the management patterns: chronic active hepatitis B, compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma. Information on liver transplant (first year of transplant and subsequent years) was obtained from published sources. Resource use for the initial diagnosis of hepatitis B was not included in this study. The questionnaire requested information on the use of anti-hepatitis B drugs and other medications, physician visits, laboratory tests to monitor disease progress, and procedures and hospital admissions over a year by the specific disease states. The participating physicians were instructed to complete the questionnaire specifically for hepatitis B-infected patients. The questions focused on the incremental resource use attributable to the CHB disease states and excluded resources that may be attributable to co-morbid states, such as human immunodeficiency virus infection. Laboratory tests included those for blood biochemistry (analysis of alanine aminotransferase, aspartate aminotransferase, alkaline phosphate, and bilirubin levels), serology (levels of antibodies to hepatitis B surface, core, and e antigens), viral load, blood cell counts, and clotting time, as well as other general tests such as urinalysis.

Physicians experienced in managing CHB patients were recruited to complete the questionnaire. Only specialists were included: gastroenterologists, internal medicine with specialty in hepatology, and infectious disease specialists. Upon completion of the questionnaire, the physicians were interviewed to discuss their responses. The physicians were paid an honorarium for participating but were not at any time informed of the identity of the sponsoring company.

The responses were collated by country into management patterns for a typical patient at each disease stage. The patterns were returned to the respondents for their review and comment. The final patterns had unit costs assigned using the perspective of the national healthcare provider (direct medical costs) from the relevant country. Indirect productivity costs and out-of-pocket costs to patients with hepatitis B were not estimated. Included costs are direct medical costs only.

French costs for hospital admissions were derived from the Diagnosis Related Groups (DRG) accounting system for the year 1999.[13] This system describes hospitalization costs associated with International Classification of Disease, 10th revision diagnoses and provides full costs (including direct medical costs and overheads) based on a representative national sample of French public hospitals. The daily DRG cost of "alcoholism and cirrhosis" was used in cost calculations for cirrhosis, and "malignant tumor of the liver system" for hepatocellular carcinoma. The Nomenclature Generale des Actes Professionnels tariffs[14] were used for consultation fees and costs of procedures and the Nomenclature des Actes de Biologie Médicale[15] tariffs were used for laboratory tests. Cost of ambulatory drugs were derived from official prices in Dictionnaire Vidal (2001).[16] Costs for liver transplantation were obtained from Fourquet et al.[17]

In Italy, hospital admission costs were derived from the National DRG tariffs[18]; physician and procedure costs from the National Ambulatory tariffs[19] and drug costs from the Ministry of Health drug database (website; *www.sanita.it*). Costs for liver transplantation were obtained from a hospital-based accounting study.[20]

The unit costs for procedures, laboratory tests, physicians, and hospital admissions in Spain were obtained from the SOIKOS healthcare unit cost database. Drug costs were obtained from the national list of pharmaceutical prices (2001).[21] Liver transplantation costs were obtained from a published study by Aranzábal et al in 1995.[22]

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For the United Kingdom, hospital costs were obtained from the National Health Service (NHS) database of the Chartered Institute of Public Finance and Accountancy[23] and physician costs were derived from the Personal Social Services Research Unit publications.[24] Procedure costs were averaged from those obtained from individual hospitals (MEDTAP Unit Cost Database[25]) and from NHS reference costs (2001).[26] Laboratory test costs from the Unit Cost Database were estimated from a national provider of laboratory services. Drug costs were derived from the British National Formulary 2002.[27]

Costs for the year of liver transplantation and the years following transplantation were obtained from authors of a report to the Department of Health entitled "Economic evaluation of the liver transplant program in England and Wales: an assessment of the costs of liver transplantation."[28]

Treatment patterns and subsequent costs of decompensated cirrhosis were calculated using a distribution by type of complication over a year: ascites (62.5%), variceal hemorrhage (27.5%), hepatic encephalopathy (10%), and bacterial peritonitis (12.2%), as reported by Wong et al in 2000.[29]

The costs from the sources above were used with the estimated treatment patterns to determine the cost for each disease state over a 1-year period within the specific country. In addition, the U.K. unit costs were applied to the other countries' resource use to calculate disease state costs when differences in prices for resource units are eliminated. This analysis will help to clarify whether differences in disease state costs are due to management patterns or prices across countries.

RESULTS

Responses to the treatment pattern questionnaires were collected principally from internal medicine specialists in hepatology. There were four respondents in France, six in Spain, nine in Italy, and seven in the United Kingdom. Some clinicians reported that their centers had CHB management protocols that were used in the analysis. All noted that CHB management depended upon the patient's severity of liver disease and complicating factors. The treatment patterns provided are an estimate of average resources used for a typical patient under care.

Treatment Patterns

The average CHB patient in these European countries was managed without antiviral therapy (61%–76%). However, some clinicians and centers managed all of their CHB patients with antiviral therapy, and in some centers antiviral therapy was restricted to those awaiting liver transplantation. For patients managed with anti-hepatitis B therapy, lamivudine and interferon-α were most commonly used. The lamivudine dose was 100 mg/day for a year and interferon-α was most commonly used at 5 million units, three times weekly for 4 to 6 months, except in Spain where this dose was used daily for 16 to 24 weeks. Interferon-α was the most commonly used treatment in Spain while lamivudine was more commonly used in the United Kingdom and France. Italian physicians used a broader range of antivirals (including interferon-β and pegylated interferon-α) but favored lamivudine in combination with interferon-α. For those who received it, antiviral therapy accounted for between 45% and 85% of the total per-patient costs within the disease states of CHB or compensated cirrhosis.

Patients taking anti-hepatitis B therapy were more likely to undergo more laboratory tests (including blood biochemistry and serology) to monitor the impact of the anti-HBV treatment and monitor its potential adverse events. The annual rates of procedures and visits to physicians were similar between those with and without anti- hepatitis B therapy. Individuals with chronic active hepatitis B did not experience hospital admissions related to their hepatitis B at this stage. Anti-hepatitis B drugs were not commonly used in patients who have progressed beyond compensated cirrhosis. An exception to this observation is that those patients awaiting liver transplantation frequently did receive anti- hepatitis B treatment.

The average management patterns by health state and country (Table 1) indicated a spectrum of care. However, the variation between countries was not greater than that observed within each country (data not shown). Following diagnosis, hepatitis B patients are typically managed by specialists, sometimes in coordination with general practitioners. The numerous laboratory tests used for monitoring the disease are not listed individually in the table but are included in cost estimates.

Chronic active hepatitis B patients in the United Kingdom, Italy, and Spain were slightly more likely to have anti-HBV treatment than those in France. Typically, French and Spanish patients were more likely to have liver biopsy at this stage. Patients with compensated cirrhosis in Spain and Italy were more likely to have anti-hepatitis B treatment than those whose disease had not progressed and more than compensated cirrhosis patients in the United Kingdom and France. Once individuals reached the compensated cirrhosis state, nearly all patients were managed exclusively by specialists (generally hepatologists or gastroenterologists) and were more intensively monitored.

Patients with decompensated cirrhosis required more intensive medical care, including physician visits and monitoring tests, consistent with the increased severity of their disease. The majority of decompensated cirrhosis patients were hospitalized for 12 to 20 days per year. Because of this inpatient hospitalization, costs for decompensated cirrhosis were considerably higher than those for compensated cirrhosis. Drug management for the complications of decompensated cirrhosis accounted for 12% to 33% of the total costs for this health state. Ascites was managed with various combinations of salt-poor albumin, spironolactone, and furosemide. Variceal hemorrhage was managed with endoscopy and banding. Drugs included propranolol to prevent recurrence, lansoprazole, and somatostatin. Lactulose was used with hepatic encephalopathy and a variety of cephalosporins were used to manage bacterial peritonitis. Nutritional supplements were used for a varying proportion of decompensated cirrhosis patients across all country settings.

Hepatocellular carcinoma patients had 11 to 30 days annually in hospital in addition to 4 to 8 specialist visits per year. Patients were more commonly hospitalized and for longer in France, while Spain had the fewest estimated number of hospital inpatient days. Chemotherapy use depended upon the physician, the type of center (eg, general or academic hospital) where the patient was managed and the patient's age and

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TABLE 1. Treatment Patterns Across Four European Countries

Test/Procedure	UK		France		Italy		Spain	
	%	No./year	%	No./year	%	No./year	%	No./year
Chronic active								
Antiviral therapy	39		24		37		33	
General practitioner visits per year	34	3.2	100	3.3	10	4	50	1.0
Specialists visits per year	100	2.3	100	2.8	100	6.0	50	1.0
Ultrasound	61	1.6	88	1.3	80	1.5	33	1.0
Liver biopsy	25	1.0	61	1.2	21	1.0	100	1.0
Endoscopy	22	1.0	28	1.0	10	1.0	50	1.00
Compensated cirrhosis								
Antiviral therapy	38		18		48		50	
General practitioner visits per year	24	2.6	100	4.0	10	12	0	0
Specialist visits per year	92	3.2	100	3.4	100	6.2	100	1.8
Ultrasound	75	1.9	100	2.5	100	2	100	1.0
Liver biopsy	26	1.2	9	1	5	1	100	1.0
Endoscopy	36	1.4	94	1	75	1	100	1.0
Decompensated cirrhosis								
Specialist visits per year	100	6	100	7.7	100	8	100	5
General practitioner visits per year	38	6	0	0	20	4	100	3
Ultrasound	80	2.6	100	2.3	100	3	100	2.7
Liver biopsy	24	1	0	0	5	1	0	0
Magnetic resonance imaging or computed tomography	49	1	0	0	60	1	33	1
Endoscopy	44	2.8	100	0.8	70	1	100	1
Hospital days	83	15–18	100	20	100	12–15	100	12
Hepatocellular carcinoma								
Specialist visits per year	100	4.7	100	8.3	100	6	100	4
General practitioner visits per year	52	5.8	100	7.5	23	2.6	0	0
Ultrasound	53	2.2	75	1.5	100	3	100	1
Magnetic resonance imaging or computed tomography	42	1.5	81	2.4	87	2	20	1
Endoscopy	38	2	29	1	42	0.9	100	1
Hospital days	95	8–15	93	10–20	100	15–30	100	7–15

condition but was not routinely employed (between 5% and 10% of patients) in any of the countries. When chemotherapy was used, it was generally epirubicin. Hospice care was provided in some countries depending upon the patient's family circumstances (approximately 50% of U.K. hepatocellular carcinoma patients received hospice care). Nutritional supplements were used for a varying proportion of hepatocellular carcinoma patients depending more upon the individual physician and patient than upon the country (approximately 20% of patients for 1–12 months). The U.K. and French physicians reported more use of nutritional supplements than those from other countries. Medications and nutritional supplements were included in the hospital costs in France.

Treatment Costs

As one might expect, the average yearly cost per patient by liver disease state (Table 2) increased with increasing disease progression and severity. Across countries, the range of annual costs for chronic active hepatitis B was €1093–€3396. These average costs were weighted for the proportion of patients receiving anti-hepatitis B therapy. Spanish treatment patterns used daily doses of interferon that resulted in higher costs for chronic active hepatitis B infection and compensated cirrhosis. Compensated cirrhosis costs were slightly more in most countries, ranging between €1134 and €3997. The average annual patient costs for decompensated cirrhosis were between three and eight times higher than those for compensated cirrhosis, reflecting the increased use of inpatient hospital services and intensity of laboratory tests. The average costs for decompensated cirrhosis ranged from €5,292 to €8,842. Management of hepatocellular carcinoma was also associated with higher costs that ranged between

TABLE 2. Average Annual Costs of Hepatitis B Health States (year 2001 €)

Health State	France	Italy	Spain	UK*
Chronic hepatitis B	1093	1841	3396	1978
Compensated cirrhosis	1134	2148	3997	2208
Decompensated cirrhosis	8842	7262	5292	8821
Hepatocellular carcinoma	9352	6974	3731	9312
Transplantation	84,568	65,516	25,165	47,153
First year post-transplant	9147	25,767	5770	16,157
Post-transplant		11,595		10,085

*£ = 1.51 €.

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€3731 and €9352. The liver transplantation costs were taken from published reports and ranged widely, from €25,165 to €84,568 per annum.

A comparison between the costs of patients with and without anti-hepatitis B drug therapy in the CHB and compensated cirrhosis states are shown in Table 3. Costs for patients with antiviral treatment were between five and 15 times higher than for those not treated with antivirals. The higher costs included the antiviral drug therapy and additional tests for monitoring the patient's status. For those patients who receive anti-hepatitis B therapy, the costs of the drug accounted for between 42% and 90% of total disease state costs. For patients in the CHB and compensated cirrhosis states, interferons were the predominant agents recommended for use in Spain (100% of patients), France (>80% of patients), and Italy (57%–72% of patients). In the United Kingdom, it was recommended for use in 20% and 48% for chronic active and compensated cirrhosis patients, respectively.

When the U.K. unit costs were applied to the resource use for France, Italy, and Spain for treating each of the four disease states, costs generally increased across countries. Table 4 demonstrates that using a constant unit price for goods and services did not eliminate country differences. For example, the annual costs of managing compensated cirrhosis cost €3997 in Spain but rose to €4341 when U.K. prices were applied. The U.K. management pattern for compensated cirrhosis cost €2208, in comparison.

DISCUSSION

This study shows the cost impact of the different states of the disease and the burden of the disease on the healthcare systems of European countries. The perspective taken was that of the national healthcare provider, and the additional costs to the patients for travel or work loss were not included. Following the onset of chronic disease, hepatitis B may progress to severe and costly disease states in terms of lives lost and healthcare resources used. Although vaccination against the disease is available, it is not universally applied and is not of value to patients who have already been infected with the hepatitis B virus. Also, increasing immigration into the European countries may increase the prevalence of hepatitis B infection as well as the potential for new infections.

TABLE 3. Average Annual Cost (year 2001 €) of Patients With and Without Antiviral Therapy

Health State	France	Italy	Spain	UK*
Chronic hepatitis B with drug therapy	3141 67% drug	4513 85% drug	8496 79% drug	3780 53% drug
Chronic hepatitis B without drug therapy	467	286	851	826
Compensated cirrhosis with drug therapy	2760 45% drug	3832 76% drug	7485 90% drug	3980 42% drug
Compensated cirrhosis without drug therapy	781	644	510	1125

*£ = 1.51 €.

TABLE 4. Comparison of Average Annual Costs (year 2001 €) Using Country Unit Costs and UK Unit Costs by Disease State and Country-Specific Resources

	France		Italy		Spain	
Health State	UK	France	UK	Italy	UK	Spain
Chronic hepatitis B	2018	1093	3208	1841	4457	3396
Compensated cirrhosis	2203	1134	4028	2148	4341	3997
Decompensated cirrhosis	9442	8842	12,873	7262	5716	5292
Hepatocellular carcinoma	9439	9352	9360	6974	5300	3731

The management patterns for CHB were collected from physicians experienced in treating the disease, but they may overestimate or underestimate actual resource use. The patterns were not identical across institutions or countries, but the basic approaches were found to be similar. Patients undergoing care regularly consulted physicians and were monitored with laboratory tests. In more advanced disease states, contact with the healthcare system increased. Costs of care increased with the severity of the liver disease state, culminating in the most expensive liver transplantation for a minority of patients who were eligible and for whom suitable organs could be found. In general, hospitalization and inpatient care were more common as disease states worsened, suggesting that effective therapy to arrest or reverse disease progression would be economically beneficial.

In cross-national studies such as this one, it is tempting to compare the treatment costs between countries. Although care was taken to estimate costs according to individual resource items, it is difficult to use identical costing methods across resources or countries. Variation in the inclusion/exclusion of overheads such as rent, staff benefits, heating, and lighting will exaggerate differences in actual costs. Country tariffs or fee schedules that may not reflect the actual costs have been used for some resources since they represent the best available estimates. Differences in treatment patterns also exaggerate differences in costs, such as the preference for interferon use in Spain compared with other countries. The within-country relationship between disease states in terms of resources and costs is consistent, with more severe states costing more, although the magnitude of cost differences between disease stages varies across countries.

Examining the use of a single price per resource unit for all the countries did not eliminate the variation in disease state costs. Unit price variation between countries appeared not to explain the overall differences in disease costs. Genuine treatment differences both between countries and between centers account for the differences in costs.

This study indicates that the cost of CHB is variable both within and between European countries. The association of disease progression with increased cost of disease management suggests that measures to prevent or delay its progression would be economically beneficial. However, cost data by themselves cannot resolve questions of health policy. The differences in treatment patterns and costs between countries, as identified in this study, may also lead to different health outcomes for patients. Data on these outcomes are an essential complement to the cost information if the cost-effectiveness of

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different management strategies and treatment options is to be estimated. The information presented here support the first phase of economic analyses required for each country to produce informed decisions regarding management of CHB.

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REFERENCES

1. World Health Organization. Available at: http://www.who.int/vaccines-diseases/diseases/hepatitis_b.shtml. Accessed June 4, 2004.
2. Centers of Disease Control and Prevention. Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/b/fact.htm. Accessed June 4, 2004.
3. Bonanni P, Pesavento G, Bechini A, et al. Impact of universal vaccination programmes on the epidemiology of hepatitis B: 10 years of experience in Italy. *Vaccine*. 2003;21:685–691.
4. Sola R, Cruz De Castro E, Hombrados M, et al. Prevalencia de virus de la hepatitis B y C en diferentes comarcas de Cataluña, España: estudio transversal [in Spanish]. *Med Clin (Barc)*. 2002;119:90–95.
5. Communicable Disease Surveillance Centre (CDSD). Surveillance of viral infections in donated blood: England and Wales, 1996. Communicable Disease Report Weekly 1997;7:258. *J Health Protection Agency.* Available at: http://www.hpa.org.uk/cdr/CDR97/cdr2997.pdf. Accessed June 4, 2004.
6. Gay NJ, Hesketh LM, Osborne KP, et al. The prevalence of hepatitis B infection in adults in England and Wales. Epidemiol Infect. 1999; 122:133–138.
7. Brissot P, Boucher E. Epidémiologie et histoire naturelle de l'hépatite virale B hors mutations [in French]. *J Actualité Hépato-gastroentérol* 1999. Available at: http://www.bmlweb.org/glaxo996.html. Accessed June 4, 2004.
8. Institut de Veille Sanitaire. *Epidemiologie de l'hépatite B en France* [in French]. 2002.
9. Da Villa G, Sepe A. Immunization programme against hepatitis B virus infection in Italy: cost-effectiveness. *Vaccine*. 1999;17:1734–1738.
10. Fattovich G, Brollo L, Giustina G, et al. Natural history and prognostic factors for chronic hepatits type B. *Gut*. 1991;32:294–298.
11. Fong Y, Kemeny N, Lawrence TA. Cancer of the liver and biliary tree. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1162.
12. Evans C. The use of consensus methods and expert panels in pharmacoeconomic studies: pPractical applications and methodological shortcomings. *Pharmacoeconomics*. 1997;12:121–129.
13. Programme de Médicalisation du Système d' Information hospitalier. Direction des Hôpitaux, Paris, 1999. Coûts de référence du secteur public [in French]. Echelle 2000. Available at: http://www.le-pmsi.fr/. (French). Accessed June 4, 2004.
14. Union des Caisses Nationales de Sécurité Sociales. *Nomenclature Générale des Actes professionnels* [in French]. Paris, 2001.
15. Union des Caisses Nationales de Sécurité Sociales. *Nomenclature des Actes de Biologie Médicale* [in French]. Paris, 2001. (French).
16. Vidal. ed. Dictionnaire Vidal. 2001 *Thesaurus Vidal, Le Dictionnaire* [in French]. Paris: French & European, 2001.
17. Fourquet F, Le Gales C, Rufat P, et al. L'évaluation medico-économique des greffes d'organe en France: l'exemple de la transplantation hépatique. *Rev Epidemiol Sante Publique.* 2001;49:259-272.
18. Ministero della Sanità. Aggiornamento delle tariffe delle prestazioni di assistenza ospedaliera (National Hospital DRG Tariff List). DM 14.12. 1994; DM 30.6.97 SO GU n° 209, 8.9.1997. http://www.cgil.it/medicimilano/leggi/lex97/Dm30697a.htm; http://www.cgil.it/medicimilano/leggi/lex97/Dm30697b.htm.
19. Ministero della Sanità. Nomenclatore Tariffario delle prestazioni ambulatoriali (National Ambulatory Outpatient Tariff). DM 22.7.96; GU n° 216, 14.9.96. http://www.ministerosalute.it/programmazione/normative/seznormativa-jsp?label-tar.
20. Tumiatti C, Bezzon C, Guasti F, et al. Azienda Ospedaliera di Padova. Il costo del trapianto d'organo. Risultati di uno studio condotto presso l'Azienda Ospedaliera di Padova [in Italian]. Fondazione Smith Kline, Padova 1999; A study by a 'company hospital worker of padova.' Available at: http://www.fondazionesmithkline.it/tendenze/0201/T-1-20009-4.doc. Accessed June 4, 2004.
21. *Catálogo de especialidades farmacéuticas: consejo general de colegios oficiales de farmacéuticos* [in Spanish]. 2001. http://www.vademecum.medicom.es.
22. Aranzábal J, Urigüen A, Darpón J. *Coste económico del transplante de órganos*: *Osakidetza-Servicio Vasco de salud* [in Spanish]. 1995.
23. Chartered Institute of Public Finance and Accountancy (CIPFA). *The Health Service Database 2001* (*Financial Year 2000-2001*). Croydon: Institute of Public Finance Limited, 2001.
24. Netten A, Dennett J. eds. *Unit Costs of Health and Social Care 2001*. Personal Social Services Research Unit, University of Kent at Canterbury, 2001.
25. Unit Cost Database MEDTAP. 2002. Available at: http://www.medtap.com/products/unitcost.cfm. Accessed June 4, 2004.
26. NHS reference costs. Available at: http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en. Accessed June 4, 2004.
27. British Medical Association. *British Medical Formulary.* British Medical Association, 2001.
28. Longworth L, Young T, Ratcliffe J. (on behalf of CELT). Economic evaluation of the liver transplant programme in England and Wales: an assessment of the costs of liver transplantation. Department of Health Report, 2001. Available at: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4005344&chk=51aLUA. Accessed June 4, 2004.
29. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. *Ann Intern Med*. 2000;133:665–676.

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