

BRIEF ARTICLES

## Point-of-care continuous <sup>13</sup>C-methacetin breath test improves decision making in acute liver disease: Results of a pilot clinical trial

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### Abstract

**AIM:** To assess the role of the <sup>13</sup>C-methacetin breath test (MBT) in patients with acute liver disease.

**METHODS:** Fifteen patients with severe acute liver disease from diverse etiologies were followed-up with <sup>13</sup>C-MBT during the acute phase of their illnesses (range 3-116 d after treatment). Patients fasted for 8 h and ingested 75 mg of methacetin prior to the MBT. We compared results from standard clinical assessment, serum liver enzymes, synthetic function, and breath test scores.

**RESULTS:** Thirteen patients recovered and two patients died. In patients that recovered, MBT parameters improved in parallel with improvements in lab results. Evidence of consistent improvement began on day 3 for MBT parameters and between days 7 and 9 for blood tests. Later convergence to normality occurred at an average of 9 d for MBT parameters and from 13 to 28 d for blood tests. In both patients that died, MBT parameters remained low despite fluctuating laboratory values.

**CONCLUSION:** The <sup>13</sup>C-MBT provides a rapid, non-invasive assessment of liver function in acute severe liver disease of diverse etiologies. The results of this pilot clinical trial suggest that the MBT may offer greater sensitivity than standard clinical tests for managing patients with severe acute liver disease.

### INTRODUCTION

Acute liver disorders, including severe acute liver disease, acute exacerbation of chronic liver disease, and fulminant hepatic failure comprise a major cause of morbidity and mortality from liver disease<sup>[1-3]</sup>. Decision-making in the treatment of patients with severe acute liver disease focuses on the early identification of patients that require liver transplantation. This identification is currently based on several clinical and laboratory parameters<sup>[4,5]</sup>, including clinical assessments, serum liver enzymes, synthetic tests, and serum ammonia levels; however, these parameters lack accuracy in assessing liver function<sup>[4,6]</sup>. In addition, frequent assessment of liver function is important in the follow-up and management of patients with severe acute liver diseases<sup>[2,7-9]</sup>.

Fulminant hepatic failure (FHF) is a medical emergency that affects approximately 2000 individuals each year in the United States, and is characterized by severe and sudden liver cell dysfunction resulting in coagulation disorders and hepatic encephalopathy in patients without previous liver disease<sup>[10,11]</sup>. FHF does not follow a homogenous course. The overall survival rates for patients with FHF are approximately 10%-30%<sup>[11]</sup>. Therefore, frequent assessment of liver function is critical. Given the significant morbidity and mortality associated with acute liver disease and FHF, there is considerable urgency in the early assessment

of the patients' clinical situation and disease severity. This early assessment affects patient placement (intensive care unit versus ward), initiation of supportive therapies, and listing for liver transplantation. Current predictors of survival in patients with FHF are far from optimal<sup>[12,13]</sup>. Thus, it is often problematic to make decisions concerning medical treatment and time of transplantation based on clinical and laboratory assessments<sup>[14-16]</sup>. A therapeutic dilemma arises from the need to provide expedient transplants to patients with a failing liver while avoiding unnecessary transplantations in patients that are likely to recover spontaneously<sup>[17-19]</sup>.

Breath tests have been used for several decades in patients with acute and chronic liver disorders<sup>[20-22]</sup>. These tests are based on measuring exhaled metabolites of labeled substrates that have been ingested and metabolized by the liver. The amount and rate of appearance of the metabolite in the exhaled breath represent liver enzymatic activity, and a decline may serve as a measure of hepatic injury. The ideal substrate would be metabolized solely by the liver and, therefore, selectively reflect liver metabolic function. <sup>13</sup>C-phenylalanine (PheBT) and <sup>13</sup>C-galactose (GBT) breath tests provide liver-specific substrates that reflect the activities of two enzymes localized to the hepatocellular cytosol<sup>[23]</sup>. Both tests have been shown to accurately predict the severity of liver cirrhosis, and correlate well with the Child-Turcotte-Pugh score (CTP). The <sup>13</sup>C-caffeine breath test can detect chronic hepatitis B virus (HBV)-related fibrosis and has been used to monitor improvement in liver function in response to long-term lamivudine therapy<sup>[24]</sup>. Additional substrates include indocyanine green and aminopyrine; however, their use is limited due to a dependence on portal flow rate and low first-pass metabolism, respectively. Though each substrate measures only one metabolic pathway, studies have shown that each reflected overall hepatic metabolism<sup>[25-27]</sup>.

Methacetin is rapidly metabolized by cytochrome P450 and lacks toxicity in small doses; thus, it is a good substrate for evaluating cytochrome P450 enzyme activity<sup>[28]</sup>. In healthy liver cells <sup>13</sup>C-methacetin is rapidly absorbed and, with a single O-dealkylation step, cytochrome P450 1A2 breaks it down into acetaminophen and <sup>13</sup>CO<sub>2</sub>. Like phenacetin, methacetin undergoes extensive first-pass clearance and any remaining labeled methacetin and metabolites are excreted in the urine<sup>[29]</sup>. In patients with histologically-proven chronic liver diseases, the rate of O-dealkylation of methacetin, assessed by the MBT, accurately reflects the degree of liver damage<sup>[30]</sup>. After oral administration of <sup>13</sup>C-methacetin, the recovery of <sup>13</sup>CO<sub>2</sub> in the exhaled air over 30-min was significantly reduced in patients with chronic hepatitis or liver cirrhosis compared to controls. The non-invasive MBT reliably distinguished between early cirrhotic (Child A) and non-cirrhotic patients with 95.0% sensitivity and 96.7% specificity<sup>[31]</sup>. Although the MBT test is potentially useful, it has not been integrated into everyday clinical practice<sup>[32]</sup>.

A major drawback in using traditional breath tests

is the cumbersome method of isotopic ratio mass spectrometry. This method requires prolonged testing and analysis, imposes patient inconvenience, and delivers limited data points. In contrast, the BreathID® continuous online <sup>13</sup>C-methacetin breath test (MBT, Exalenz, Israel) is based on the measurement of <sup>12</sup>CO<sub>2</sub> and <sup>13</sup>CO<sub>2</sub> concentrations by molecular correlation spectroscopy (MCSTM) that can detect variations less than 1/1000 in the <sup>13</sup>CO<sub>2</sub>/<sup>12</sup>CO<sub>2</sub> ratio<sup>[33,34]</sup>. A recent study showed its effectiveness in assessing liver function in patients with chronic liver disorders<sup>[35]</sup>.

The aim of this study was to assess the role of the MBT for evaluation and follow-up in patients with severe acute liver disease. The data suggest that the MBT correlated with standard parameters and may serve as a more sensitive decision-making tool than conventional laboratory tests for follow-up of patients with severe acute liver disease.

## MATERIALS AND METHODS

### Patients

Between August, 2005, and September, 2007, all consenting adult patients with severe acute liver disease were recruited to the study group. Inclusion criteria consisted of age  $\geq$  18 years, and an acute elevation of transaminases  $\geq$  10  $\times$  ULN or elevation of bilirubin  $\geq$  10  $\times$  ULN with or without an elevated INR  $\geq$  1.5. All patients gave written informed consent to their participation in the study. Patients with significant encephalopathy that were unable to give informed consent were not recruited. The study was conducted in strict adherence to the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board (IRB) committees and the Israel Ministry of Health Committee for Human Clinical Trials.

### Biochemical analysis

All patients underwent a biochemical work-up which included a complete blood count and the activities of: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP),  $\gamma$ -glutamyltranspeptidase (GGTP), lactate dehydrogenase (LDH), albumin, total bilirubin, and prothrombin. Routine biochemical tests were performed with commercially available kits. Coagulation tests included INR and serum levels of coagulation factors 5 and 7. In cases where several blood tests were drawn in one day, statistical calculations were based either on the set of tests taken closest to the time of the breath test or the earliest and most complete set of tests for each date. Obstruction was ruled out in patients with elevated bilirubin.

### Noninvasive evaluation of liver injury by breath test

Following an 8 h overnight fast, in the morning, patients were connected to the breath testing unit *via* a nasal cannula (IDcircuit™) and received 75 mg of N-(4-methoxy-<sup>13</sup>C-phenyl) acetamide (Methacetin, Isotec,

USA) dissolved in 150 mL of water. As a solution, its absorption is not affected by gastric motility. Breath samples were automatically collected by the BreathID device (Exalenz, Israel) before and for 60 min after the labeled substrate was administered to the patient. The  $^{13}\text{C}/^{12}\text{C}$  ratio in the breath samples was determined every 2-3 min. During the test period patients continued fasting and remained at rest to eliminate any variability in  $\text{CO}_2$  production due to the ingestion of food or physical activity. Number of tests performed was not constant.

### Analysis of breath test data

Results obtained from the device were expressed as percentage of administered dose of  $^{13}\text{C}$  recovery (PDR) and the cumulative percentage of  $^{13}\text{C}$  recovery over time (CPDR) at 20, 30 and 60 min after ingestion of methacetin, respectively, as well as the PDR peak, and peak time. PDR refers to the rate at which the  $^{13}\text{C}$  substrate is metabolized and exhaled expressed as percent per hour. PDR is based on the change in  $^{13}\text{C}/^{12}\text{C}$  ratio for each patient, taking into account their specific parameters affecting overall  $\text{CO}_2$ , normalizing the results for any weight, height, dose and substrate type and purity<sup>[36,37]</sup>. CPDR is the numeric integral of PDR, and describes the total percent of substrate metabolized at any given accumulated time. Data are expressed in units of percent. The BreathID® device plots the PDR and CPDR in real time and the PDR peak value is then calculated.

### Statistical analysis

The correlation of the Breath test parameters and blood test values was calculated using Pearson Correlation. A model of recovery based on exponential function  $[1 - \text{const.} \cdot \exp(-\text{time\_from\_baseline}/\text{time\_constant})]$  for MBT returning to normal metabolic function and  $[1 + \text{const.} \cdot \exp(-\text{time\_from\_baseline}/\text{time\_constant})]$  for blood test value decrease and return to normality was used to extract the time to recovery. Statistical analysis was performed only for patients who had at least 3 breath tests and 3 sets of blood tests over at least three different days. Generalized Reduced Gradient (GRG2) with nonlinear optimization was used to determine the functions constants.

### Normal values

Normal values were determined using a group of 100 healthy volunteers (57 males and 43 females). These healthy controls were screened by medical history, physical examination, routine liver function tests, and abdominal ultrasound. All healthy volunteers had blood test results within normal limits. None had a history of active or previous liver disease, alcohol abuse, drug abuse, and none were taking medications. Based on the analysis of MBT results from 100 normal volunteers, a PDR Peak value of 30% h was considered to be normal. The average PDR Peak value was  $35\% \pm 9\%$  h in healthy volunteers, with a minimum of 20% h and a maximum of 60% h. Because the blood test results were considered normal within a range of  $\pm 30\%$  of

**Table 1** Definition of normality for breath test parameters and blood tests

	Units	Normal values	$\pm 30\%$ of normal
Breath test	%/h	> 30	> 21
ALT	U/L	< 53	< 69
AST	U/L	< 60	< 78
INR	U/L	1.00	< 1.30
BIL	$\mu\text{mol/L}$	< 17	< 22

**Table 2** Liver disease etiology and outcome

Etiology	Number of patients	Number recovered	Number deceased
Autoimmune hepatitis	5	4	1
Drug induced liver injury	3	3	0
Acute HBV	2	2	0
Acute HAV	2	2	0
Wilson's disease	1	1	0
Pregnancy associated	1	1	0
Space occupying lesion	1	0	1

normal, we decided to set a similar range for normal PDR peak values. Furthermore, the normal ranges for blood tests typically take into account that a high value is critical, while the low value is less relevant. Therefore, the normal range is expressed as anything below the normal value + 30% (Table 1). Similarly, the PDR peak had critical significance at low values, but high values were less relevant. Therefore, we set the normal range as anything above 21% h (Table 1).

## RESULTS

### Patient population

Fifteen adult patients had severe acute liver disease of diverse etiologies, including autoimmune hepatitis ( $n = 5$ ), acute hepatitis A virus (HAV) ( $n = 2$ ), acute HBV ( $n = 2$ ), drug-induced liver injury ( $n = 3$ ), neoplastic disease ( $n = 1$ ), Wilson's disease ( $n = 1$ ), and pregnancy associated liver disease ( $n = 1$ ). The demographic and clinical characteristics are summarized in Tables 2 and 3. In two patients a grade 2 hepatic encephalopathy developed.

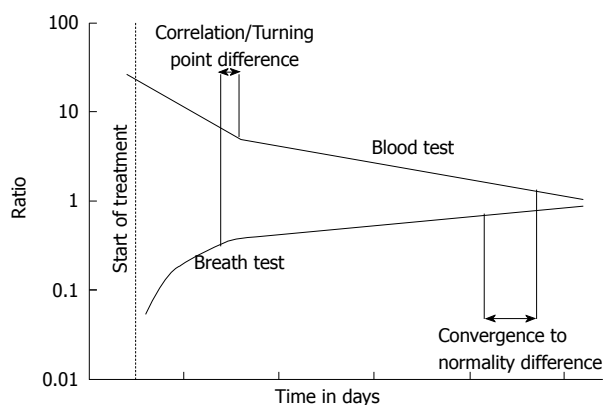
### Patient outcomes

Thirteen patients ultimately recovered from their illness, based on both clinical and biochemical assessments (average recovery time 28 d, SD 22 d); two patients died (1 autoimmune hepatitis, 1 neoplastic disease); and none of the patients were transplanted. The first patient that showed an unfavorable course of illness died of sepsis before a transplant could be provided. The second patient died from metastatic cancer.

### Correlation of MBT with clinical course

Figure 1 illustrates the method of comparing results from the breath test versus the blood tests along the clinical course of recovery. In all patients that eventually recovered, clinical improvement and normalization

Parameter	Female	Male	Overall
No. of patients	8	7	15
Weight (kg)	70.13 $\pm$ 20.03 (52-115)	82 $\pm$ 19.59 (55-115)	75.67 $\pm$ 20.07 (52-115)
Height (cm)	163.75 $\pm$ 6.69 (155-176)	175.57 $\pm$ 5.32 (167-184)	169.27 $\pm$ 8.47 (155-184)
BMI (kg/m <sup>2</sup> )	25.91 $\pm$ 5.69 (19.95-37.13)	26.53 $\pm$ 5.86 (18.59-35.89)	26.20 $\pm$ 5.57 (18.59-37.13)
Age (yr)	33.50 $\pm$ 17.04 (18-61)	31.14 $\pm$ 14.02 (14-53)	32.40 $\pm$ 15.19 (14-61)
ALT (IU)	1162.38 $\pm$ 1926.69 (45-5795)	2807.86 $\pm$ 2468.82 (58-7535)	1930.27 $\pm$ 2278.22 (45-7535)
AST (IU)	996.88 $\pm$ 1306.56 (50-3928)	1475.71 $\pm$ 1104.09 (96-3294)	1220.33 $\pm$ 1198.8 (50-3928)
Bilirubin ( $\mu$ mol/L)	193.50 $\pm$ 207.39 (9-565)	232.86 $\pm$ 194.49 (41-599)	211.87 $\pm$ 195.27 (9-599)
INR (SI)	2.09 $\pm$ 0.90 (1.00-4.06)	1.80 $\pm$ 0.62 (1.26-3.02)	1.95 $\pm$ 0.77 (1.00-4.06)

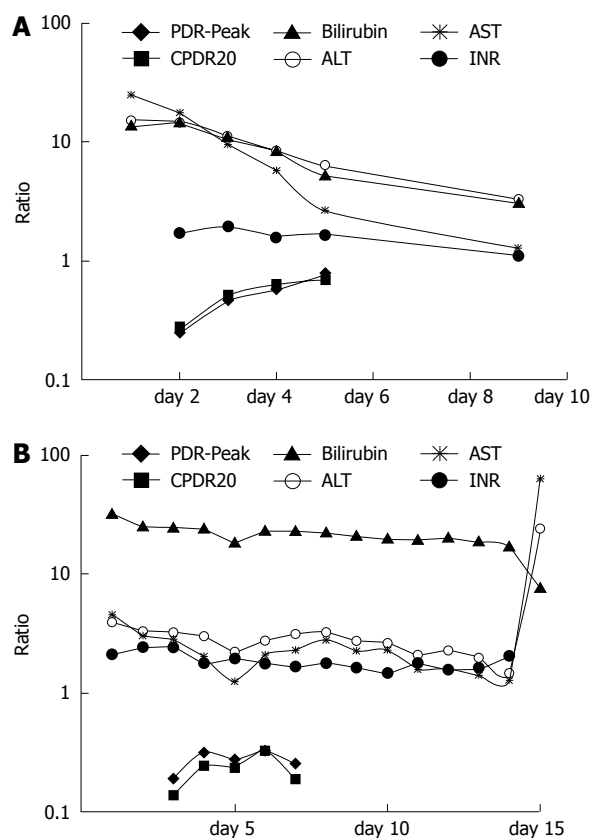


**Figure 1** This is an illustration of typical breath test and blood test results plotted over the clinical time course. The wide green line indicates the range of normal values. As the patient recovered, test results converged toward normality.

of biochemical parameters followed the progressive improvement of BreathID® <sup>13</sup>C-MBT scores (Figure 2A). In the two patients that died, breath test parameters deteriorated or failed to improve (Figure 2B). Overall, breath test parameters showed better correlation with clinical improvement than all other tests. Correlations between the breath test parameters and the blood test values varied between 0.2 and 0.7 (Table 4). The comparisons showed a trend for correlation; however, statistical significance was not reached due to the small number of patients and tests.

### MBT results detect improvement in liver function prior to standard tests

The MBT indicated improvement in hepatic function prior to lab results. For this analysis, we defined 2 clinically relevant points. The first was the “point of stable improvement”, which was defined as the point in time after which a continuous improvement was observed in patient MBT scores or blood tests results. The second was “convergence to normality,” which was the point in time at which normal values were achieved



**Figure 2** The clinical course of a patient with fulminant auto-immune hepatitis. A: Upon admission, aminotransferase levels were well above 10  $\times$  ULN, INR was increased, and breath test values were low. The patient received treatment with steroids and recovered rapidly. The breath test values normalized within 3 d, but blood tests began normalizing 2 d later; B: Despite therapy with steroids, this patient failed to improve, developed gram negative sepsis, and died. Note that despite stable blood tests, there was a lack of improvement in breath test values. The low breath test values may have been a negative prognostic factor in this patient and may have provided a rationale for early transplantation.

(normal values are defined in the Methods). As shown in Table 5, the average point of stable improvement for MBT parameters occurred at 3 d, while for blood tests it occurred between 7 and 9 d after treatment. Later, the average convergence to normality for MBT parameters occurred at 9 d, while for blood tests it occurred within 13 to 28 d after treatment.

### MBT parameters detect deterioration in liver function prior to other tests

In both patients that died, MBT parameters were extremely low at presentation and remained low throughout the course of the illnesses (despite medical therapy in the case of autoimmune hepatitis). In contrast, patient blood test parameters fluctuated during the course of the illnesses and finally deteriorated shortly before death (< 24 h).

## DISCUSSION

The BreathID® <sup>13</sup>C-MBT is a rapid, non-invasive tool for the assessment of liver function in acute liver disease. This study showed that using the MBT to evaluate



**Table 4 Correlation coefficients for blood test versus breath test parameters**

	PDR peak	Peak time	PDR10	PDR15	PDR20	PDR30	PDR60	CPDR10	CPDR15	CPDR20	CPDR30	CPDR60
BIL	-0.556	0.394	-0.519	-0.544	-0.575	-0.588	-0.519	-0.456	-0.513	-0.540	-0.580	-0.595
ALT	-0.276	0.235	-0.258	-0.279	-0.293	-0.318	-0.403	-0.248	-0.266	-0.276	-0.306	-0.326
AST	-0.338	0.226	-0.306	-0.337	-0.358	-0.384	-0.451	-0.279	-0.311	-0.329	-0.362	-0.405
AP	-0.239	0.219	-0.308	-0.280	-0.268	-0.172	-0.110	-0.283	-0.301	-0.296	-0.282	-0.198
GGT	0.504	-0.344	0.510	0.538	0.507	0.418	0.203	0.340	0.449	0.483	0.497	0.438
LDH	-0.313	0.221	-0.313	-0.329	-0.329	-0.325	-0.314	-0.264	-0.302	-0.317	-0.333	-0.332
INR	-0.436	0.441	-0.412	-0.435	-0.452	-0.431	-0.386	-0.390	-0.420	-0.437	-0.458	-0.562
PTT	-0.565	0.239	-0.413	-0.509	-0.579	-0.632	-0.471	-0.360	-0.420	-0.471	-0.543	-0.598
PT%	0.628	-0.364	0.475	0.573	0.635	0.673	0.513	0.440	0.489	0.540	0.609	0.660
F-VII%	0.648	-0.828	0.720	0.737	0.723	0.613	0.581	0.661	0.694	0.715	0.725	0.688
F-V %	0.576	-0.495	0.598	0.521	0.546	0.579	0.503	0.527	0.548	0.554	0.582	0.591

Results obtained from the device were expressed as percentage of administered dose of <sup>13</sup>C recovery (PDR) and the cumulative percentage of <sup>13</sup>C recovery over time (CPDR) at 10, 15, 20, 30 and 60 min after ingestion of methacetin, as well as the PDR peak, and peak time. PDR refers to the rate at which the <sup>13</sup>C substrate is metabolized and exhaled expressed as percent per hour. PDR is based on the change in <sup>13</sup>C/<sup>12</sup>C ratio for each patient. CPDR is the numeric integral of PDR, and describes the total percent of substrate metabolized at any given accumulated time. Data are expressed in units of percent. ALT: Alanine aminotransferase; AST: Aspartate amino transferase; GGT: Gamma glutamyl transpeptidase; AP: Alkaline phosphatase; F-V, F-VII: Factor 5 and 7; PDR: Percent dose recovery at different time points in minutes; CPDR: Cumulative percent dose recovery at different time points.

**Table 5 Blood tests versus breath test parameters (mean, SD)**

	Point of stable improvement (days after treatment)	Convergence to normality (days after treatment)
Breath test	2.85, 2.23	8.89, 11.5
ALT	7.33, 11.06	28.24, 21.69
AST	7.62, 11.44	12.96, 6.96
INR	8.62, 12.1	16.02, 24.71
BIL	7, 10.61	23.63, 22.61

patients with acute severe liver disease enabled detection of improvement 4-6 d earlier than the currently used laboratory tests, irrespective of disease etiology. Furthermore, breath test results indicated normalization of liver function 4-19 d earlier than blood test values in patients that recovered from their illnesses. The data of the present study suggests that the MBT may serve as a more sensitive decision-making tool than standard test parameters in the setting of severe acute liver disease.

In fulminant hepatic failure (FHF) an early prognosis is essential in determining the need and appropriate timing of orthotopic liver transplantation (OLT). Several reports have described laboratory parameters that served as predictive criteria. Since its publication by O’Grady and colleagues in 1989<sup>[38]</sup>, the King’s College Criteria have been widely used to define patients with poor prognoses using pH, thrombin time, serum creatinine, and bilirubin levels. Recently, the Acute Physiology and Chronic Health Evaluation (APACHE II) score was described for determining prognosis in the setting of FHF. The APACHE II used a combination of both clinical and laboratory parameters and its sensitivity was comparable to that of the King’s College Criteria<sup>[39]</sup>. A recent study in 120 consecutive patients with FHF investigated the prognostic efficacies of King’s College criteria, Clichy’s criteria, the Model for End-Stage Liver Disease (MELD), and the Pediatric End-Stage Liver Disease (PELD). MELD scores were significantly higher

in patients that died compared to those that survived without OLT. Logistic regression analysis yielded concordance statistics that were significantly higher for MELD (0.95) and PELD (0.99) compared to King’s College (0.74) and Clichy’s criteria (0.68). In a Cox model analysis, the data included patients that received transplants and censored the time from admission; this analysis showed the concordance statistics for MELD (0.77) and PELD (0.79) remained significantly higher than that of King’s College criteria, but not higher than that of Clichy’s criteria<sup>[40]</sup>. However, the MELD and PELD were not effective for follow-up on a daily basis, thus they were not useful for decision-making in the acute setting. The lack of an effective measure of liver function in the acute setting makes it difficult to reach an appropriate clinical decision in hepatology<sup>[41,42]</sup>.

Noninvasive tests were used previously to assess liver function in acute liver disease. In 1993, Luketic *et al*<sup>[43]</sup> demonstrated that hepatic lidocaine metabolism was useful in the selection of patients for liver transplantation<sup>[44]</sup>. The study evaluated hepatic conversion of lidocaine to its primary metabolite, monoethylglycin exylodide, and compared the results to liver histological findings in 225 patients with chronic hepatitis. A decline in monoethylglycinexylodide production was correlated with worsening liver histological findings. A further stepwise decline in monoethylglycinexylodide production was correlated with a worsening Child class score. In contrast, no relationship was observed between liver histological status and serum transaminases (AST or ALT), bilirubin, albumin, or prothrombin time. Thirty-five patients underwent a follow-up histological evaluation and monoethylglycinexylodide testing after receiving at least 6 mo treatment for chronic hepatitis (interferon for hepatitis B and C and corticosteroids for autoimmune hepatitis). The change in monoethylglycinexylodide production was linearly related to the change in the Knodell histological index.

MBT has several advantages compared with the

above tests. It is a noninvasive, easily preformed, bedside test and is not associated with patient discomfort. It provides real time results and does not require any expertise for data analysis. It has no known side effects and is not limited by patient-specific parameters. Finally, the test is sensitive to minor changes in liver metabolism, thus enabling daily follow-ups in the acute setting.

The cause of acute liver failure (ALF)<sup>[6]</sup> is a major determinant of its outcome. Thus, the prognosis for ALF due to acetaminophen (paracetamol) overdose is relatively good, but the mortality rate for ALF from other causes may be significantly higher. In the current study, only 2 patients (13%) had acute liver damage due to paracetamol, but a far greater percent presented with acute autoimmune hepatitis. This may be explained by the observation that paracetamol is the etiological agent for a large percentage of ALF cases in England and the US, but it accounts for far fewer incidents in Europe and Israel (unpublished results). In a study performed in Spain, 267 cases of ALF were analyzed retrospectively. Acetaminophen overdose accounted for only 2.2% of the patients and overall survival was 58%. Liver transplants were performed in 150 patients, with a survival of 69%. Patients that fulfilled the criteria, but were not provided transplants due to contraindications, had a survival rate of only 7.8%. Those that did not fulfill the transplant criteria had a 85.5% survival rate<sup>[45]</sup>. The high survival rate in our group of patients might be explained by the fact that only 2 patients (13%) fulfilled the transplant criteria. One (autoimmune hepatitis) patient died from sepsis before transplantation was possible, and the other patient began to recover spontaneously a few hours before the scheduled transplantation. In this patient, the breath test made it possible to follow liver function even after correction of coagulopathy with fresh frozen plasma in preparation for liver transplantation.

Orthotopic liver transplantation is the most definitive solution to the problem of sudden hepatocyte loss. However, the selection of a lifetime surgical solution for an acute, potentially self-limiting problem is a stressful decision for physicians. Several obstacles to successful transplantation may arise, including transporting a patient with cerebral edema safely to the transplantation center, securing funding in a timely fashion, and obtaining a suitable organ rapidly. The overall one year survival rate of patients with acute liver failure that undergo liver transplantation exceeds 60 percent. However, due to the logistic hurdles that must be overcome, it is estimated that currently only 10 percent of patients with acute liver failure receive a liver graft. Subsequently, any test that may help in determining recovery at an earlier stage, thus deferring the need for transplantation, is of great value.

The current study had several limitations. The cohort only included 15 patients. The requirement for obtaining informed consent excluded patients with encephalopathy; thus, patients on that end of the spectrum were not assessed. Indeed, only two patients in this cohort displayed an indication for liver transplantation. In order to demonstrate an effect of MBT on decisions regarding

liver transplantation, a larger group of patients with fulminant liver failure must be studied. However, even in the limited number of cases studied here, we found the MBT test offered an advantage as a decision-making tool because improvement in MBT parameters provided a rationale for avoiding unnecessary liver transplantation in one of these patients.

In summary, the results of the present preliminary study suggest that a point of care, on-line breath test system may provide an important tool for decision-making in clinical hepatology in the setting of acute severe liver disease. Further large scale studies are required for assessment of the general utility of this test.

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