Treatment of Chronic Hepatitis C in Young Children Reduces Adverse Outcomes and Is Cost-Effective Compared with Deferring Treatment to Adulthood

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Objective To evaluate the cost-effectiveness of treating young children with chronic hepatitis C virus (HCV) with new direct-acting antivirals.

Study design A state-transition model of chronic HCV was developed to conduct a cost-effectiveness analysis comparing treatment at age 6 years vs delaying treatment until age 18 years. Model inputs were derived from recently conducted systematic reviews, published literature, and government statistics. Medical care costs were obtained from linked population level laboratory and administrative data (Ontario, Canada). Outcomes are expressed in expected quality-adjusted life-years and costs (CAD$). Analysis included a base-case to estimate the expected value and one-way and probabilistic sensitivity analyses to evaluate the impact of uncertainty of the model inputs.

Results After 20 years, treating 10 000 children early would prevent 330 cases of cirrhosis, 18 cases of hepatocellular carcinoma, and 48 liver-related deaths. The incremental cost-effectiveness ratio of early treatment compared to delayed treatment was approximately $12 690/quality-adjusted life-years gained and considered cost-effective. Model results were robust to variation in fibrosis progression rates, disease state-based costs, treatment costs, and utilities.

Conclusions Delaying treatment until age 18 years results in an increased lifetime risk of late-stage liver complications. Early treatment in children is cost effective. Our work supports clinical and health policies that broaden HCV treatment access to young children. *(J Pediatr 2021;230:38-45)*.

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Chronic hepatitis C virus (HCV) infection is a major global health concern, with an estimated 71 million infected persons worldwide. Children may acquire the infection by transmission from mother to infant around the time of birth.[1,2] The global prevalence of HCV in the pediatric population is estimated at 0.13%, including 0.03% in Canada, 0.06% in the US, 0.04% in Western Europe, and 0.4% in Eastern Europe.[3]

Chronic HCV in children is usually asymptomatic and cirrhosis rarely develops before 18 years of age.[4-7] However, HCV infection is associated with impaired quality of life for children and their families, who must live with the stigma of this infectious disease.[8,9] The availability of highly effective direct-acting antiviral (DAA) therapies now provides an opportunity to ameliorate the impact of chronic HCV on the health and quality of life of affected children and their families. These new therapies also may reduce future transmission of the virus. Any comprehensive global strategy to tackle the elimination of HCV must, therefore, also target children and should aim to treat children before they can pass the virus on to others, especially through high-risk behaviors in adolescence and early adulthood.

These DAAs, however, are expensive and their use in children, particularly young children, may be delayed by discussions of affordability that require cost-effectiveness evidence. The aim of this study was to evaluate, from a societal perspective, the value of treating very young children with chronic HCV with new DAA therapy.

CAD$	Canadian dollars	LDV	Ledipasvir
DAA	Direct-acting antiviral	ODB	Ontario Drug Benefit
GLE	Glecaprevir	OHIP	Ontario Health Insurance Plan
HCC	Hepatocellular carcinoma	PIB	Pibrentasvir
HCV	Hepatitis C virus	QALY	Quality adjusted life-year
ICER	Incremental cost-effectiveness ratio	SOF	Sofosbuvir
ICES	Institute for Clinical and Evaluative Studies	SVR	Sustained virologic response

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Methods

A state-transition model of chronic HCV mono-infection (genotype 1) was constructed to conduct a cost-effectiveness analysis comparing our two treatment strategies.

Cohort

The cohort of children considered for the baseline analysis had a mean age of 6 years and was assumed to have vertically acquired HCV genotype 1 mono-infection with no comorbidities. Fibrosis stage was categorized according to the

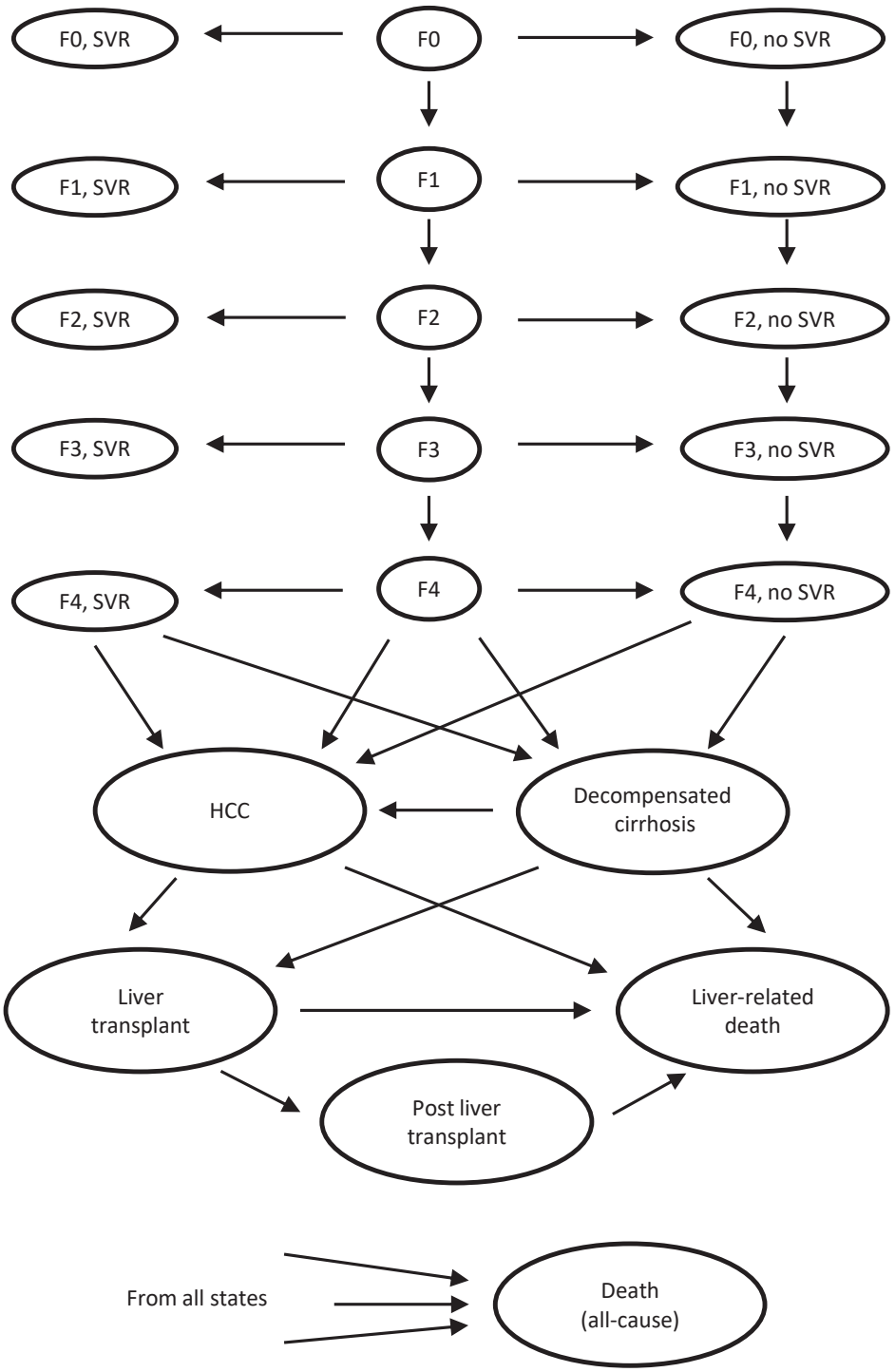

Figure 1. State-transition model for chronic HCV.

Table I. Cohort characteristics, model inputs, and assumptions

Cohort characteristics				References
Starting condition	Chronic HCV, genotype 1, fibrosis stage F0			
Starting age	6 y			
Cycle length	1 mo			
Annual discount	1.5%			
Treatment uptake	100%			Assumption
	Base estimate	**Lower limit (95% CI)**	**Upper limit (95% CI)**	**References**
Probability of SVR				
SOF/LDV (12 wk)	0.99	0.94	1.0	18
GLE/PIB (8 wk)	1.0	0.924	1.0	19
Annual probability for fibrosis progression				
F0-F1	0.201	0.074	0.550	10
F1-F2	0.087	0.015	0.506	10
F2-F3	0.096	0.107	0.125	10
F3-F4	0.055	0.028	0.585	10
Annual probability for cirrhosis progression				
F4—decompensated cirrhosis (non-SVR)	0.035	0.027	0.043	11
F4—decompensated cirrhosis (SVR)	0.002	0.0001	0.005	11
F4—HCC (non-SVR)	0.024	0.018	0.031	11
F4—HCC (SVR)	0.005	0.001	0.009	11
Annual probability of liver transplantation				
From decompensated cirrhosis	0.033	0.017	0.049	12
From HCC	0.033	0.017	0.049	12
Mortality (chronic HCV-related)				
HCC	0.411	0.31	0.51	14
Decompensated cirrhosis	0.216	0.162	0.27	13
Liver transplant (first year)	0.143	0.124	0.159	15
Liver transplant (>1 y)	0.034	0.024	0.043	15
Utility for chronic HCV infection-related health states				
F0-F3	0.806	0.767	0.845	16
Compensated cirrhosis (F4)	0.726	0.680	0.772	16
Decompensated cirrhosis	0.657	0.602	0.711	16
HCC	0.717	0.647	0.788	16
Liver transplant	0.712	0.657	0.767	16
HCV cured (no cirrhosis and RNA negative)	0.841	0.801	0.880	16
30-d disease state-based costs (CAD)				
No cirrhosis and RNA positive (total cost – ODB)				Unpublished data
Total cost	386.36	264.26	508.47	
ODB	78.32	44.83	111.82	
No cirrhosis and RNA negative (total 30-day cost – ODB)				Unpublished data
Total cost	677.41	213	1141.37	
ODB	236.5	15.78	457.22	
Compensated cirrhosis (F4)	1487.23	1375.47	1598.99	17
Decompensated cirrhosis	3659.15	3279.4	4038.89	17
HCC	4238.12	3480.33	4995.91	17
Liver transplantation	4539.32	3745.86	5332.78	17
Treatment cost (CAD)				
SOF/LDV (12 wk)	$46 900			Assumption
GLE/PIB (8 wk)	$46 900			Assumption

METAVIR scoring system in which fibrosis score is assessed histologically on a 5-point scale as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. All cohort members entered the model with a METAVIR fibrosis stage of F0, F1, or F2 and were assumed to be treatment-naive.

Strategies

The goal of HCV treatment is an undetectable serum level of HCV RNA 12 weeks after completion of therapy, also termed a sustained virologic response (SVR). For the base case analysis, the treatment regimen evaluated was combination therapy with sofosbuvir and ledipasvir (SOF/LDV) for 12 weeks.

All patients entered the state-transition model at age 6 years and the treatment strategies compared were treatment at age 6 years (early treatment) vs deferring treatment until age 18 years (deferred treatment). Treatment uptake and completion were assumed to be 100%. Scenario analyses were conducted using combination therapy with glecaprevir and pibrentasvir (GLE/PIB) as a pan-genotypic option.

Decision Model

We developed a state-transition model of chronic HCV mono-infection using TreeAge Pro 2018 software (TreeAge Software, Inc, Williamstown, Massachusetts). Cohort members move between predefined health states in weekly cycles until death (lifetime horizon). The predefined health states and permitted transitions between these health states are illustrated in Figure 1. In both treatment arms, only 1 course of DAA therapy is offered. The model assumed no spontaneous remission.

Model Parameters and Inputs

Cohort characteristics, model inputs and assumptions used to inform our model are summarized in Table I.[10-19]

Disease-Progression Rates. Fibrosis progression rates from fibrosis stages F0 through to F4, specific to patients infected as children, were derived from a recently conducted systematic review.[4,10,20] Probabilities for transition from F4 to decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation were taken from the published literature.[11,12]

Mortality. All-cause mortality probabilities were obtained from publicly available government statistics.[21] It was assumed that mortality risk for patients with SVR was the same as all-cause mortality for the general population, considering the very low prevalence of advanced fibrosis or cirrhosis among cohorts of children with HCV infection.[21] We took from the published literature the probabilities of liver-related death for patients in the decompensated cirrhosis,[13] HCC,[14] and liver transplantation states.[15]

Utilities. Utilities are numerical values (on a scale from 0 to 1) that reflect how an individual or the society *values* or *feels* about a state of health.[22] Health states utilities (EQ5D-5L) for HCV were derived from a recently conducted systematic review.[16] This systematic review did not identify pediatric utilities for HCV and, as such, adult utilities from the study were used.

Disease State–Based Medical Costs. Medical care costs based on disease states for adults infected with HCV were obtained from a recently conducted population-based retrospective analysis of administrative health data held at the Institute for Clinical and Evaluative Studies (ICES) in Ontario, Canada.[17] An additional subanalysis using the same data was conducted for children. The analysis used a health-state approach combined with natural history data to estimate the longitudinal costs related to HCV.

Patients with chronic HCV infection were identified based on HCV antibody and HCV RNA test results documented in the Public Health Ontario Laboratory database between January 1, 2003, and December 30, 2014. Patients with a confirmed diagnosis of chronic HCV were then linked to the administrative databases held at ICES. Exclusion criteria included lack of a valid Ontario Health Insurance Plan (OHIP) health card number or age older than 105 years at the time of cohort entry, missing age or sex data, and/or co-infection with HIV or hepatitis B virus.

Patients were allocated to 9 mutually exclusive, exhaustive health states from the time of HCV diagnosis until the end of the follow-up period. Health state definitions were derived from diagnostic, procedure, and death codes in the administrative data, using validated algorithms.[23] These health states included no cirrhosis and RNA positive, no cirrhosis and RNA negative (ie, cured HCV), compensated cirrhosis, decompensated cirrhosis, HCC, both HCC and decompensated cirrhosis, liver transplantation, and 2 health states that included up to 6 months before death (terminal liver-related and terminal non-liver-related). Once allocated to a health state, the individual remained in that state until they met the criteria for entry into another health state or until the end of follow-up. Individuals were followed from the time of cohort entry until December 30, 2016, or until loss of OHIP eligibility, age 106 years or death, whichever occurred first.

All costs paid for by the Ontario Ministry of Health and Long-term Care were included whereas costs borne by patients/families or private insurers were excluded. All costs were adjusted for inflation to 2018 Canadian dollars (CAD$) using the Statistics Canada Consumer Price Index for health care and personal items for Ontario.[24] Data on patient demographics and resource use were obtained from the administrative databases held at ICES.[25] These databases included OHIP physician claims database, Canadian Institute for Health Information Discharge Abstract Database, Canadian Institute for Health Information National Ambulatory Care Reporting System database, Ontario Drug Benefit (ODB) program data, Ontario Home Care Database, Continuing Care Reporting System, Ontario Cancer Registry, Ontario Registered Persons Database, and Canada census data. The databases were linked using unique identifiers and the data was analyzed at ICES. Direct medical costs per 30-day period were then calculated for each health state, based on the time spent and the resources used while in each health state.

Within the model, pediatric disease state-based costs were used for fibrosis stages F0-F3. After transition to fibrosis stage 4 (F4) or the development of late-stage liver complications (decompensated cirrhosis, HCC, or liver transplantation) adult cost data were used, as these stages occur almost exclusively among adults.

Outpatient prescription drug costs were recorded in the ODB database. We were, however, unable to break this down further into drugs used to treat HCV vs other drugs. For both adult and pediatric cohorts in the early stages of disease (fibrosis stages F0-F3) this ODB cost was significantly greater for patients who had achieved SVR. It was thus assumed that for these early stages of disease, this greater cost was, at least in part, attributable to drugs used to treat HCV (likely interferon-based therapy given the

Table II. Comparison of clinical outcomes–base case analysis

Treatment strategies		Cirrhosis 20 years	HCC 20 years	Liver related death 20 years
Early treatment (SOF/LDV)	% of cohort	0.1%	0.015%	0.02%
	Cases per 10 000 patients	~10	~2	~2
Deferred treatment (SOF/LDV)	% of cohort	3.4%	0.2%	0.45%
	Cases per 10 000 patients	~340	~20	~45

time period of the study). So as not to duplicate the cost of HCV therapy in our model, we therefore subtracted this ODB cost from the total disease-state cost for patients in fibrosis stages F0-F3. This was not done for patients who had transitioned to fibrosis stage 4 (F4) or those who had developed late-stage liver complications (decompensated cirrhosis, HCC, or liver transplantation), as ODB costs for these patients were more likely to also include the cost of drugs not used to treat HCV.

Treatment Costs. Costs for DAA treatment of HCV were based on wholesale acquisition estimates. All cost data are expressed in 2018 CAD$. A drug cost agreement was finalized in 2017 by the pan-Canadian Pharmaceutical Alliance, which negotiated drug costs for HCV treatment on behalf of the several Canadian Provincial and Federal drug plans.[26] The exact negotiated prices remained confidential and ranged between CAD$45 000 and CAD$100 000 at that time. Base case DAA treatment cost included in this analysis is a best estimate based on all available information since this negotiation occurred.

Treatment Efficacy and Safety. Efficacy of treatment was assumed based on SVR achieved in the relevant published pediatric clinical trials. Based on evidence from these published trials, treatment regimens also were assumed to be safe with no significant adverse effects.[18,19,27]

Economic Assumptions

The analysis was conducted from the perspective of a provincial Ministry of Health in Canada. Costs are expressed in 2018 Canadian dollars. Outcomes are expressed in expected quality adjusted life-years (QALYs) and costs (CAD$). Future costs and health benefits were discounted at 1.5% annually. The threshold of cost-effectiveness was $50 000 per QALY.[28]

Analyses

Analyses included validation of the model against other published models, base-case analysis to estimate the expected value using deterministic calculations, and one-way and probabilistic sensitivity analyses to evaluate the impact of the uncertainty of the model inputs.

Results

Base-Case Analysis

Clinical Outcomes. Table II outlines the key clinical outcomes of our model. After 20 years, 0.1% of the cohort in the early treatment arm (those treated at age 6 years) developed cirrhosis and 0.02% died with a diagnosis of decompensated cirrhosis or HCC compared with 3.4% and 0.45% respectively, in the deferred treatment arm (those treated at age 18 years). That is, after 20 years, treating 10 000 children early would prevent an additional 330 cases of cirrhosis, 18 cases of HCC, and 43 liver-related deaths. This results in a gain in quality-adjusted life expectancy of O.63 QALYs (approximately 8 months).

Economic Outcomes. Table III summarizes the results of our base case analysis, comparing costs and outcomes associated with early treatment at age 6 years and deferred treatment at age 18 years with SOF/LDV for genotype 1 HCV monoinfection, as well as the results of our scenario analysis for GLE/PIB. We found that early treatment with SOF/LDV results in an additional cost of $7975 (later treatment costs are discounted). There was a net increase in cost over the life expectancy of each child treated because the additional cost of early treatment was not completely offset by the cost savings associated with prevention of late stage disease. The incremental cost-effectiveness ratio (ICER) of early treatment compared with deferred treatment was $12 687/QALY gained. This is considered cost effective under a $50 000/QALY gained threshold of cost-effectiveness. Under other commonly cited thresholds of $100 000 to $150 000 per QALY, early treatment represents even greater value for money.

Sensitivity and Scenario Analyses

In our sensitivity analyses (**Table IV**; available at www.jpeds.com), we varied model parameters by 20% and found that model results were robust to these changes in fibrosis progression rates, disease state-based costs, treatment costs, and utilities. Model results varied most with variations in utilities but even with these variations the ICER remained below the $50 000/QALY threshold of cost-effectiveness.

Table III. Outcomes and cost-effectiveness of early vs deferred treatment

Treatment strategies	Cost	Incremental cost	QALYs	Incremental QALYs	ICER
Base case analysis (SOF/LDV)					
Treat age 18 y (deferred treatment)	$46 846		37.05		
Treat age 6 y (early treatment)	$54 821	$7975	37.68	0.63	$12 687
Scenario analysis (GLE/PIB)					
Treat age 18 y (deferred treatment)	$46 826		37.14		
Treat age 6 y (early treatment)	$54 802	$7976	37.77	0.63	$12 563

At a cost effectiveness threshold of $50 000/QALY the probability that early treatment is cost-effective is 80% (**Figure 2**; available at www.jpeds.com). **Figure 3** (available at www.jpeds.com) illustrates the incremental cost-effectiveness scatterplot.

Table V (available at www.jpeds.com) summarizes our scenario analyses. Treating children earlier (at age 3 years) produced largely similar results with an additional cost of $7943 and 0.64 QALYs per person, resulting in an ICER of $12 497/QALY gained compared to deferring treatment to age 18 years.

If SOF/LVD and GLE/PIB are equivalent in terms of cost, treating early (at age 6 years) with GLE/PIB is similarly cost-effective with an additional $7976 and 0.63 QALYs per person and an ICER of $12 563/QALY gained compared with deferring treatment to age 18 years.

If, as a possible "worst case" scenario, we assume 40% loss to follow-up in the deferred treatment arm, QALYs gained per person increases significantly to 3.8 (**Table V**).[19] The ICER of early treatment compared with deferred treatment falls to $5926/QALY. Thus, loss to follow-up in the deferred treatment arm makes early treatment even more cost-effective as compared with the base case.

In anticipation of lower DAA costs in the future, we also conducted a scenario analysis in which the cost of treating at 18 years of age is cheaper than the cost of treating at age 6 years due to drug price reductions in the intervening 12 years. Deferred treatment would be the more cost-effective option, at a $50 000/QALY threshold, if DAA costs were reduced by 61% in 12 years.

Discussion

As regulatory authorities around the world move toward approvals for the use of DAAs in children as young as 3 years, health plans and healthcare systems concerned about costs will require cost-effectiveness evidence when considering coverage for the treatment of HCV in young children. We have highlighted the significant clinical consequences of delaying treatment by 12 years. Our model shows that, after 20 years, treating 10 000 children at age 6 years vs deferring treatment until age 18 years would prevent an additional 330 cases of cirrhosis, 18 cases of HCC, and 43 liver-related deaths. In our base-case analysis, we found that early treatment with SOF/LDV at age 6 years is cost effective compared with later treatment at age 18 years, with an additional $7975 and 0.63 QALYs per person and an ICER of $12 687/QALY gained. In our scenario analysis, we found that early treatment with GLE/PIB and treating as early as age 3 years were also cost-effective.

A 2019 study by Nguyen et al[29] evaluated the cost-effectiveness of treating adolescents at age 12 years vs deferring treatment until age 18 years. They also found that early treatment was more cost-effective than deferred treatment. Some of the major strengths of our model lie in the quality of the data inputs. In our model, fibrosis progression rates were obtained from a recently conducted systematic review of the world literature describing HCV prognosis.[10] In contrast to the study by Nguyen et al, we have incorporated fibrosis progression rates specific to patients infected with HCV as children to more accurately simulate the natural history of HCV in this population. Also, in contrast to the study by Nguyen et al, our model incorporates high quality, longitudinal, contemporary cost data specific to children in the early stages of disease.

Our model includes several assumptions and has some limitations. First, our model does not prioritize patients for treatment based on fibrosis stage. We chose to model in this way for a few reasons, including that the likelihood of advanced liver fibrosis is minimal at age 6 years; that current guidelines for the management of children and adults with HCV recommend treatment regardless of fibrosis stage once an acceptable treatment regimen is available[30]; and that adult literature supports the cost-effectiveness of treating all patients with HCV regardless of fibrosis stage.[31] Hence our assumption that all patients, at age 6 years or age 18 years, would be treated regardless of fibrosis stage.

In addition, the fibrosis progression probabilities used in our model were adjusted for age but no other individual characteristics. There are few data available describing fibrosis progression rates in different subsets of children infected with HCV. The systematic review from which the transition probabilities for our model were obtained,[10] specifies only that the included studies refer to patients who were infected as children. Characteristics that influence fibrosis progression rates identified in adult groups in that systematic review included HCV genotype, source of infection, and comorbidities (such as kidney transplant, dialysis, and intravenous drug use). These characteristics are either uniform in a young pediatric population and/or were accounted for in our model. For example, we fixed HCV genotype as genotype 1, we modeled a group of children with no comorbidities, and the source of infection is mostly vertical in young children. Recognizing that there are limitations in the available data for determinants of fibrosis progression rates in children, we tested fibrosis progression probabilities in our sensitivity analyses.

Our base-case analysis assumed that patients who are successfully treated have no further progression of liver damage. The model also assumes that patients who achieve SVR have no risk of reinfection with HCV, which may over-estimate cost-effectiveness. However, the risk of reinfection after age 18 years would be the same in both treatment arms and so for reinfection to have an unbalanced impact on our model, children treated at age 6 years would have to be reinfected before age 18 years. Although a small subgroup of children who contracted HCV vertically will be at risk of reinfection during childhood due to high risk behaviors or healthcare practices when visiting other countries, we believe the risk of reinfection overall in the whole group is unlikely to be higher than the very low risk in the general population of 12- to 18-year-olds.

The model does not incorporate the impact of the potential reduction in transmission of HCV to others as a consequence of successful therapy and therefore underestimates the economic benefit of treatment to the wider society.

It is assumed in our model that each patient is offered treatment only once. We do not consider the possibility of additional therapy for those who do not achieve SVR. This would of course add to the cost of treatment for those

patients, but this group constitutes only 0-2% of patients included in the pediatric treatment trials.[18,19,27]

Our model assumed 100% treatment uptake in both arms. We believe that 6-year-old children are more likely to be adherent to treatment under the supervision of parents/guardians, compared with young adults at age 18 years, among whom poor compliance with medical recommendations is known to be common. Young children also represent a captive audience, as they interface routinely with healthcare services on a regular basis (for well-child visits, vaccinations, etc). At age 18 years, the cost of treatment will likely be lower but by this time a significant proportion of the cohort may be lost to follow-up or may not be interested in treatment and, thus, may miss the opportunity for treatment altogether. This underscores the importance of treating children early. In our scenario analyses, we found that early treatment remains cost-effective even with 40% loss to follow-up for those waiting for deferred treatment at age 18 years. In this scenario, the incremental cost of early treatment compared to deferred treatment is greater than in our base case analysis as patients lost to follow-up do not incur the cost of HCV treatment. Nonadherence also was explored in our scenario analyses. These patients would incur the cost of treatment without the benefit of cure. In such a scenario early treatment becomes much more cost-effective.

Utilities used in the model are adult utilities, as there are no published utilities for children with HCV. However, we show that treatment remains cost effective even with significant changes in utilities.

Finally, our base case model did not consider the likely decrease in drug costs over time. To address this, we conducted a scenario analysis where we reduced future treatment costs and found that if DAA costs fell by 60% over 12 years, deferred treatment would be the more cost-effective option.

In summary, delaying treatment of HCV among children until age 18 years results in an unacceptably increased lifetime risk of late-stage liver complications. Early treatment in children 6 years old is cost effective using conventional cost effectiveness thresholds. These results therefore support clinical and health policies that broaden treatment access for HCV infection to very young children, which is essential to achieve the global elimination of HCV. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Diagnosing the Etiology of Childhood Diarrhea by Clinical Features: An Update

Nelson JD, Haltalin KC. Accuracy of diagnosis of bacterial diarrheal disease by clinical features. J Pediatr 1971;78:519-22.

Diarrhea continues to be a preventable cause of childhood morbidity and mortality. An accurate assessment and identification of the potential pathogen is required for appropriate management and prevention of mortality. Fifty years ago, Nelson et al studied the consistency of clinical features of diarrhea in determining the probable etiology so as to dictate the need for culture or prescribing antibiotics. They concluded that correct assessment can be made on the basis of history and examination with approximately 70% reliability.

Over the last 2 decades, the global incidence of diarrheal episodes among children younger than 5 years has declined and the number of deaths reduced by 60%.[1] However, diarrheal disease still remains the second-leading cause of mortality among children younger than 5 years and the leading cause of malnutrition. It is crucial to determine the underlying pathogen accurately and timely for adequate treatment and prevention of deaths. Available conventional diagnostic methods include stool culture, microscopy, and antigen-based modalities, but these are time-consuming, less sensitive, and are not available for all relevant pathogens. Stool culture reports are available after 48-72 hours of sample collection, and by this time, the diarrheal episode is already improved, with or without any specific antimicrobial therapy. Moreover, an etiological agent cannot be identified in 40% cases of diarrhea.[2] A good history and detailed physical examination remain the key foundation in the diagnostic evaluation of diarrhea. Low-grade fever and acute, watery, non-bloody diarrhea typically indicate viral pathogen, whereas high-grade fever (>104°F) indicates severe bacterial etiology. Nucleic acid amplification from stool samples can offer rapid diagnosis, but it is expensive and requires sophisticated equipment. Specific diagnostic evaluation is currently not recommended routinely in all cases of diarrhea in children. Diagnostic effort is warranted only in cases of outbreaks, bloody diarrhea, and in children with underlying chronic diseases and immunodeficient states. Hence, accurate clinical assessment by the treating physician still remains the mainstay for management decisions.

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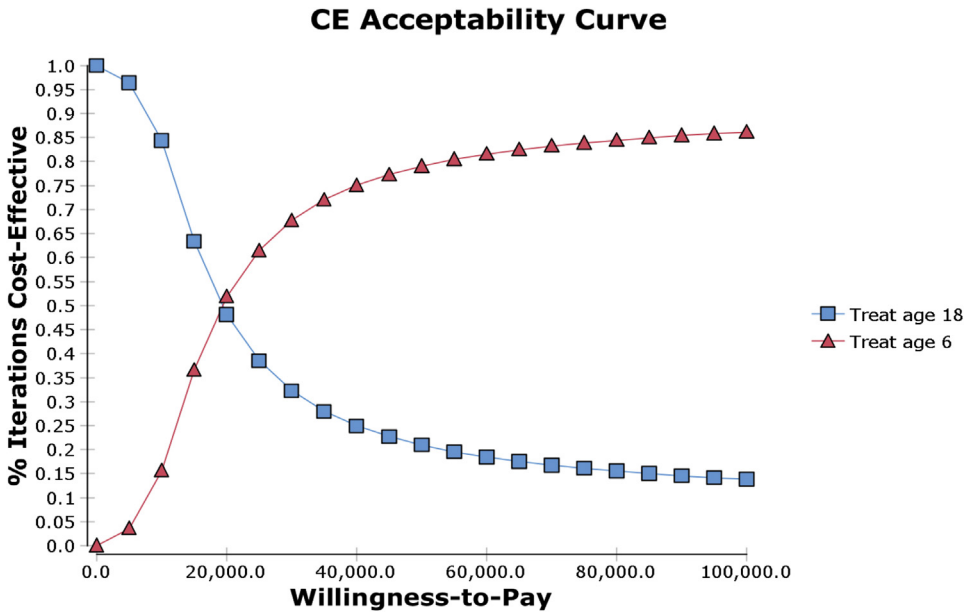

Figure 2. Cost-effectiveness acceptability curve. *CE*, cost-effectiveness.

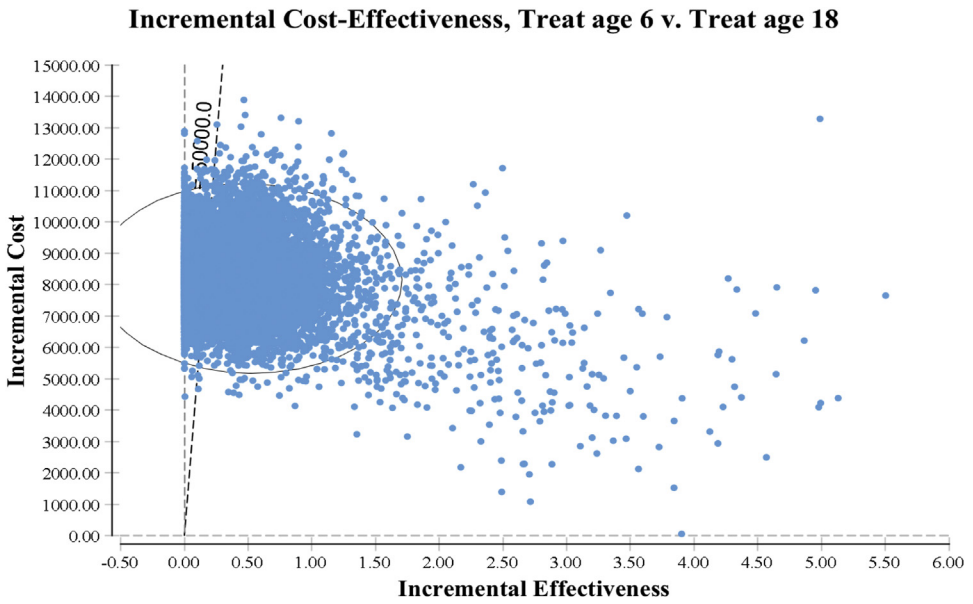

Figure 3. Incremental cost-effectiveness scatter plot.

Table IV. Sensitivity analyses of ICERs for combined SOF/LDV treatment

Inputs	Base case (range*)	ICER ($/QALY) Lower limit	ICER ($/QALY) Upper limit
Probability of SVR	0.99 (0.8-1.0)	12 563	15 649
Fibrosis progression			
F0-F1	0.201 (0.161-0.241)	12 009	13 555
F1-F2	0.087 (0.07-0.104)	11 852	13 706
F2-F3	0.096 (0.077-0.115)	11 858	13 705
F3-F4	0.055 (0.044-0.066)	11 772	13 791
Utilities			
F0 – F3	0.806 (0.645-0.967)	3275	19 652
F4 (compensated cirrhosis)	0.726 (0.581-0.871)	10 249	14 598
HCV cure (RNA negative, no cirrhosis)	0.841 (0.673-1.0)	3163	37 639
Treatment cost			
SOF/LDV for 12 wk	$46 900 ($37 520-$56 280)	10 193	15 181
SOF/LDV for 12 wk			
Varied by 30%	$46 900 ($32 830-$60 970)	8947	16 428
Increased by 400%	$187 000		49 934
Increased by 430%	$200 000		53 390
Disease state-based costs			
No cirrhosis and RNA positive (*t*otal		12 273	13 101
30-day cost – ODB)			
Total cost	386.36 (309.09-463.63)		
ODB	78.32 (62.6-93.98)		
No cirrhosis and RNA negative (total		12 028	13 346
30-day cost – ODB)			
Total cost	677.41 (541.93-812.89)		
ODB	236.5 (189.2-283.8)		

Table V. Summary of scenario analyses

	Analyses	Comparator	Cost ($)	Total QALYs	ICER ($/QALY)
	Base case	Deferred treatment (age 18 y)	46 846	37.05	
		Early treatment (age 6 y)	54 821	37.68	12 687
1	Earlier treatment - at age 3 y	Deferred treatment (age 18 y)	47 040	37.84	
		Early treatment (age 3 y)	54 983	38.48	12 497
2	Treatment with GLE/PIB[19]	Deferred treatment (age 18 y)	46 826	37.14	
		Early treatment (age 6 y)	54 802	37.77	12 563
3	Treatment with SOF/LDV – ∼60% cheaper in 12 y	Deferred treatment (age 18 y)	28 359	37.05	
		Early treatment (age 3 y)	54 821	37.68	50 054
4	Disease state-based costs (ODB included) – adult costs only[17]	Deferred treatment (age 18 y)	51 805	37.05	
		Early treatment (age 6 y)	58 744	37.68	11 039
5	Disease state-based costs (ODB excluded for fibrosis stages F0-F3) – adult costs only[17]	Deferred treatment (age 18 y)	48 236	37.05	
		Early treatment (age 6 y)	54 956	37.68	10 691
6	No utility benefit from treatment	Deferred treatment (age 18 y)	46 846	35.92	
		Early treatment (age 6 y)	54 821	36.13	37 639
7	40% loss to follow-up in deferred treatment arm	Deferred treatment (age 18 y)	32 015	33.83	
		Early treatment (age 6 y)	54 821	37.68	5923
8	40% nonadherence in the deferred treatment arm	Deferred treatment (age 18 y)	47 640	33.83	
		Early treatment (age 6 y)	54 821	37.68	1866