Fatal and Nonfatal Hemorrhagic Complications of Living Kidney Donation

To the Editor:

I read with interest and appreciated the paper by Friedman et al,[1] which analyzed hemorrhagic complications during live kidney donation. They have done a large amount of work, sending questionnaire to 893 surgeons and studied the 24% respondents' surveys.

The methodology is interesting, but I don't fully agree with the conclusion of the authors. They concluded that "hemorrhage appears to be associated more frequently with surgical clips that with other methods of arterial and venous control" and "perception that suture or staple transfixion of the renal artery is the safest and more appropriate way to manage the living kidney donor renal vasculature."

How do they arrive to this conclusion?

The only statistical calculation is summarized on Table 5. They found that "non transfixion techniques were associated with worse outcomes compared with the transfixion technique ($P < 0.01$)." When analyzing the nontransfixion technique, they mixed nonlocking clips, locking clips, and simples or multiple ties.

It is methodologically incorrect to incorporate these three different methods into one group and then to compare this group with the transfixion group. Indeed, one of these methods, the nonlocking clips, is according to the company, contraindicated for controlling the renal artery ("do not use the endoclip on the renal artery" is written on the package); the second method, using simple or multiple ties, is known to be an unreliable technique when performed laparoscopically,[2] which is becoming the approach of choice for this procedure. The third method, using multiple locking clips, is considered by users themselves "very safe" in this article,[1] and as safe as an endo GIA, TA, or an oversew (Table 4). Friedman, herself, in her article admitted "that hemorrhagic events with non locking clips are most likely to be associated ($P < 0.001$) with class 4b and 5 complications" (ie, worse complications), when compared with the locking clips. With such a difference ($P < 0.001$), how could she mix these different devices to compare them, together, to the transfixion techniques?

This methodologic error makes their conclusion about the locking clips invalid.

The authors should have compared transfixion closure technique, considered by them as the best technique, to multiple locking clips. This comparison is unfortunately not available in this paper.

Furthermore, looking carefully at the different tables of this paper when can see:

1. A mistake in the results. They reported 12 accidents with locking clips in Table 2, which decreased to 10, in Table 5, where they analyze the severity of these accidents.
2. We observed that transfixion techniques were choice chosen 249 times in the survey (addition of suture ligature with or without tie, oversew, GIA, and TA in Table 1) and locking clips (single or multiple) 59 times. Thus, the transfixion technique seems to be used 4.22 times more often than locking clips. This rate is comparable when we consider the 42 hemorrhagic events with transfixion technique (Table 5) and the 10 hemorrhagic events with locking clips technique (Table 5).
3. A total of 10% of locking clip users place only one clip on the patient side, which shouldn't be done according to the "instruction for use." These recommend placing 2 locking clips. This unsuitable usage could have been the cause of the few accidents reported with locking clips in this study. One more important "instruction for use" is to keep a 1- or 2-mm cuff of artery, which maybe, is not done by all surgeons as they may try to keep the artery as long as possible. In our experience,[3] we can follow these instructions for use and have a good renal transplant recovery function.

Properly used, following the instruction for use, the multiple locking clips are an interesting alternative to the endo GIA or TA. They are equivalent to hand ties under supraphysiologic conditions for occluding a renal artery, and better than vascular staple lines.[4] They can be used on the artery and on the vein as well,[3,5] and provide a longer length of vein.[6] Their use avoids the exceptional primary malfunction of the endo GIA that has been described leading to severe morbidity even few deaths.[7–9]

For all these reasons, we contest strongly the conclusions of the authors, and we still believe that the use of multiple locking clips is a safe and cost-effective option, to control the renal pedicle during live donor nephrectomy.

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Reply:

We appreciate the interest Dr. Baumert has taken in our article.[1] It is appropriate to clarify that the use of nonlocking clips on the renal artery is eschewed by one manufacturer,[2] but not

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all. This technique has been published in the peer-reviewed literature[3] of laparoscopic live donor nephrectomies and is taught in surgical courses supported by at least one of these companies.[4,5] We have been unable to identify any evidence basis demonstrating the safety or lack thereof for nonlocking clips on these large vessels, other than single institution series or case reports. No manufacturer provided any data, despite specific requests. No surgeon reported use of one or more ties on the renal artery in laparoscopic cases.

Locking clips were used in 12 of the arterial hemorrhages reported to us, but no data regarding the severity of the outcome were provided in 2 cases, explaining the different event numbers in Tables 2 and 5. Although we are unable to identify any evidence basis for the use of more than 1 locking clip on the renal artery stump (or for the safety of locking clips without identification of the number used), surgeons clearly felt the use of more than 1 was safest (Table 4) with single locking clips rated as unsafe[2] on the Likert scale of 1 to 5 for both open and laparoscopic procedures.

Collectively, respondents reported 6 severe arterial hemorrhages following use of 2 or more locking clips on renal arteries. At least 3 of these (timing of the hemorrhage was not always provided) occurred following completion of the procedure.

Our statistical analyses were limited by the relatively (fortunately) small sample and by the lack of detail provided by some respondents who opted to remain anonymous. Without case volumes (which were not collected), it is not possible to calculate rates or frequencies. The comparison of transfixion and nontransfixion techniques was performed without respect to whether they were used laparoscopically or open. Indeed, several of the clip failures were reported from open cases. We concur that only one of the safer, transfixion, techniques is currently applicable to a laparoscopic donor nephrectomy, which has become the approach of choice.

Finally, it is appropriate to remark that many respondents indicated that hemorrhage followed the attempt to control a short arterial stump, left in trying to preserve an early bifurcation as a single vessel. It would seem apparent that, particularly in the case of a short cuff, use of the most secure technique, which currently means a stapler in the laparoscopic approach, is paramount to safety of the live kidney donor (Fig. 1).

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Surgical Management of Complications Associated With Percutaneous and/or Endoscopic Management of Pseudocyst of the Pancreas

To the Editor:

With great interest, I read the article by Nealon and Walser[1] regarding the patients presenting with complications associated with percutaneous and/or endoscopic management of pseudocyst of the pancreas. The authors described excellent outcome in patient with multiple complications. A total of 39% of the patients had sepsis; even then, most of these patients could be internally drained. Infected pseudocyst or pancreatic abscess (according to Atlanta classification)[2] needs external drainage. As it could be drained internally, was it a simple colonization of the fluid with bacteria or drain tract infection only. External drainage is usually required in the patients with infection.[3,4] Surgery in these patients carries high morbidity and mortality and repeated interventions.[4]

Also unclear is about the hemorrhage, seen in 12% of the patients. Was it significant bleed requiring urgent surgery and what was the etiology of bleed? Bleeding during the procedure, if significant, usually requires urgent intervention. Later bleeding can occur either from small pseudoaneurysms in the wall of cyst or major vessel pseudoaneurysms, later requiring urgent surgery with high mortality.[5,6]

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Possible Intergel Reaction Syndrome (pIRS)

To the Editor:

The recent report by Tang et al[1] heightens concerns about the effects of Intergel (ferric hyaluronate, FeHA) and the

Please note that the author has consulted for, and/or holds shares in a number of companies with interests in this area, some of whom may benefit, and some of whom may not benefit from the contents of this letter.

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mechanism of what has been termed "Intergel Belly"[6] or "possible Intergel Reaction Syndrome" (pIRS).[2]

The authors sought to examine the effect of Intergel in 700 patients undergoing colorectal surgery and ileostomy reversal. After 32 patients, the study was terminated because of unacceptably high morbidity: Intergel was associated with prolonged ileus and "predisposed to the development of late postoperative peritonitis and anastomotic dehiscence." There was one death in the control group due to myocardial infarct secondary to a postoperative bleed. With Intergel, 1 patient developed pulmonary embolism after relaparotomy for dehiscence and subsequently died.

Despite the availability of these data in 2001,[3] the package label continued in both U.S.[4] and international versions to state that Intergel "has not been studied . . . in patients having surgery which involves opening of the gastrointestinal or urinary tract," and remained silent on the issue of contamination.

The availability of these data might well have prevented at least 2 deaths in patients where Intergel was used and where the bowel had been perforated. According to an account given to a leading patient group,[5] surgeons thought that the postoperative pain in these patients may have been related to the "late onset, postoperative pain following use of the device" as well as "noninfectious peritoneal inflammation," described in a company announcement. Not considering infection to be another cause of pain, its treatment was delayed, and patients died.

Tang et al note their caution. They appropriately considered the increase in mortality due to FeHA in inoculated rats[6] and considered conclusions from a similar study[7] that "intraperitoneal administration of INTERGEL Adhesion Prevention Solution at dose volumes up to 15 mL/kg does not potentiate mortality or abscessformation following bacterially induced peritonitis." However, this conclusion, made despite a numerical increase in mortality from 25% to 45% (high-dose FeHA), may have been subject to a type II error.

The study was repeated with 60 animals per group[8]: mortality in control (37%) and Intergel (40%) groups was comparable, but the conclusion that "placement of 5 mL/kg Intergel Solution in the peritoneal cavity concurrently with a bacterial inoculum did not affect the course of host resistance to the infection" was flawed because:

1. Unlike the previous study, no positive control (dextran) was used to demonstrate that this notoriously difficult model was capable of detecting potentiation of infection.
2. Only the lower of the 2 doses (1× human dose equivalent) was retested (15%–25% increase in mortality, previously). The 3× dose (25%–45% increase in mortality, previously) was omitted.
3. Inocula were frozen not in bulk (as in the Tzianabos study[6]) but as single doses. Bacterial virulence is more likely to be lost using the latter method, but in either event its variable preservation necessitates the use of a positive control in every experiment.
4. In the first study, the reduction in the abscesses in INTERGEL-treated animals was considered to support the (erroneous) conclusion regarding infection potentiation. However, since abscess formation was only assessed in surviving animals, the increased mortality observed in INTERGEL-treated animals resulted in a selection bias with regard to abscess assessment. When similar mortality rates were observed in the repeated study, there was no change in abscess rates.[8]

Tang et al do not appear to have had the opportunity to review with their supporters' even earlier data which, it seems, have emerged not in the regulatory record, nor in the scientific literature, but in plaintiff's discovery.[2] This low-powered study (15 animals per group) also showed a nonstatistically significant increase (40%–67%) in mortality with high-viscosity FeHA compared dose for dose with the low viscosity equivalent, or Ringer's lactate.

A number of reported effects of FeHA in animals may also illuminate the mechanism(s) of pIRS: dystrophic calcification in rabbits, granulomatous peritonitis in rats, an increased death rate in rats following severe peritoneal trauma applied laparoscopically, and a possible reduction in Intergel's efficacy in a bleeding field.[2] Clinical findings may further clarify the mechanisms of pIRS: the lack of efficacy (in laparoscopy) in endometriosis patients in whom there was also an associative trend of reactivity;[2] an increase in the rate of infection;[4] a trend toward more reactivity in patients undergoing extensive surgery;[2] changes in lymphocyte, neutrophil, and basophil counts;[9] and shifts in calcium levels.[9]

Intergel contains both iron and ammonia. The toxicity and role of iron in a variety of pathologic processes including free-radical generation, carcinogenesis, and asbestosis has been extensively described. The contribution of iron hydroxide particulates found in the Intergel to pIRS has not been determined. Iron in vitro has been shown to be toxic to mouse peritoneal macrophages via an oxidative mechanism, at a concentration almost 70 times[10] lower than that found in Intergel.[11] Intergel toxicity may also be mediated via its ammonia content, which is similar to or exceeds that required to compromise macrophage[12] or lymphocyte function[13] in vitro.

These comments are not intended to criticize Tang et al. I have every confidence based on their responsible actions that, had they had full access to data and analyses existent prior to their study, they would either have not initiated it or, would have exercised even greater caution, and would have not agreed to their sponsor's requests to delay publication of their data.[3] Arguably, this may have helped avoid later adverse events.

I commend the authors for their account and anticipate that it will contribute to a determination of the mechanism of pIRS, its possible long-term sequelae and treatment; as well to a heightened caution regarding the planned reintroduction of Intergel.

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Peritoneal Carcinomatosis of Colorectal Origin: Standard of Care

To the Editor:

I read with great interest the recent article by Koppe et al.[1] The article thoroughly reviewed the current evidence of the treatment strategies for peritoneal carcinomatosis of colorectal origin. With better insight into the natural history of colorectal peritoneal carcinomatosis (CRPC), where peritoneal dissemination is a result of transcoelomic invasion by the cancer or intraperitoneal seeding during surgical manipulation, a local-regional treatment combining cytoreductive surgery (CRS), and perioperative intraperitoneal chemotherapy (PIC) have been suggested.[2–11] In the past, CRPC was considered a form of systemic metastases and treated as a preterminal condition with systemic chemotherapy. Surgery was only used to palliate complications, such as intestinal obstruction. Patients did not seem to respond to these treatments and usually died of their disease within 12 months.[12–15] Systemic chemotherapy has limited effects on peritoneal tumors, due to its limited penetration. Prevention and eradication of peritoneal carcinomatosis through the use of intraperitoneal chemotherapy was declared standard of practice by the National Cancer Institute after a recent phase III study in ovarian cancer.[16]

Especially in the last 5 years, numerous phase II studies have shown that CRS combined with PIC can achieve an improved survival for CRPC, as compared with historical controls using systemic chemotherapy.[2–9] In 2003, the Dutch group reported the results of a randomized controlled trial (RCT) comparing systemic chemotherapy with CRS and intraperitoneal hyperthermic chemotherapy (IPHC), which demonstrated the superiority in survival of the latter group.[10] This important trial has contributed to the treatment of CRPC with combined CRS and IPHC as a standard of care in Italy, France, and Holland. In 2004, a multi-institutional registry study from 28 international treatment centers reported that the median survival was 19 months and 3-year survival was 39% in 506 CRPC patients who were treated with CRS and PIC.[3]

Currently, 12 referral centers are operational for the treatment of peritoneal carcinomatosis using CRS and PIC in the United States. In Italy there are 44 and in Spain there are 8 active centers that currently perform the combined treatment of peritoneal surface malignancy. In the United Kingdom, CRS combined with PIC has become a part of the National Healthcare System. In 1994, Moran et al initiated their treatment program in Basingstoke and a second treatment center was established in 2002 in Manchester due to increased demand. In Holland, CRS and IPHC have become a part of the clinical practice at the Netherlands Cancer Institute, where 50 cytoreductions are performed every year. In Sydney, Australia, the number of patients referred for CRS and PIC doubled twice in the past 2 years; at any given time, there are 20 to 30 patients on the waiting list. Because of the long delay in treatment of up to 6 months rendering some patients inoperable, the Australian Federal Government recently increased funding to allow 2 cases to be performed per week.

In the current literature, there are no published data that specifically document the efficacy of modern systemic chemotherapy, mainly 5-fluorouracil/leucovorin combined with oxaliplatin/irinotecan with or without biologic agents, for isolated CRPC. Should we use systemic chemotherapy as the standard of care just because it has been traditionally used, but in fact there are no available data to substantiate its efficacy? There is still a great degree of controversy on whether another RCT is required to establish the combined treatment as the standard of care for patients with CRPC. However, given the promising results achieved by CRS and PIC, recruiting patients to compare palliative treatment with a potentially curative therapy may not be practical or even ethical. By comparison, there was never a RCT demonstrating the superiority of hepatectomy over systemic chemotherapy for colorectal liver metastases and there was never a RCT for liver transplant surgery either. Yet, as the evidence appeared so overwhelmingly in favor of these experimental therapies, both procedures have matured into standard of care in current clinical practice.

Obviously, not everyone with CRPC is eligible for CRS and PIC; just like hepatectomy for colorectal liver metastases, careful patient selection is of utmost importance. With increased experience and decreased morbidity and mortality, CRS and PIC should be offered to patients with low volume of peritoneal carcinomatosis, good performance status, and absence of systemic metastases.[3,10,17] In January 2006, an International Symposium on Regional Cancer Therapies was held in Colorado and subsequently in March 2006,

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a Peritoneal Surface Oncology Group Meeting was held in San Diego. After discussing the medical and surgical treatment options, the consensus for the treatment of CRPC was reached and approved by the surgical oncology experts on peritoneal surface malignancy from North America, France, Italy, Germany, Holland, Spain, and Australia. The consensus stated that patients who have isolated CRPC and are likely to receive a complete cytoreduction, as determined by preoperative CT scans, will undergo CRS; and if complete cytoreduction is achieved, intraperitoneal hyperthermic mitomycin C is given (at 15–35 mg/m^2, 39C–42°C, for 60–120 minutes, either by closed or open instillation), followed by best adjuvant systemic chemotherapy. A prospective multi-institutional phase II study using this regimen is currently in progress. In Sydney, Australia, a proposal for a RCT comparing CRS and IPHC versus CRS and modern systemic chemotherapy is being considered. Also, in Amsterdam, Holland, a RCT comparing CRS and intraperitoneal hyperthermic mitomycin C versus CRS and intraperitoneal hyperthermic oxaliplatin is undergoing the IRB approval process.

After the RCT by the Dutch group,[10] CRS and IPHC should be regarded as the standard of care for patients with isolated CRPC, unless further studies on systemic chemotherapy or other treatment options demonstrate superior results in this selected group of patients.

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Reply:

In his comment, Dr. Yan appeals for acceptance of cytoreductive surgery (CS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) as standard of care in patients with resectable peritoneal carcinomatosis (PC) of colorectal origin. We agree that this aggressive approach has been proven more effective than systemic palliative 5-fluorouracil-based chemotherapy and palliative surgery when needed in selected patients. However, important issues remain to be resolved.

Tumor load and completeness of resection have consistently been shown to be the most important prognostic factors. Patients with extensive PC that cannot be resected completely most likely do not benefit from this treatment. Therefore, accurate patient selection is warranted. Although computed tomography (CT) has been suggested as a valuable tool for preoperative selection of patients with peritoneal mesothelioma,[1] De Bree et al[2,3] concluded in a retrospective analysis that this imaging modality may have limited value in predicting tumor load in patients with colorectal carcinomatosis. In patients with colorectal liver metastases, FDG-positron emission tomography (PET) combined with CT has been shown to be a sensitive tool for detecting or excluding extrahepatic disease prior to liver resection.[4] Addition of FDG-PET to the diagnostic workup of patients with PC of colorectal origin might therefore be of added value, mainly by excluding patients with unexpected extraperitoneal disease.

The efficacy of adjuvant intraperitoneal chemotherapy is still a matter of debate. To date, there has been no evidence supporting or against adjuvant intraperitoneal chemotherapy after CS in patients with PC of colorectal origin. Although postoperative morbidity is mostly surgery-related, it cannot be excluded that intraperitoneal chemotherapy affects wound healing, thus having an effect on postoperative complications. Nevertheless, in the most favorable patient group, namely, those in whom a complete (R1) cytoreduction has been achieved, intraperitoneal recurrence rates remain high. This at least suggests that more effective adjuvant treatments are necessary to improve the results in this patient category. Whereas mitomycin-C has been the most frequently used cytostatic agent in hyperthermic intraperitoneal chemotherapy, several new cytostatic agents have been introduced and

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used for intraperitoneal chemotherapy, such as oxaliplatin.

Furthermore, whereas 5-fluorouracil has been the only cytostatic agent that was used for chemotherapy in patients with colorectal cancer (CRC) for 40 years, 2 new cytostatic agents, irinotecan and oxaliplatin, have been introduced in the new millennium.[5] In addition, targeted therapies using the antivascular endothelial growth factor monoclonal antibody (MAb) Bevacizumab and the antiepidermal growth factor receptor MAb Cetuximab, have been added to the therapeutic armamentarium.[6] These changes represent important progress for patients with recurrent CRC. To date, there are few data with regard to the efficacy of these agents in patients with PC of colorectal origin. The exact role of chemotherapy and immunotherapy remains to be elucidated.

Finally, after initial skepticism among both medical and surgical oncologists, it has taken more than 2 decades (but only one randomized trial) for CS followed by HIPEC to be acknowledged as one of the treatment options in patients with PC of colorectal origin. Indeed, despite the absence of a randomized trial confirming the superiority of liver resection for colorectal metastases over systemic chemotherapy alone, resection of liver metastases has matured into standard of care. Generally, acceptance of new treatment modalities should be sought by means of well-designed, preferably randomized trials. Both CS combined with HIPEC for the treatment of PC as well as liver resection for metastases of colorectal origin might have been accepted earlier as standard of care, had these treatment regimens been compared earlier to standard treatments in randomized trials.

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The Study of Cavitational Ultrasonically Aspirated Material During Surgery for Colorectal Liver Metastases as a New Concept in Resection Margin

To the Editor:

We read with interest the recent report by Pawlik et al.[1] In their article, the authors describe the effect of positive surgical margin status on survival and site of recurrence in patients after hepatic resection for colorectal metastases. The results of this study give rise to some comments.

First, it is well known that surgical margin of less than 1 cm is risk factor for recurrence and death following liver resection. However, it is very difficult for the pathologist to assess the exact distance between the tumor and the end of the liver with great accuracy. Liver section can cause liver fractures along the line of the cut, completely changing the distance to be measured. Moreover, the positive ink margin can sometimes make the definition of a positive margin quite subjective (as Dr. Choti mentions in the discussion section of the article). The definition of positive margin is imperative. In our opinion, the exact surgical margin is the piece of liver that becomes aspirated by the cavitational ultrasonic surgical aspirator. This should be the real definition of liver surgical margin. The effect of surgical margin after hepatic resection should include the study of this aspirated tissue. In our experience (unpublished data), in 2 of 18 last hepatectomies, microscopic analysis showed a positive margin. However, none of them has the cavitational ultrasonic surgical aspirator line affected in the initial pathologic study. Currently, both patients are free of disease. The analysis of this aspirated hepatic material has been completed with molecular analysis techniques.

Second, the growth of liver metastases is important in understanding local recurrence. The rounding zone for liver metastasis should also be analyzed because it is an important area in the formation of new vessels.[2] A classification of liver metastases found differences, depending on the characteristics of the cut surface of the tumor. Nodular liver metastases had a better prognosis than confluent nodular[3] ones. This discovery suggests that tumor growth is centered in the rounding zone, and oncologic and prognostic studies may also be included in this.

Third, recently published data suggest that surgical margin is being overestimated.[4] Experienced liver surgeons plan the hepatic section line preserving a safety zone. However, the position of the tumor involving hepatic veins or its size can impose changes in the section line, reducing the margin. The significance of surgical margin status in long-term survival after resection of colorectal metastases remains controversial.

Finally, our congratulations to the authors for their extensive study, which will help toward understanding the progress of colorectal cancer patients. The usefulness of performing pathologic study of the margin has been very thoroughly reviewed.

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Predictive Indices of Morbidity and Mortality After Liver Resection

To the Editor:

Dr. Schroeder et al evaluated the predictive indices of the Model for End-Stage Liver Disease (MELD), Child-Turcotte-Pugh scores, and the American Society of Anesthesiology physical status classification on morbidity and mortality for patients after hepatic resection.[1] American Society of Anesthesiology and Child-Turcotte-Pugh scores were predictive of mortality but not morbidity, but MELD had no predictive value. Although we agree with the authors that the application of MELD as a prognostic tool for patients other than those awaiting hepatic transplantation requires further investigation before clinical application, we dispute the conclusion that MELD should not be used in the setting of elective hepatic resection.

MELD was specifically designed to predict liver failure specific mortality in patients with end-stage liver disease (cirrhosis) after transjugular intrahepatic portosystemic shunt.[2] The model has been repeatedly, independently validated in this clinical setting and has become the primary method for stratifying candidacy for hepatic transplantation.[3] Importantly, MELD was developed as a reliable objective method to determine mortality risk in patients with cirrhosis only. The applicability of MELD in patients without cirrhosis, regardless of intervention, is unknown. Indeed, MELD would not be expected to stratify patients without end-stage or chronic established liver disease because the model was developed in patients with cirrhosis. Although the analysis performed by Schroeder et al was detailed extensively, we think that the conclusion regarding MELD cannot be drawn without data on the specific number of patients with cirrhosis and the exclusion of patients with chronic renal failure and anticoagulants that affect serum creatinine and INR (essential components of MELD score calculation). Indeed, analysis between patients with and without cirrhosis (CPT codes) is warranted, especially detailing the cause of death, liver failure, or otherwise.

Table 2 showed that 166 patients had primary liver malignancies and were at risk for cirrhosis. The remaining 361 patients with metastatic and benign liver tumors were at expectedly far less risk for cirrhosis and liver failure-related morbidity. Moreover, if the majority of patients did not have cirrhosis, their MELD score is likely to be low; therefore, MELD may not be discriminatory. Although the 50 patients who died were deleted from the distribution of tumor type, the sample size should provide basis to assess the predictive value of MELD after hepatic resection for patients with and without cirrhosis. In contrast to the authors' findings, we have shown that MELD is predictive of postoperative mortality after hepatic resection for patients with cirrhosis and hepatocellular cancer.[4] Others have also shown that MELD is predictive of perioperative mortality after other operations in patients with cirrhosis.[5–8]

Tables 5 and 6 summarize the predictive accuracy of the indices for 30-day mortality and morbidity. None of the indices had a receiver operating area under the curve (ROC-AUC) greater than 0.7, the level above which an index has clinically useful predictive accuracy.[9] Thus, the only clear conclusion that can be drawn from this study is that there is no index that is clinically useful in predicting operative risk, either mortality or morbidity, in this group of patients. The data also confirm that it is difficult to make meaningful conclusions from retrospective studies in heterogeneous groups of patients drawn from a large number of institutions, which may have varying levels of surgical expertise.

We think that MELD can be clinically useful in counseling patients and families on the risks of operative mortality after elective hepatic resection in patients with cirrhosis. Although the authors failed to show the predictive value of MELD in the setting of elective hepatic resection, we think that clarification of their data by the presence or absence of cirrhosis and exclusion of patients with chronic renal failure and systemic anticoagulation is necessary before the predictive utility of MELD is dismissed.

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To the Editor:

The article by Schroeder et al[1] is a very interesting retrospective study evaluating predictive indices of morbidity and mortality in a large cohort of patients requiring partial hepatectomy.

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Among 587 patients undergoing elective liver resections, the authors investigated the possibility of MELD score, Child-Pugh score, ASA classification, Charlson index of comorbidity , and age to predict postoperative morbidity and mortality. From their analysis, they concluded that preoperative MELD score should not be used to predict outcome in patients requiring liver resections.

Postoperative liver failure remains one of the most dreadful complications after partial hepatectomy and the precise evaluation of liver function is one of the key point to select patients undergoing liver surgery in the intent to reduce postoperative morbidity and mortality. In the last 20 years, several approaches have been introduced to assess hepatic function, such as common biochemical tests (total bilirubin, prothrombin time, serum albumin, transaminases), quantitative tests (galactose elimination capacity, indocyanine green clearance test, lidocaine MEGX test),[2,3] and predictive score such as Child-Pugh score.[4]

Actually, in patients with preserved liver function, it is well known that the balance between extension of liver resection and remaining liver volume is the key point to minimize postoperative risks.[5] The assessment of total liver volume and remaining liver volume through the CT scan,[6] concept of standard liver volume or GRWR coming from experience with living donor liver transplantation, and introduction of selective portal vein embolization to increase the remaining liver[7] have dramatically reduced postoperative morbidity and mortality in liver surgery in the last 10 years[8]; in case of normal livers, the limit to the extension of partial hepatectomy is strongly related to the remaining liver functional volume and it cannot be derived by the common biochemical laboratory tests or quantitative tests.[5]

On the other hand, postoperative morbidity and mortality remain significant in cirrhotic patients and, in these cases, a precise evaluation of functional reserve is essential. Child-Pugh classification[4] remains the most widely accepted system that provides an initial clue to the extent of resection that a cirrhotic patient can tolerate.[8,9] Child-Pugh class C cirrhosis is considered an absolute contraindication for hepatic resection in most of the major hepatobiliary centers, and only minor resection would be considered for Child-Pugh class B cirrhotic patients. For patients with Child-Pugh class A cirrhosis, the decision for hepatectomy often requires additional liver function quantitative tests that provide more refined evaluation of functional reserve.[2,3]

Extrahepatic surgery, in particular cardiovascular and abdominal surgery, is associated with an increased incidence of postoperative morbidity and mortality in cirrhotic patients[10,11]; large studies investigated the comorbidities that increased significantly postoperative risks after extrahepatic surgery, such as preoperative ascites, INR, creatinemia, ASA status, and total bilirubin.[11,12] In the intent to summarize these factors, MELD score and Child-Pugh classification have been reported to accurately predict postoperative outcome in cirrhotic patents undergoing extrahepatic surgery.[11,13,14]

The model for end-stage liver disease (MELD) was developed to predict mortality of cirrhotic patients undergoing transjugular intrahepatic portosystemic shunts[15] and subsequently applied as a disease severity index for priority in waiting list for liver transplantation.[16] Since MELD score is not a reliable index in case of patients with preserved hepatic function, several modifications of MELD score have been introduced in the selection of the best candidates to liver transplantation.[17]

We have recently reported that MELD score is a reliable index in the preoperative evaluation of liver function in cirrhotic patients undergoing partial hepatectomy for hepatocellular carcinoma (HCC). In this study, we analyzed the postoperative outcome on 154 resected cirrhotic patients (92% Child A and 8% Child B patients). MELD score was below 9 in 49% of cases, between 9 and 10 in 35%, and 11 or above in 16%. A significant different in postoperative mortality, morbidity, hospital stay, and 1-year survival was reported in these 3 groups.[18] We have further shown that MELD score provides a more accurate partition of Child-Pugh class A patients, and it is able to identify those patients who are at high risk of postoperative liver failure and those who can be safely treated with partial hepatectomy.

A recent similar study was reported by the Mayo Clinic group. Among 82 cirrhotic patients, 45 (54.9%) showed a preoperative MELD score above 9; 43 of 80 Child A patients had a MELD score above 9. As in our study, a significant difference in morbidity, mortality, and 1-year survival depending on MELD score was shown.[19]

In the reported study by Schroeder et al, the mean ± SD MELD score was 6.5 ± 4.5; in the session "discussion," the same authors stated that 91% of patients had minimal or completely no evidence of liver disease. It is evident that in this series the common population was not cirrhotic.

In our series, as well as in the study from the Mayo Clinic, the median MELD score was 9, ie, there was a significant difference between Child A and Child B patients. Furthermore, in our experience of liver resection for HCC in patients with chronic hepatitis, the median MELD score was 8 and all of them below 10 (for this reason, they were excluded from the analysis of our study).

Even if other large controlled studied are needed, from the data available in the literature and our experience, MELD score seems to predict accurately postoperative liver failure and morbidity in patients with HCC on cirrhosis undergoing hepatic resection, and it is recommended in the preoperative assessment of liver function prior to hepatic resection in cirrhotic patients as well as in cirrhotic patients requiring extrahepatic surgery.

It should not be applied to predict outcome in the setting of noncirrhotic patients since it has not developed for these patients.

G. Ercolani

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Reply:

We appreciate the interest shown in our recent study evaluating a variety of clinical indices for their ability to predict morbidity and mortality after elective hepatic resection. Both Professor Ercolani and Dr. Nagorney make a significant point with reference to our study, which is the relevance MELD scoring to patients with known cirrhosis and to those in whom such status is unknown. Our series included patients from a variety of centers, undergoing elective hepatic resection for a variety of indications. Much of the work noted in response to our study deals exclusively with patients with cirrhosis, or those undergoing resection of hepatocellular carcinoma, a population with a very high incidence of cirrhosis. It is not surprising that MELD would predict outcomes in these populations, as their work bears out.

Our review of cases points out that MELD scoring was inferior to Child-Pugh scoring in predicting outcome after elective hepatic resection in a large group of unselected patients from multiple centers. As Ercolani points out, "a precise evaluation of functional reserve is essential," and MELD scoring in Child-Pugh class B or C patients may serve this role. This was not the aim of our review. In an ideal world, the surgeon would know the degree of liver impairment prior to any hepatic resection. This, however, is not the case. Our analysis simply does not support MELD as a prognostic tool when the presence of cirrhosis is not known. As Nagorney emphasizes, other etiologies of renal impairment or coagulation abnormalities may cause factitiously elevated MELD scores not at all related to liver disease.

We would also like to point out that this article was submitted for publication in late 2004. The additional references listed by Nagorney and Ercolani were not available at the time of our final submission and some are not even available now. If available, we would certainly have benefited from their analyses.

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Evidence-Based Treatment of Acute Pancreatitis: Antibiotic Prophylaxis in Necrotizing Pancreatitis

To the Editor:

With interest we read the article by Heinrich et al.[1] The authors have to be congratulated for their attempt to review the literature in acute pancreatitis in a rigorous "evidence-based" manner. We agree with the authors that there is a clear need for further clinical trials on acute pancreatitis. For this reason, in 2004, the Dutch Acute Pancreatitis Study Group embarked on a randomized double-blind placebo-controlled multicenter trial on *pro*biotic prophylaxis in patients with predicted severe acute pancreatitis.[2] Recently, our group initiated a second randomized controlled multicenter trial in 20 hospitals in which patients with infected necrotizing pancreatitis are randomized to single necrosectomy with postoperative lavage versus a minimally invasive "step-up approach," exactly the trial design suggested by Heinrich et al.[3] Concerning the author's recommendations on antibiotic prophylaxis, it should be noted that these may need tempering.

Based on the same literature as reviewed by Heinrich et al, an international group of renowned pancreatologists in 2004 recommended against the routine use of prophylactic systemic antibacterial or antifungal agents in patients with necrotizing pancreatitis. The main reason for this was the inconclusive evidence and divided expert opinion.[4] The 2005 U.K. guidelines for the management of acute pancreatitis stated: "The evidence to enable a recommendation about antibiotic prophylaxis against infection of pancreatic necrosis is conflicting and difficult to interpret. Some trials show benefit, others do not. At present there is no consensus on this issue . . . (recommendation grade C)".[5] Furthermore, we recently analyzed the methodological quality of the randomized controlled trials on systemic antibiotic prophylaxis in acute pancreatitis based on a previously published scoring system.[6] We demonstrated that the bet-

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ter the trial, the less impact of antibiotic prophylaxis on mortality was observed.[7] Therefore, it is surprising that Heinrich et al conclude that there is "level A" evidence that imipenem or meropenem prophylaxis decreases the risk of infected necrosis and mortality. In their analysis, the authors excluded the mortality data of the Isenmann trial and added a particular subgroup analysis. In our opinion, any argument to exclude all mortality data from methodologically the best trial yet can hardly be considered "evidence based." Furthermore, the authors state that they excluded all non-English studies but did include the Schwarz et al trial,[8] published only in German, which favors antibiotic prophylaxis. In contrast, the authors did not include 2 randomized controlled Czech trials of Spicak et al, both of which failed to show an effect of antibiotic prophylaxis.[9,10]

In addition, we would like to note that Dellinger et al recently presented the results of a randomized, double-blind, placebo-controlled, multicenter trial with meropenem prophylaxis in 100 patients with severe acute pancreatitis, including 57 patients with >30% pancreatic necrosis. This trial failed to demonstrate a beneficial effect of meropenem prophylaxis on infection of pancreatic necrosis and mortality.[11] Maybe that with the publication of this well-designed study the discussion on antibiotic prophylaxis in necrotizing pancreatitis can finally be closed. Nevertheless, we would like to encourage (national) multicenter groups to embark on well-designed, randomized controlled trials studying promising prophylactic or surgical strategies to unequivocally shift treatment paradigms in acute pancreatitis.

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Reply:

We thank Dr. Besselink and colleagues for their interest in our recent evidence-based analysis of the treatment of acute pancreatitis (AP), and the critical discussion of controversial issues.[1] We congratulate this group for the initiation of 2 important randomized trials, 1 of which will be the first randomized trial comparing 2 surgical interventions.

Dr. Besselink et al challenge our recommendation on the use of antibiotic prophylaxis in patients with necrotizing AP,[1] mostly because our recommendation is in contrast to the consensus statement by Nathens et al.[2] Furthermore, they question the exclusion of the mortality data of the Isenmann et al trial[3] from our analysis, while we included data of the Schwarz et al trial[4] published in German only. They also wonder why 2 randomized trials on antibiotic prophylaxis for AP by Spicak et al[5,6] published in Czech were not included in our analysis.

We welcome these comments as in fact they reinforce the value of an "evidence-based" approach to address specific questions in controversial areas such as the indication of antibiotic prophylaxis in AP, where most trials are small and underpowered to detect differences in morbidity or mortality. The strategy to address such issues through official guidelines and recommendations from a panel of experts or national societies is laudable, but, of note, ranks at the lowest level in the methodology of "evidence-based medicine." Also, the subjectivity of such "expert" discussions is well illustrated by opposite recommendations as some conclude for no indication of antibiotic prophylaxis,[2] while others remain indifferent,[7] or clearly recommend the routine use of antibiotics in the presence of necrosis.[8]

The evidence-based methodology relies exclusively on strict inclusion criteria of the available publications, and allows meta-analyses whenever 2 or more randomized trials are available to solve conflicting results. Statisticians familiar with this methodology are paramount partners in such analyses, and the "random-effects model" is preferable to take into account inhomogeneity among different studies by comparing treatment effects of each trial, rather than pooling inhomogeneous data.

The issue of antibiotic prophylaxis in necrotizing AP relates not only to the availability of underpowered or inadequate trials but also to the use of different antibiotic regimens with obviously different effects. For example, in the study by Isenmann et al,[3] 20% of the isolated bacteria in the placebo group were resistant to the antibiotic regimen (ciprofloxacin/metronidazole) used. Therefore, one cannot exclude that the negative results of this study is due to the ineffectiveness of the regimen used. We have been able to include important data of this trial after personal communication with the first

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author, but excluded the mortality data of this trial[3] from our analysis because the therapy for infected necrosis was neither uniform among participating centers nor were the patients stratified for center specific treatment protocols. We included the study by Schwarz et al.[4] to enhance the power of our meta-analysis. Although this trial was not published in English, the methodology was well described and fulfilled the inclusion criteria of our analysis. In contrast, we did not include the studies by Spicak et al.[5,6] since they were neither published in English nor available in a Medline cited journal. By performing our own meta-analysis to compare the treatment effects of the available trials, we achieved strong evidence (level A) favoring antibiotic prophylaxis in the presence of documented necrosis.[9]

The results of the Dellinger et al trial have recently been presented in an abstract form and are proposed by Besselink et al to definitively close the debate on the role of prophylactic antibiotics in AP.[10] We have to challenge this statement. Similarly to the study by Isenmann et al,[3] patients were included on the basis of "predicted" severe AP rather than proven necrotizing AP, and only about half of those patients eventually developed necrotizing AP. While this trial is available only in an abstract and therefore cannot be included in an evidence-based analysis, it fits with our recommendations that antibiotic prophylaxis should not be used for predicted severe AP but should be initiated in the presence of documented necrosis, eg, by CT scan.[1] It is possible that, with the availability of better prognostic criteria, antibiotic may be initiated earlier in the course of the disease.

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