Portal Hypertension III

Proceedings of the
Third Baverno International Consensus Workshop
on Definitions, Methodology and
Therapeutic Strategies

EDITED BY
ROBERTO DE FRANCHIS MD
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Preface

Portal hypertension is the haemodynamic abnormality associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy and bleeding from gastroesophageal varices. Since variceal bleeding is a medical emergency associated with significant morbidity and mortality, the evaluation of diagnostic tools and the design and conduct of good clinical trials for the treatment of this condition have always been difficult. Awareness of these difficulties has led to the organisation of a series of meetings aimed at reaching consensus on the definitions of some key events related to portal hypertension and variceal bleeding, and at producing guidelines for the conduct of trials in this field. Such meetings took place in Groningen, the Netherlands in 1986, in Baveno, Italy in 1990 (Baveno I) and in 1995 (Baveno II), in Milan, Italy in 1992, and in Reston, USA, in 1996. All these meetings were successful and produced consensus statements on some important points, although several issues remained unsettled.

In addition, since the Baveno II meeting, a great number of studies have expanded our knowledge on the pathophysiology of portal hypertension. Moreover, new diagnostic tools and new therapeutic approaches have been developed, which might lead to important changes in the management of this condition. Thus, my colleagues in the New Italian Endoscopic Club and I considered that the time had come to evaluate the impact of this new knowledge and of these new tools on the diagnostic and therapeutic strategies that we follow in managing patients with portal hypertension. Therefore, with the help and encouragement of a group of friends from 13 countries, many of whom had taken part in the previous two Baveno meetings, we organised a Baveno III workshop which took place on April 13–14, 2000. We decided to keep the name Baveno, although the workshop took place in Stresa, because we felt that Baveno had become a trademark for consensus in portal hypertension.

The aims of the Baveno III workshop were the same as in Baveno I and II, i.e. to refine and extend the definitions of key events concerning the bleeding episode, and to review and put into perspective the recent advances in our knowledge of the pathophysiology of portal hypertension, as well as the role

of the available diagnostic and therapeutic techniques that have been developed in studies carried out during the past five years. In addition, we continued the effort that was begun in Groningen and continued in the following workshops, of producing updated guidelines aimed at improving the quality of our future studies. We were very fortunate in being able to bring to this workshop many of the experts responsible for most of the major achievements of the last five years in this field.

The structure of the Baveno III workshop comprised nine sessions and four lectures. The first session was devoted to verifying the appropriateness and practicality of the definitions of key events that had been given in Baveno I and II, and an attempt was made to develop consensus definitions on points that were not addressed—or not agreed upon—in the previous workshops. In each of sessions 2 to 7 the Chairpersons and the Panellists reviewed an important topic related to the diagnosis or the treatment of portal hypertension. At the end of each session, the Chairpersons proposed a series of statements which were discussed within the panel and with the other experts on the floor, with the aim of reaching consensus on some important diagnostic or therapeutic issues. Session 8 was devoted to develop consensus definitions on the most important complications of therapies for portal hypertension. Such definitions should be adopted when reporting future trials, in order to make interpretation of the value of new treatments easier. Session 9 focused on three important methodological issues, i.e. prognostic stratification, quality of life evaluation and cost analysis, all three of which should be addressed in major future studies.

The four lectures were different in scope. The first one summarised the consensus reached in the Baveno I and II workshops and the impact of publications derived from those workshops in the medical literature. The second and third lectures addressed two exciting new areas of research, i.e. the possible role of stellate cells and of anti-fibrotic drugs in the pathophysiology and treatment of portal hypertension. The fourth lecture analysed the quality of trials in portal hypertension and other fields of hepatology.

These proceedings follow closely the structure of the workshop. The order of lectures and sessions is exactly the same, and the consensus statements that were agreed upon at the end of each session are reported at the end of the pertinent chapters.

Our deepest thanks go to all the friends who agreed to give lectures and to serve as Chairpersons and Panellists of the sessions, and who helped us by working hard in the preparation of the workshop and of the chapters. We also wish to thank Sandra Covre and her staff of Area Congressi, who managed brilliantly the organisation of the workshop, and Paolo Carnevale and Luca de Franchis who skilfully operated the computer-videoprojector systems throughout the workshop. In addition, we are grateful to the European As-

sociation for the Study of the Liver (EASL), the Associazione Italiana per lo Studio del Fegato (AISF) and the Società Italiana di Gastroenterologia, (SIGE) who endorsed the meeting, to the companies who sponsored the workshop and especially to UCB Pharma S.A., who made the publication of this book possible through a generous grant, to Catherine Pelissier and Nirjihar Chatterjee for their encouragement and co-operation in this project, and to Blackwell Science for the timely and excellent production of this volume.

ROBERTO DE FRANCHIS

On behalf of the New Italian Endoscopic Club

LECTURE

What Have We Accomplished?

Roberto de Franchis

INTRODUCTION

The idea of holding consensus meetings on portal hypertension was born in 1986, when Andy Burroughs organized the first such meeting in Groningen, the Netherlands [1]. After Groningen, other meetings followed, in Baveno, Italy in 1990 (Baveno I) [2] and in 1995 (Baveno II) [3,4], in Milan, Italy in 1992 [5], and in Reston, USA [6]. This is the sixth meeting of this kind.

This review covers the following points:

1 A summary of the consensus reached at the Baveno I and II meetings.
2 The publications derived from the Baveno I and II workshops.
3 The quantitative impact of the Baveno I and II consensus on the medical literature.
4 The attendance at the Baveno workshops.

SUMMARY OF THE CONSENSUS REACHED AT THE BAVENO I AND II MEETINGS

- Definitions of key events.
- Diagnostic evaluation of patients with portal hypertension.
- Prognostic factors for first bleeding, rebleeding and survival.
- Therapeutic strategies in patients with portal hypertension.
- Methodological requirements of future trials.

Definitions of key events

I Time zero

The time of admission to the first hospital the patient is taken to is time zero.

II Bleeding

Haematemesis and/or melaena, or gastric aspirate containing blood.

III Clinically significant bleeding

A bleeding episode is clinically significant when there is:
1 transfusion requirement of ≥ 2 units of blood within 24 hours of time zero, *and*
2 systolic blood pressure < 100 mmHg or a postural change of > 20 mmHg, *and/or*
3 pulse rate > 100/min at time zero.

IV Death related to variceal bleeding

Any death within 6 weeks of time zero would be a death related to variceal bleeding, regardless of the mode of death. Thirty-day mortality (a surgical convention) and deaths during admission should also be reported. The starting point for all three intervals is time zero. The immediately precipitating causes of death should be described, and represent the mode of death.

V Time frame for acute bleeding

The acute bleeding episode is represented by an interval of 48 hours from time zero with no evidence of clinically significant bleeding between 24 and 48 hours. Evidence of any bleeding after 48 hours is the first rebleeding episode

VI Failure to control bleeding

The definition of failure to control bleeding was divided into 2 time frames:
Within 6 hours: any of the following factors:
1 transfusion of 4 units of blood or more, and inability to achieve an increase in systolic blood pressure of 20 mmHg or to 70 mmHg or more, *and/or*
2 pulse reduction to less than 100 mmHg or a reduction of 20/min from baseline pulse rate.
After 6 hours: any of the following factors:
1 the occurrence of haematemesis,
2 reduction in blood pressure of more than 20 mmHg from the 6-hour point, *and/or*
3 increase of pulse rate of more than 20/min from the 6-hour point on 2 consecutive readings 1 hour apart,

4 transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the Hct to above 27% or Hb to above 9 g/dl.

VII Rebleeding

The occurrence of new haematemesis or new melaena after a period of 24 hours or more from the 24-hour point of stable vital signs and hct/hb following an episode of acute bleeding.

VIII Rebleeding index

Episodes of rebleeding + 1/months of follow-up per patient
This index should be used to evaluate:
1 patients with > 1 rebleed;
2 patients who never rebleed;
3 the interval without rebleeding;
4 as a measure of distribution.

Diagnostic evaluation of patients with portal hypertension

I Diagnosis of portal hypertension

1 Endoscopy and ultrasonography (preferably with Doppler) should be used routinely for the assessment of portal hypertension in patients with cirrhosis without previous bleeding.
2 The main parameter to use for assessing the risk of bleeding is variceal size. Optional parameters are the Child–Pugh score, hepatic vein pressure gradient (HVPG), variceal pressure and Doppler ultrasound.
3 In nontreated patients at low or intermediate bleeding risk, follow-up endoscopy should be done at 12-month intervals
4 The efficacy of new pharmacological treatments must be evaluated by HVPG measurement

II Criteria for diagnosis of variceal bleeding:

1 Endoscopy should be done as soon as possible.
2 The timing of endoscopy with respect to bleeding must be reported.
3 Active bleeding: diagnosis certain.
4 Signs of recent bleeding:
   (a) 'white nipple'—certain;
   (b) if clot—wash!

5 Varices without other potential bleeding sources: diagnosis certain when blood is present in stomach and/or if endoscopy is made within 24 hours.

III Criteria for diagnosis of bleeding due to portal hypertensive gastropathy (PHG)

1 Acute bleeding: endoscopic evidence of an active bleeding lesion, assessed after washing or removing clots, with the stomach fully distended. If gastric or oesophageal varices are present, endoscopy should be repeated after 24 hours
2 Chronic bleeding should be assessed by the following criteria:
(a) presence of endoscopic lesions;
(b) evidence of faecal blood loss;
(c) > 2 g drop in Hb level in 3 months;
(d) low serum transferrin saturation
in the absence of:
(a) portal-hypertension related colonic or duodenal lesions;
(b) bone marrow suppression;
(c) associated renal disease and
(d) history of nonsteroidal anti-inflammatory drugs (NSAID) use.

IV Criteria for diagnosis of bleeding from gastric varices

The relationship between the existing classifications and bleeding events needs to be evaluated.

Prognostic factors for first bleeding, rebleeding and survival

I Risk factors for first bleeding

1 Assessment of the risk of first bleeding is important.
2 Simple endoscopic criteria such as variceal size and red colour signs must be used, possibly in conjunction with the Child–Pugh score as in the NIEC index.
3 The existing prospective information on the risk of first bleeding is insufficient and should be extended by further studies, including possibly additional parameters.

II Risk factors for early and late rebleeding and death

No consensus was reached on these points, mainly because of insufficient available information.

Therapeutic strategies in patients with portal hypertension

I Prevention of the first bleeding episode

1 Pharmacologic treatment with vasoactive drugs is the only recommended therapy.
2 Non-cardioselective β-adrenergic blockers are the drugs of choice.
3 Isosorbide-5-mononitrate is a possible alternative in case of intolerance or contraindications to β-blockers.
4 Sclerotherapy is definitely not indicated
5 Endoscopic rubber-band ligation needs further evaluation.

II Treatment of acute variceal bleeding

1 Both endoscopic treatments (sclerotherapy and band ligation) and pharmacologic treatments (terlipressin and somatostatin) are effective. More information is needed on octreotide.
2 Injection of tissue adhesives or thrombin for bleeding gastric varices appears to be effective but requires confirmation.
3 TIPS can be used as salvage treatment in variceal bleeding uncontrolled by endoscopic and pharmacologic therapy.

III Prevention of rebleeding

1 Band ligation has replaced injection sclerosis as the optimum endoscopic treatment to prevent recurrent bleeding from oesophageal varices.
2 Drug treatment with nonselective β-blockers is also a valuable option.
3 If there are no contraindications, the association of β-blockers and endoscopic therapy could be used.
4 Insufficient information is available on the use of combinations of drugs. This option needs to be tested.
5 Only patients with severe PHG and bleeding should be treated with vasoactive drugs to prevent rebleeding.
6 TIPS could be used to prevent rebleeding in patients with frequent repeated episodes of variceal haemorrhage, despite adequate elective treatment. However, this indication needs testing in appropriately designed randomized controlled trials.
7 Surgical shunts and, in selected cases, devascularization are appropriate treatments for patients with portal hypertension and preserved liver function who cannot be managed by endoscopic an/or pharmacologic therapy.

8 Liver transplant is the treatment of choice in patients with portal hypertension and end-stage liver disease. The decision to transplant is based on appropriate selection criteria which may vary according to the disease.

Methodological requirements of future trials

I General requirements

1 Randomized clinical trials (RCTs) should meet good clinical practice (GCP) requirements.
2 Larger trials should be performed to achieve sufficient statistical power.
3 If possible, RCTs should include complications, quality of life and health-economic assessments using appropriate methodology; they should include data on end-points on which there exists consensus, and should use structured reporting.
4 All therapies should be monitored by cumulative meta-analysis in order to avoid unnecessary duplication.
5 Meta-analysis on individual patient data could be performed in order to identify prognostic and therapeutic variables.

II Major outcome measures

1 Prevention of first bleeding:
   (a) first variceal bleeding;
   (b) death before variceal bleeding;
   (c) course, including death, after variceal bleeding.
2 Treatment of acute bleeding:
   (a) control of bleeding;
   (b) death within 42 days after bleeding.
3 Prevention of rebleeding:
   (a) variceal rebleeding;
   (b) death before variceal rebleeding;
   (c) course, including death, after variceal rebleeding.

III Subsidiary outcome measures

1 Clinical course:
   (a) causes of death, especially bleeding;
   (b) liver function (encephalopathy);
   (c) upper gastrointestinal bleeding from nonvariceal sources.
2 Cost of treatment:
   (a) side effects and complications;

(b) time in hospital and intensive care unit.
3 Additional treatments:
(a) transfusion;
(b) ancillary treatment.
4 Overall result
(a) quality of life;
(b) cost-benefit.
5 Paraclinical effects as surrogates of potential clinical effects:
(a) variceal size;
(b) haemodynamics.

IV Sample size calculation

1 Essential part of the planning of trials expected to produce conclusive results on major end-points.
2 It should be included in the final report of any trial

V Double blindness

1 Useful to avoid biased assessment of outcomes in which there is a subjective component, either for the physician or the patient.
2 Useful to avoid biased approaches to patients, by physicians, staff, relatives, and patients themselves, with possible influence on the clinical course.
3 Necessary for the distinction between specific biological effects and general effects of administration of the treatment.
4 Should be used whenever possible.

VI Randomization

1 Use randomization for allocation of treatments to be compared.
2 Randomization must be closed, i.e. the treatment must not be known before the decision to include the patients is made.

VII Stratification in randomization

1 Always by centre in multicentre trials.
2 By one or two well-defined and easily accessible variables of great prognostic significance in trials including less than 100 patients.

VIII Exclusion before randomization

1 Patients evaluated and fulfilling the entry criteria, but not randomized must be reported.

IX Intention to treat analysis

1 Include all randomized patients with outcomes recorded at any time until closure of the trial in the analysis.
2 An analysis 'as per treatment received' should be performed that excludes only patients who did not actually start the treatment. This analysis should include entry characteristics to establish balance.

X Exclusion after randomization

1 Patients withdrawn from the trial or lost to follow-up need to be described and analysed.

XI Competing end-points

1 Should be taken into account in the analysis and interpretation of the results.

XII Stratification in analysis

1 Several variables may be taken into account in multivariate analysis, but it is advisable to decide which variables in the planning of the trial.
2 The variables used in stratification before randomization should be included.

XIII Management of patients in the control group

1 Prevention of first bleeding: no consensus was reached on whether no treatment is still justified.
2 Treatment of acute bleeding: some accepted form of treatment should be given.
3 Prevention of rebleeding: no treatment is not justified—sclerotherapy, band ligation, β-blockers or surgery must be used.

PUBLICATIONS DERIVED FROM THE BAVENO I AND II WORKSHOPS

- The Baveno I workshop was reported in the *Journal of Hepatology* in 1992 [1].
- A report of the Baveno II workshop was published in the *Journal of Hepatology* in 1996 [3].
- The proceedings book of the Baveno II workshop was published by Blackwell Science in 1996 [4].

QUANTITATIVE IMPACT OF THE BAVENO CONSENSUS ON THE MEDICAL LITERATURE

Figure 1 shows the number of citations of the Baveno III publications in the medical literature between January 1993 and June 1999. The journals where such citations appeared are listed in Table 1.

ATTENDANCE AT THE BAVENO WORKSHOPS

Two hundred and five participants took part in the Baveno I workshop; 81% of them were from Italy, 19% from other countries. Eighteen countries were represented.

The Baveno II workshop was attended by 252 participants, of whom 74% were from Italy, and 26% from other countries. Eighteen countries were represented.

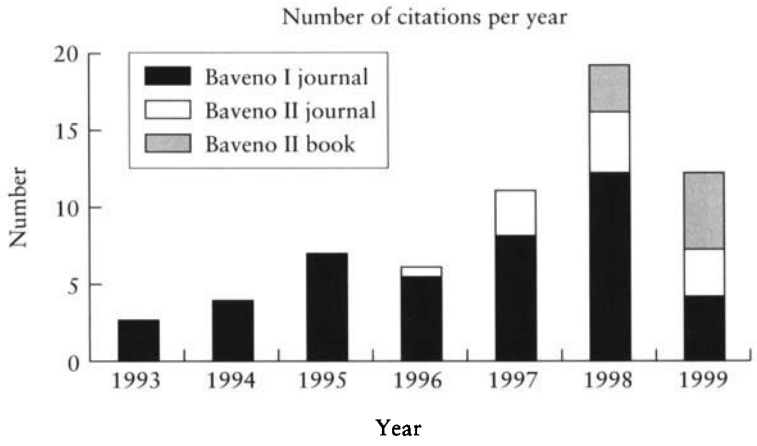

Fig. 1 Citations of the Baveno reports.

Table 1 Journals where the Baveno Reports were cited.

Journal	Number of citations
Hepatology	12
Journal of Hepatology	7
Gastroenterology	6
American Journal of Gastroenterology	5
Gastroenterologie Clinique et Biologique	5
Bailliere's Clinical Gastroenterology	3
Seminars in Liver Disease	3
Lancet	2
New England Journal of Medicine	2
Alimentary Pharmacology and Therapeutics	1
Current Problems in Surgery	1
Deutsche Medizinische Wochenschrift	1
Digestion	1
Digestive Disease and Sciences	1
Quarterly Journal of Medicine	1
Regulatory Peptides	1
Scandinavian Journal of Gastroenterology	1

The attendance of the Baveno III workshop was 385. Of those, 49% were from Italy, 51% from other countries. Twenty-nine countries were represented.

These data are shown graphically in Fig. 2.

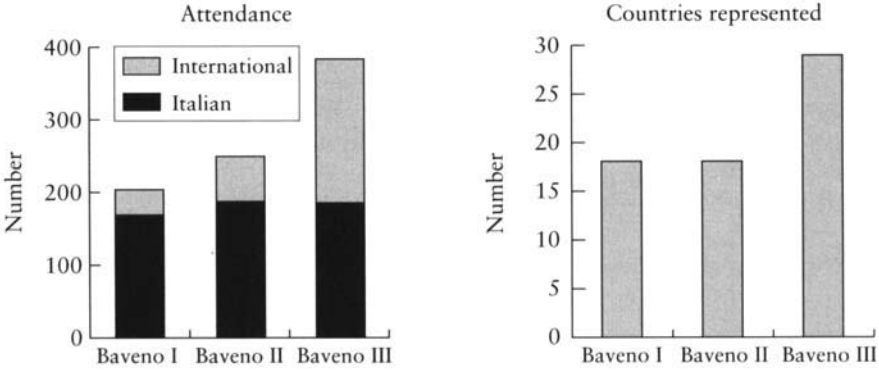

Fig. 2 Attendance at the Baveno workshops.

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SESSION 1

Definition of Key Events: Let's Try Again

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INTRODUCTION

In Baveno II there were several issues, particularly regarding acute bleeding, for which no agreement was reached [1]. For this session of Baveno III a questionnaire covering these issues was sent to all panellists from all the sessions in Baveno III. There were 44 panellists and 24 responses. The results of the questionnaire were commented on by the session panellists and the audience and were the basis for discussion.

ACUTE BLEEDING

At Baveno II there was no consensus on the significance of active bleeding at endoscopy. New issues that have arisen since then are: documentation of infection and/or antibiotics, failure of endoscopic therapy, and significance of blood transfusion requirement. Some new data was presented with regard to validating 'failure to control bleeding' criteria.

Active bleeding at endoscopy

It was recognized that there was no study that distinguished venous spurting from oozing at the oesophago-gastric junction, in terms of prognosis or other clinical differences. At Baveno III active bleeding at endoscopy defined as either of the above was felt to be prognostic for both survival and bleeding, whether or not vasoactive drugs had been used beforehand. It was also felt to be an endpoint for failure of drug therapy if it had been used before diagnostic endoscopy (Table 2).

The consensus statement after the discussion was as follows:

> Active bleeding at endoscopy is blood emanating from a varix. Active bleeding at endoscopy has prognostic value with regard to failure to control bleeding over the next few days.

Table 2 Clinical significance of active bleeding at diagnostic endoscopy: responses to Baveno III questionnaire.

	Without prior vasoactive drugs			With prior vasoactive drugs		
	yes	no	don't know	yes	no	don't know
6 week mortality	12	8	4	10	8	6
Failure to control bleeding <48 hours	16	5	3	15	4	5
Failure to control bleeding <5 days	13	5	6	12	5	7
Diagnostic for failure of drug therapy	–	–	–	15	7	2

Data from the Royal Free Hospital in patients treated after diagnostic endoscopy [2], (who had not fulfilled haemodynamic criteria of failure to control bleeding), showed that there was no time bias with regard to the interval to endoscopy between those found to have active bleeding and those who did not, i.e. potentially earlier in those with active bleeding (Table 3).

Infection and acute bleeding

Since Baveno II, a meta-analysis of prophylactic antibiotics in variceal bleeding in cirrhotics has been published [3] showing reduced morbidity as a result of infection, and also reduced mortality. In addition the potential causal relationship between infection and bleeding has been hypothesized [4], and a strong association between presence of infection, or use of therapeutic antibiotics, and failure to control bleeding has been shown [5].

Responses to issues concerning documentation of infection in acute bleeding are shown in Table 4.

Table 3 Timing of endoscopy from admission to hospital (Royal Free Hospital) in relation to the presence or absence of active bleeding (spurting or oozing).

$n = 264$	No active bleeding	Active bleeding
Admissions	160	106
Median interval to endoscopy (h)	9	7
Interquartile range (h)	(5–20)	(4–15)

Table 4 Inclusion and need for documentation of clinical aspects of infection in acute variceal bleeding. Responses to Baveno III questionnaire.

Clinical feature	Yes	No	Don't know
White cell count on admission	19	4	1
Culture positive infection	15	7	2
Site of infection	16	6	2
Use of therapeutic antibiotics	15	7	2
Confirmation of prophylactic antibiotic use	20	3	1
Do you use prophylactic antibiotics?	17	6	1

The agreement was that evaluation of infection and antibiotic use was relevant to survival analysis, and that it should be looked at in relation to control of bleeding.

Definition of failure of a therapeutic regimen has always been difficult to agree on. However, failure of endoscopic control of acute bleeding (within 5 days of time zero—i.e. admission to the first hospital the patient is taken to) is perhaps the most important one. This question was asked in terms of sessions of endoscopic therapy, with or without use of vasoactive drugs before diagnostic endoscopy (Table 5).

Duration of vasoactive therapy

In view of evidence from randomized studies concerning longer duration of therapy, panellists were asked for how long they used vasoactive drugs. Most used them for 5 days ($n = 13$), and others for 24 hours ($n = 3$), 2 days ($n = 2$), 3 days ($n = 2$), and 2 or 5 days ($n = 2$).

Evaluation of blood transfusion differences in clinical trials

As mortality may be an endpoint which is difficult to assess as a result of sample size problems, control of bleeding is often a primary endpoint in trials of acute bleeding. Blood transfusion differences are part of this evaluation.

Table 5 Definition of failure of endoscopic control within 5 days of time zero. Responses to questionnaire for Baveno III.

Number of endoscopic sessions	?	1	2	3	4
With prior use of vasoactive drugs	1	4	17	2	0
Without prior use of vasoactive drugs	3	5	13	2	1

Panellists were asked what median difference, in terms of units of blood transfused, would represent a clinically relevant difference (if statistically significant) (Table 6).

They were also asked if authors' definition of control of bleeding showed a significant benefit statistically in favour of one treatment but, if no differences were found in transfusion requirement, would they consider benefit to be proven (Table 7).

Blood transfusion requirement was considered one of the most objective measurements of clinical efficacy of any therapy. This was also the conclusion of a prospective study concerning the applicability of the Baveno II criteria for acute bleeding by Calès *et al.* [6], in the context of a double blind multicentre clinical trial. The key feature of the study was the blinded (to therapy) overall clinical judgement for haemodynamic stability, separately recorded by the clinical investigator as compared to the Steering Committee. The study showed that haemodynamic and blood transfusion criteria at 6 hours (as defined at Baveno II) did not match subsequent haemodynamic instability, and moreover 13% of patients had not had endoscopy by 6 hours. In particular, the criterion of pulse rate > 100 x within 6 hours as indicating failure to control bleeding was found to be too soft. In 15% of cases deemed to have failed

Table 6 Statistically significant differences in median blood unit requirement between 2 treatments considered to be clinically significant. Baveno III responses to questionnaire.

Difference in units of blood considered clinically significant	No. of respondents
Any differences	1
1 unit	4
2 units	14
3 units	4
? units	1

Table 7 Proven statistically significant differences between treatments in a trial but no differences in blood transfusion requirements. Baveno III questionnaire responses.

Benefit considered to be	No. of respondents
Proven benefit as stated by authors	4
Possible proven benefit	11
Possible unproven benefit	4
Unproven benefit	3

by the Baveno II criteria, the tachycardia criterion was the parameter that defined this failure, but this was not corroborated by overall clinical judgement. Another 17 cases of failure also did not tally with overall clinical judgement.

A time dependent evaluation, i.e. time of failure, was found to be a better reflection for trial events. This type of evaluation is in contrast to the time frame for acute bleeding at Baveno II, which was said to be represented by an interval of 48 hours from time zero without evidence of clinically significant bleeding between 24 and 48 hours, i.e. a dichotomous variable. Evidence of bleeding after 48 hours is the first rebleeding episode [1].

The authors [6] also found a time dependent evaluation would be useful for transfusion requirement. At Baveno II, the agreement was to express transfusion as units/hour up to the time of failure or end of trial infusion. The panellists and the audience agreed that the data presented by Calès *et al.* [6] reflected their own experience of the Baveno II criteria in clinical practice, and consensus was reached to obtain further data to validate the Baveno II consensus definitions (and Reston 1996) [7] on failure to control bleeding and its time frames. This led to the consensus statement:

> The Baveno II and Reston 1996 criteria should be re-evaluated, in particular the use of haemodynamic criteria without evidence of clinical bleeding.

At the end of the discussion on acute bleeding, there were several recommendations as to new information which was needed in this area:

New information to be obtained was defined in a consensus statement.

- Whether the clinical or prognostic significance of active bleeding with or without drug therapy is the same.
- Whether active bleeding is related to mortality.
- Validation of Baveno II and Reston 1996 failure to control acute bleeding criteria, in particular haemodynamic indices.
- Relationship of infection to failure to control bleeding and mortality.
- Trials of salvage therapy following failure to control bleeding.

REBLEEDING

At Baveno II there was no consensus on: evaluation of rebleeding (whether for clinically significant episodes, sources of rebleeding or number of rebleeding episodes), nor on what constituted failure to prevent rebleeding, nor failure of a particular treatment strategy for rebleeding, New issues that have arisen since Baveno II, were: the clinical significance of measuring portal pressure particularly in patients given drug therapy [8,9]. Amongst the panellists the majority still agreed with Baveno II consensus definitions: for rebleeding (yes, $n = 21$), for sources to be included for rebleeding (yes, $n = 20$) and for rebleeding index (yes, $n = 22$).

Calculation of the start of the interval for rebleeding

There was still considerable variation in when the start of the interval for the calculation of rebleeding would start, in relation to stability from acute bleeding: 12 hours ($n = 1$), 24 hours ($n = 1$), 48 hours ($n = 7$), 6 days ($n = 5$), at start of preventative therapy ($n = 12$).

Failure of therapy to prevent bleeding

There was still initial disagreement on what constituted failure of therapy assuming documentation of portal hypertensive sources (Table 8), and there were different definitions for different treatments.

Following discussion the consensus was:

> Failure of secondary prevention is a single episode of clinically significant rebleeding from portal hypertensive sources (as previously defined in Baveno II).

Table 8 Definition of failure of prevention of rebleeding (assuming documented portal hypertensive sources) in terms of number of episodes of clinically significant rebleeding. Responses to Baveno questionnaire.

Therapy	Endoscopic	Drugs
One clinically significant rebleed	12	16
Two clinically significant rebleeds	7	6
Three clinically significant rebleeds	1	0
Depends on time interval	3	2

Portal pressure measurements

Panellists were asked whether a single measurement (after baseline) of portal pressure was predictive of therapeutic response to medical therapy. Fifteen believed this to be true, nine disagreed and one answered 'do not know'. Greater variation in responses occurred with respect to the timing of the measurement. To date published literature has associated failure to achieve target reductions in wedged hepatic venous pressure at 3 months, with rebleeding [9]. The answers were: at 1 month ($n = 12$), 3 months ($n = 3$), do not know ($n = 4$) and multiple measurements ($n = 5$). The discussion confirmed that many patients rebleed within 3 months, as shown in a recent trial of banding versus beta-blockers [10] so that earlier measurement would be indicated.

A third question was asked as to whether a failure to achieve the published target reductions of > 20% from baseline HVPG or < 12 mmHg [8,9] HVPG, would lead to abandoning drug therapy providing maximally tolerated doses were being given. Only eight would do so, 13 would not and two did not know.

PRIMARY PROPHYLAXIS

This was the subject of Session 5 at Baveno III. The results of questions asked in Session 1 questionnaire are set out here for completeness. All panellists screened for varices, using endoscopy. If large varices (> 5 mm diameter) were found, 22 used beta-blocker prophylaxis as first choice. If small varices were found, 15 would re-endoscope at intervals, six would use beta-blockers, and one each would either randomize in a trial or measure pressure, one had no answer. Asked their opinion as to whether published randomized trials of drugs versus banding would change their current clinical practice, 19 would continue to use drugs, one would use banding and two had no preference, one did not know.

If contraindications or tolerance to drug therapy was present the treatment preferred by the panellists would be: banding ($n = 8$), a controlled trial ($n = 6$), nitrates alone ($n = 4$), no therapy ($n = 4$), did not know ($n = 2$). Lastly, asked whether the published study on prevention of varices was sufficient evidence to suggest drug therapy was ineffective, only two thought so, eighteen did not and four did not know. Further studies were felt necessary by 22, and not so by two.

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Baveno III Consensus Statements: Definitions of Key Events

Andrew K. Burroughs (Chairman), Jaime Bosch, Guadalupe Garcia-Tsao, J. Mike Henderson, Loren Laine, Frederik Nevens, Oliviero Riggio

1 Active bleeding at endoscopy is blood emanating from a varix.

2 Active bleeding at endoscopy has prognostic value with regard to failure to control bleeding over the next few days.

3 The Baveno II and Reston 1996 criteria should be re-evaluated, in particular the use of haemodynamic criteria without evidence of clinical bleeding.

4 Failure of secondary prevention is a single episode of clinically significant rebleeding from portal hypertensive sources (as previously defined in Baveno II).

5 New information to be obtained in future studies:

(a) Whether the clinical or prognostic significance of active bleeding with or without drug therapy is the same.

(b) Whether active bleeding is related to mortality.

(c) Validation of Baveno II and Reston 1996 failure to control acute bleeding criteria, in particular haemodynamic indices.

(d) Relationship of infection to failure to control bleeding and mortality.

(e) Trials of salvage therapy following failure to prevent early rebleeding.

LECTURE

Stellate Cells: Do They Have a Role in Portal Hypertension?

Massimo Pinzani

INTRODUCTION

In the past ten years we have witnessed an exponential increase in the knowledge on the development and progression of liver fibrosis. At present, liver fibrogenesis is referred to as a dynamic process involving complex cellular and molecular mechanisms, resulting from the chronic activation of the tissue repair mechanisms that follows reiterated liver tissue injury. The identification and characterization of the cell types and of the different mediators involved in this process has allowed a 'revisitation' of several issues related to liver cirrhosis and its immediate consequences. Among these, evaluation of the relationships occurring between fibrogenesis on one hand, and portal hypertension, cholestasis and the development of hepatocellular carcinoma on the other, represent some of the hottest areas of research in the field of hepatology. Following extensive demonstrations that hepatic stellate cells, (liver-specific pericytes playing a key role in the progression of hepatic fibrogenesis), are able to contract in response to different stimuli, the concept that this cell type may play an important role in the development of portal hypertension has considerably expanded. The main aim of this article is to clarify this latter issue in order to reach a wide consensus and to sharpen the aims of further intervention in the treatment of portal hypertension.

WHY THIS TOPIC?

Hepatic stellate cells (HSC) are located in the space of Disse in close contact with hepatocytes and sinusoidal endothelial cells. In human liver, HSC are disposed along the sinusoids with a nucleus-to-nucleus distance of 40 μm, indicating that the sinusoids are equipped with HSC at certain fixed distances [1]. Overall, these observations suggest that although the total number of HSC constitute a small percentage of the total number of liver cells (approximately 5–8%), their spatial disposition and spatial extension may be sufficient to cover the entire hepatic sinusoidal microcirculatory network. The most con-

spicuous ultrastructural feature of HSC in the normal adult liver is the presence of cytoplasmic lipid droplets ranging in diameter 1–2 μm (i.e., 'fat-storing cells' or 'lipocytes') [1]. These lipid droplets are important in the hepatic storage of retinyl esters, and, accordingly HSC have been shown to play a key role in the metabolism of retinoids.

Studies performed in the last decade have extensively characterized the key role of HSC in the progression of liver fibrosis. As a consequence of chronic liver tissue damage, HSC, as well as other extracellular matrix-producing cells (e.g. fibroblasts and myofibroblasts constitutively present in the portal tract), undergo a process of activation that leads to a phenotype characterized by increased proliferative, motile and contractile attitudes.

The recognition that HSC are provided with contractile properties represent one of the most important acquisitions in the knowledge of the biology of this cell type (see [2] for review). Contraction of activated HSC occurs *in vitro* in response to different vasoconstrictors (Table 9). However, this experimental evidence is likely to be more representative of HSC contractile status in fibrotic liver, where contraction of activated HSC in response to various stimuli may have important implications in the pathogenesis of portal hypertension and in the contraction of mature scar tissue. Following two pioneer studies published in 1992 [3,4] demonstrating the contraction of HSC in response to different vasoconstrictors, the assumption of a role of this cell type in the genesis and progression of portal hypertension has reached a level of potential misunderstanding. For this reason, it is necessary to revisit this problem and reach some clear-cut conclusions.

In order to proceed in a rational order, this chapter is organized in order to address three specific issues:

Table 9 Action of vasoactive agents on hepatic stellate cells.

Agent	Contraction	Relaxation	$[Ca^{2+}]i$ increase
Endothelin-1	++++		Coupled
Thrombin	++++		Coupled
Angiotensin-II	+++		Coupled
Substance P	+++		
Adenosine	+++		(Coupled)
Thromboxane	+++		
Vasopressin	++++		Coupled
Adrenomedullin		++	
Nitric oxide		++	
Platelet-activating factor	+		Coupled
Agents increasing intracellular cAMP		+++	
Lipo PGE_1		++	

1 Do stellate cells play a role in the regulation of sinusoidal tone in normal liver?
2 Do stellate cells influence portal pressure in conditions of developing fibrosis and 'capillarization' of sinusoids?
3 Do stellate cells influence portal pressure in cirrhotic liver?

DO STELLATE CELLS PLAY A ROLE IN THE REGULATION OF SINUSOIDAL TONE IN NORMAL LIVER?

Because of their anatomical location, ultrastructural features, and similarities with pericytes regulating blood flow in other organs, HSC have been proposed to function as liver-specific pericytes. Branches of the autonomic nerve fibres coursing through the space of Disse show a contact surface with HSC [5]. In addition, nerve endings containing substance P and vasoactive intestinal peptide have been demonstrated in the vicinity of HSC [6]. In this context, Knittel and co-workers demonstrated that, in both normal and fibrotic livers, the expression of N-CAM, a central nervous system typical adhesion molecule detected in hepatic nerves, and the expression of glial fibrillary acidic protein (GFAP) are restricted, among liver cell types, to HSC [7]. These observations raised a current key issue concerning the origin of this cell type, previously considered to be of myogenic origin by reason of the expression of desmin and smooth muscle α-actin (α-SMA). Moreover, Niki and co-workers have recently demonstrated that activated HSC express nestin, a class VI intermediate filament protein originally identified as a marker for neural stem cells [8]. It is generally accepted that cephalic neural crest cells give rise to a variety of cell types, including neurones, glial cells, cartilage, bone and smooth muscle cells. Consequently, a key question is the following: 'is there a common precursor cell in the neural crest from which stellate cells originate?' Further studies on the embryonic origin of these cells are required in order to clarify this important issue.

In spite of the evidence suggesting a potential role of HSC in the regulation of sinusoidal blood flow, there is still substantial controversy. In a recent review article Ekataksin and Kaneda [9] make several considerations, mostly from the anatomical standpoint, arguing against the role of HSC in the regulation of sinusoidal blood flow. Firstly, in their spatial disposition HSC do not have a stellate form (typical of their aspect in bidimensional culture on plastic) but rather a 'spider-like' appearance ('arachnocytes') in respect of their small cell body with a series of radiating and parallel slender processes. According to these authors, cells with this tridimensional disposition are not likely to be 'contraction ready'. Additional limitations to effective cell contraction are offered by the spatial limitation of the space of Disse, by the intracytoplasmic

presence of lipid droplets that prevent microfilaments from assembly in a long span, and by the ultrastructural evidence of a limited development of contractile filaments in quiescent HSC. Regardless, studies evaluating the hepatic microcirculation by intravital microscopy techniques have suggested that HSC may be effectively involved in the regulation of sinusoidal tone in the normal liver [10,11].

DO STELLATE CELLS INFLUENCE PORTAL PRESSURE IN CONDITIONS OF DEVELOPING FIBROSIS AND 'CAPILLARIZATION' OF SINUSOIDS?

As stated previously, a remarkable increase in HSC contractile properties is likely to be a key feature of their activated state [3,4,12,13]. At this stage, HSC have been shown to express a large number of voltage-operated calcium channels, the activation of which is associated with an increased intracellular calcium concentration followed by marked cell contraction [14]. These changes are possibly dependent on intracellular and extracellular factors. First, as previously mentioned, the complete transition to the 'myofibroblast-like' phenotype is ultrastructurally characterized by the appearance of massive contractile structures including dense bodies and patches of myofilaments diffused throughout the cytoplasm. Second, HSC activation is accompanied by increased expression of α-SMA, and it is increasingly likely that this cytoskeletal protein is directly responsible for increased cell contractility. Interestingly, both pro-fibrogenic agents and vasoconstrictors represent potential regulators of the α-SMA gene, and, in this context, the transcription factor c-myb has been shown to form complexes with a regulatory element of the α-SMA gene, suggesting that induction of this gene may be transcriptionally regulated [15]. Among 'external' factors that could affect HSC contractility, the modified ECM pattern typical of fibrotic liver is also likely to play an important role. Finally, it is logical to hypothesize that HSC contractile status could be conditioned by the presence of vasoactive substances present in the microenvironment of hepatic tissue undergoing active fibrogenesis.

As a consequence of their activated state, HSC contribute to profound alteration of the sinusoidal structure during developing hepatic fibrogenesis. As shown in Fig. 3, capillarized sinusoids are characterized by accumulation of fibrillar extracellular matrix in the space of Disse. In addition, in capillarized sinusoids endothelial cells have lost their fenestrations and have acquired a 'generic' endothelial cell phenotype (denoted by the positivity for factor VIII). These changes are associated with: (a) impairment in the metabolic exchange between blood and hepatocytes, (b) impairment in the natural dispersion of hydrostatic forces that occurs in the normal sinusoidal sieve. As illustrated in Fig. 4, capillarization of sinusoids is likely to represent an initial cause of

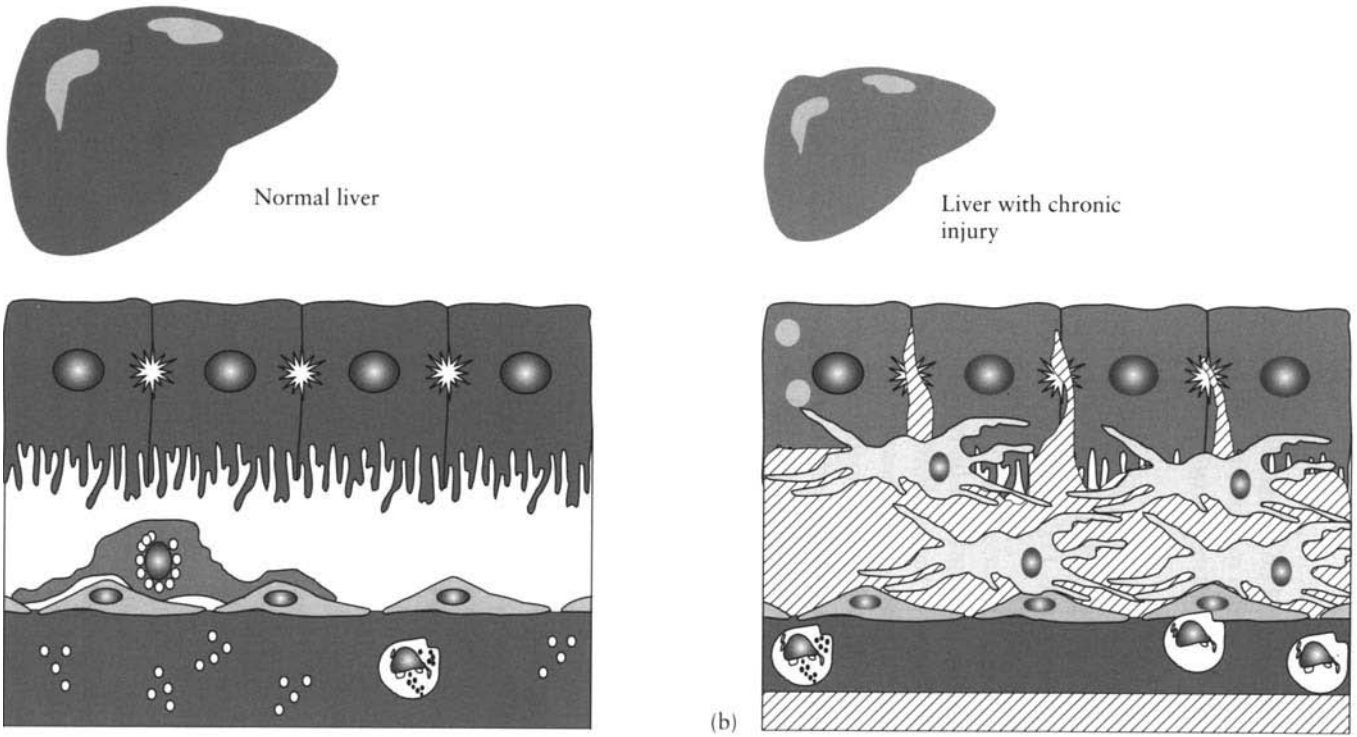


Fig. 3 Capillarization of sinusoids.

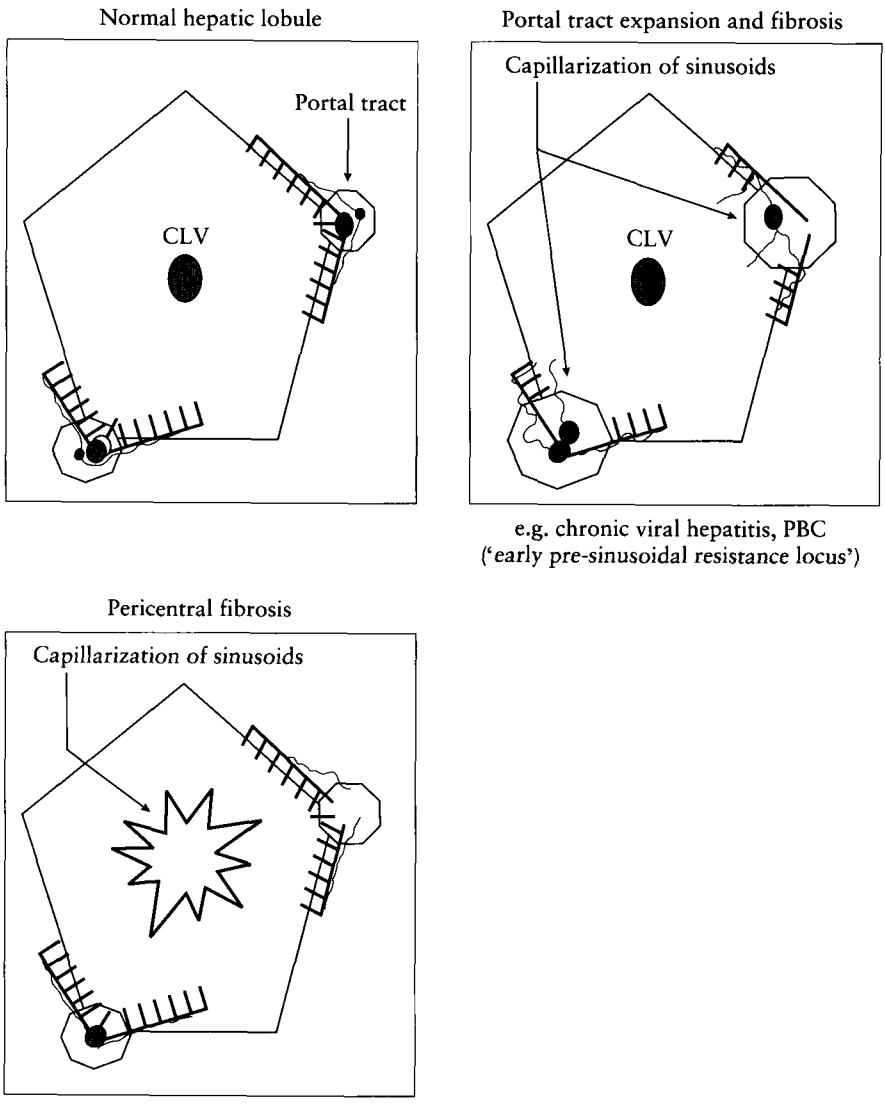


Fig. 4 Fibrogenesis and portal hypertension.

portal hypertension during the early development of hepatic fibrosis. In conditions characterized by portal tract expansion and periportal fibrosis, such as chronic viral hepatitis and primary biliary cirrhosis, HSC activation occurs in periportal sinusoids, thus contributing to the so-called 'early pre-sinusoidal resistance locus'. In other conditions, such as chronic alcoholic hepatitis and non-alcoholic steatohepatitis, capillarization of sinusoids is initially limited in

the centre of the liver lobule, around the centrilobular vein, with consequent obstacle to sinusoidal blood flow. These conditions of initial fibrotic transformation of liver tissue are probably the only ones in which HSC play a prevalent role in the development of portal hypertension.

DO STELLATE CELLS INFLUENCE PORTAL PRESSURE IN CIRRHOTIC LIVER?

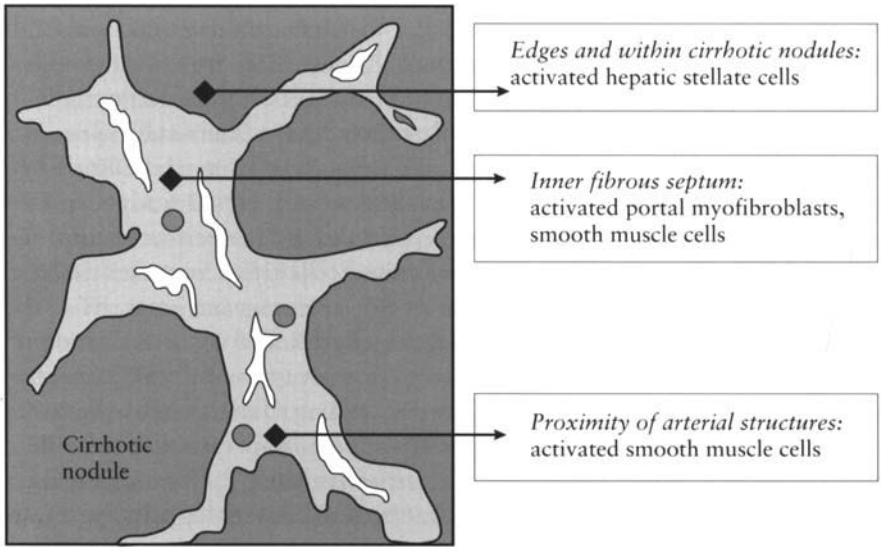
The hallmark of any form of cirrhosis is a profound alteration of the liver angioarchitecture with two prominent features: (a) development of septal fibrosis establishing portal-central anastomoses, and (b) arterialization and capillarization of sinusoids due to both reduction of portal flow and formation of 'feeding vessels' derived from the hepatic artery. These changes could be *per se* sufficient to explain the increase in portal pressure typical of liver cirrhosis [15]. Indeed, portal-central anastomoses, although representing direct connections between the portal and the systemic circulation, follow irregular patterns and are embedded in a developing scar tissue undergoing, to a certain extent, spontaneous retraction. These general alterations, typical of postnecrotic cirrhosis, may apply to other forms of cirrhosis, in which, however other factors may play an important role. Particularly, in alcoholic cirrhosis, compression of hepatic venules by scar tissue that develops around the central vein (pericentral fibrosis) and a marked hepatocellular swelling may represent additional causes of portal hypertension. In other forms of chronic liver disease such as primary or secondary biliary cirrhosis, distortion of portal vein branches connecting portal tracts secondary to a progressive portal-portal fibrosis, may represent a 'presinusoidal' cause of portal hypertension.

It is very clear that all these potential causes of portal hypertension retain an advanced degree of irreversibility and are not likely to be affected by pharmacological treatments. Particularly, in the case of septal fibrosis the establishment of portal-central anastomoses represents a 'point of no-return' for the fibrogenic process: the profound disturbance of hepatic angioarchitecture causes additional liver tissue damage, thus perpetuating and aggravating the fibroproliferative process. However, this absolute and somewhat pessimistic view probably has the same defect as the classic concept of fibrosis, considered as a mere deposition of fibrillar extracellular matrix in a tissue context. Indeed, the altered angioarchitecture of the cirrhotic liver is characterized by neoformed venous vessels (i.e. portal-central anastomoses) embedded in a actively evolving scar tissue where a complex interplay between several cell types and soluble mediators occurs. This new biological microenvironment may support the experimental evidence indicating the existence of a 'reversible' intrahepatic tissue component responsible for portal hypertension: several classes of vasodilators administered in the portal vein of cirrhotic rats have

been shown to decrease portal pressure and to favourably influence microvascular exchange and function [16–18]. In agreement with the role of activated HSC in the progression of liver fibrosis, their topographical distribution, and their biological features, there is no doubt that this cellular element may constitute a key element in this context. However, as illustrated in Fig. 5, several other contractile cell types may contribute to the contraction of the evolving scar tissue typical of the cirrhotic liver. In particular, while activated HSC may be important at the edge and within cirrhotic nodules where sinusoids are capillarized, activated portal myofibroblasts and smooth muscle cells, derived from portal arterial vessels, are likely to strongly affect the neoformed vascular structures located in the inner part of fibrous septa. It should be stressed that all these cell types contribute to the progression of liver fibrosis and that no major difference in their contractile potential are likely to occur.

VASOACTING AGENTS AFFECTING HSC BIOLOGY AND THEIR POTENTIAL ROLE IN PORTAL HYPERTENSION

Although several agents have been shown to be effective on activated HSC in culture (Table 9), the role of two vasoregulatory compounds, namely endothelin 1 (ET-1) and nitric oxide (NO), has been particularly highlighted.



Activated HSC, portal myofibroblasts, smooth muscle cells: no major differences in pro-fibrogenic and contractile features

Fig. 5 Cell types potentially affecting scar tissue contraction in cirrhotic liver.

Endothelin-1, a potent vasoactive 21-amino-acid peptide secreted by endothelial as well as other cell types, has been shown to exert a multifunctional role in a variety of tissues and cells [19–21], including the liver. Infusion of ET-1 in the isolated perfused rat liver causes a sustained and dose-dependent increase in portal pressure associated with increased glycogenolysis and oxygen consumption [22–24]. ET-1 stimulates glycogenolysis, phosphoinositide turnover and repetitive, sustained intracellular calcium transients in isolated rat hepatocytes [25,26]. Other studies indicate that ET-1 may also have important interactions with liver nonparenchymal cells. Cultured sinusoidal endothelial cells isolated from rat liver have been shown to release ET-1 [27], and preferential binding sites for ET-1 have been identified, both *in vivo* and *in vitro* [28,29], on HSC. As previously mentioned, ET-1 induces a dose-dependent increase in intracellular-free calcium, coupled with cell contraction in this cell type. Importantly, activated rat and human HSC have been shown to express preproET-1 mRNA [30,31] and to release ET-1 in cell supernatants [32], thus raising the possibility of a paracrine and autocrine action of ET-1 [33]. Overall, it is increasingly evident that the process of HSC activation and phenotypical modulation is characterized by close and complex relationship with the ET system. The ability to synthesize and release ET-1 is associated with a progressive shift in the relative predominance of ET_A and ET_B receptors observed during serial subculture: ET_A are predominant in the early phases of activation, whereas ET_B become increasingly more abundant in 'myofibroblast-like' cells [31,24]. This shift in the relative receptor densities may be directed at differentiating the possible paracrine and autocrine effects of ET-1 on HSC during the activation process. Indeed, when HSC are provided with a majority of ET_A receptors (early phases of activation), stimulation with ET-1 causes a dose-dependent increase in cell growth, ERK activity and expression of c-*fos*. These effects, likely to be related to the activation of the Ras-ERK pathway, are completely blocked by pretreatment with BQ-123, a specific ET_A receptor antagonist [31], and are in agreement with studies performed in other vascular pericytes such as glomerular mesangial cells [35]. Conversely, in later stages of activation, when the number of ET_B receptors increases, ET-1 appears to induce a prevalent antiproliferative effect linked to the activation of this receptor subtype [36]. In this setting the activation of the ET_B receptor stimulates the production of prostaglandins, leading to an increase in intracellular cAMP, which in turn reduces the activation of both ERK and JNK [37]. In addition, both cAMP and prostaglandins upregulate ET_B binding sites, thus suggesting the possibility of a positive feedback regulatory loop. In aggregate these observations suggest that ET-1 may act as a potent vasoconstrictor agonist regulating intrahepatic blood flow in cirrhotic liver with a potential role in the pathogenesis of portal hypertension. Along these lines, morphological studies have clearly indicated that ET-1 (both at mRNA and protein levels)

is markedly over-expressed in different cellular elements present within cirrhotic liver tissue, and particularly in sinusoidal endothelial and HSC in their activated phenotype located in the sinusoids of the regenerating nodules, at the edges of fibrous septa, and in the ECM embedding neoformed vessels within fibrous bands [31]. In addition, clinical studies indicate that a direct relationship exists between ET receptor mRNA abundance and the degree of portal hypertension in cirrhotic patients [38].

Nitric oxide is a small, relatively stable, free-radical gas that readily diffuses into cells and membranes where it reacts with molecular targets [39]. Importantly, the precise biochemical reactions, which are realized in any biological setting, depend on the concentration of NO achieved and often on subtle variations in the composition of the intra- and extra-cellular milieu. Accordingly, the biological actions of NO are often defined as a 'double-edged sword'. Nitric oxide may act as a key signalling molecule in physiological processes as diverse as host-defence, neuronal communication, and regulation of vascular tone. On the other hand, excessive or not adequately regulated NO synthesis has been implicated as causal or contributing to several pathophysiological conditions including vascular shock, diabetes, and chronic inflammation. Although, NO is characterized by a very short half-life, its biochemical interactions with oxyradicals lead to the production of longer-lived compounds such as peroxynitrite, with important local effects. NO is produced from L-arginine by one of the three isoforms of nitric oxide synthase (NOS). The 'constitutive' forms of NOS, which respond to changes in intracellular calcium concentration and typically produce small amounts of NO, are expressed by endothelial cells and in neurones, whereas a wide variety of other cells express the 'inducible' form of this enzyme, which binds calmodulin at virtually all calcium concentrations and produces remarkably higher amounts of NO. The constitutive forms are regulated by hypoxia, stretch or cytokines, whereas the inducible form is regulated by a large variety of stimuli including cytokines and lipopolysaccharide. By reason of the complex regulation of NOS expression and activity and of the diverse and often opposite effects of NO, the involvement of this system in several disease states is open to conjecture, and this obviously applies to liver physiology and pathology [40]. In patients with decompensated cirrhosis circulating nitrite/nitrate levels (likely to be reflecting NO production in the systemic circulation) are elevated [40]. Since the intraportal administration of the NOS inhibitor, N^{ω}-nitro-L-arginine, increases portal pressure [41], NO has been postulated to be a regulator of sinusoidal blood flow in the normal liver. Along these lines, *in vitro* and *in vivo* evidence indicate that sinusoidal endothelial cells express constitutive nitric oxide synthase (eNOS) and produce NO, and increase their production in response to flow [42]. However, an endothelial dysfunction associated with a decreased production of NO in the intrahepatic microcirculation

have been extensively documented in cirrhotic livers [43,44], and these defects could directly contribute to the increased intrahepatic resistance typical of portal hypertension.

As in the case of ET-1, circumstantial evidence for a relevance of NO in HSC biology has derived from *in vitro* studies. Exogenous NO is able not only to prevent ET-1 induced contraction and to relax precontracted cells, but also to reduce the expression of α-SMA [45]. In addition, interferon-γ and other cytokines with or without lipopolysaccharide, as well as hyaluronan fragments induce the expression of the inducible form of NOS and the production of NO in HSC [46,47]. However, at least in human HSC, this effect is very limited and the possibility of an autocrine action of NO in HSC appears merely speculative. In addition to these effects on HSC contraction and contractile proteins, NO appears to markedly reduce the expression of procollagen type I mRNA and the secretion of the encoded protein [46]. It is therefore possible that NO may influence the progression of portal hypertension by reducing the accumulation of fibrillar matrix in key areas such as the fibrous septa, as suggested by evidences deriving from animal models of liver fibrosis [48]. Along these lines, the beneficial effects of portal pressure observed following the long-term oral administration of nitrovasodilators, could be better explained and reconsidered from a different point of view. Indeed, a possible direct antifibrogenic effect of NO-donors is suggested by *in vitro* studies demonstrating an antiproliferative and antichemotactic actions of these compounds in cell types morphologically and functionally analogous to HSC [49,50]. Considering that these potential actions have been recently confirmed in activated human HSC [51], all this evidence offers a sound rationale for the use of NO-donors in the treatment of portal hypertension.

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SESSION 2

Diagnosis of Portal Hypertension: How and When

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INTRODUCTION

The diagnosis of portal hypertension bears important prognostic and therapeutic consequences [1]. Patients likely to have portal hypertension should be screened to detect it when present. Similarly to the definition of arterial hypertension, the definition of portal hypertension is based on a pressure measurement. This is usually determined indirectly by subtracting the free hepatic venous pressure (or the inferior vena cava pressure) from the wedged hepatic venous pressure, the so-called hepatic venous pressure gradient or HVPG. Values above the normal upper limit of 5 mmHg denote portal hypertension [2].

In contrast with arterial pressure, portal pressure measurement is not immediate and is performed only in a limited number of specialized centres. As a consequence, the bulk of available information on the relationships between levels of portal pressure and prognosis and between treatment and changes of portal pressure is far more limited than the corresponding information on arterial pressure. For this reason most of the present knowledge on the prognostic and therapeutic implications of portal hypertension is based on the relationships between its clinical manifestations, mainly oesophago-gastric varices, and clinically important outcomes such as bleeding and death.

There is a great disparity of opinion on how and when to diagnose portal hypertension and what degree of portal hypertension is considered 'clinically significant'. Clinically significant portal hypertension (CSPH) would presume the pressure level or condition at which a patient is at a high risk of developing complications and who is therefore a candidate for prophylactic treatment. A widely acceptable and applicable definition requires at least one reliable diagnostic test with enough sensitivity and specificity to correctly identify patients according to that definition.

* Dr D'Amico and Dr Garcia-Tsao share the principal authorship of this article.

The aims of this workshop were therefore to define CSPH based on currently available scientific evidence and on the opinion of experts in portal hypertension, and to achieve consensus on how and when to diagnose portal hypertension.

METHODS

Four areas of special interest were identified in which great controversy still exists

1 definition of clinically significant portal hypertension (CSPH)
2 timing of first and subsequent evaluation for CSPH
3 reliability and accuracy of noninvasive tests for CSPH
4 monitoring of treatment effects

STUDY DESIGN

A questionnaire addressing the above-mentioned areas was designed by GD and GGT and administered to experts in the field of portal hypertension who agreed to participate in this consensus conference. The questionnaire consisted of 13 questions that dealt with the four main objectives mentioned previously (Fig. 6).

In addition, scientific evidence pertinent to each area of interest was systematically reviewed.

For areas concerning clinical relevance of definitions, studies dealing mostly with prognosis or, less frequently, with treatment were reviewed. For areas concerning the reliability and accuracy of diagnosis, studies dealing with diagnostic tests were reviewed. Where applicable, widely accepted guidelines for critical appraisal of published studies were utilized [3–5] (Table 10).

RESULTS

Clinically significant portal hypertension

Twenty-eight experts responded to the question 'What do you consider a "clinically significant" portal hypertension?' Twenty-one gave a single response: presence of varices ($n = 8$), HVPG > 12 mmHg ($n = 7$), HVPG > 10 mmHg ($n = 6$), spleen > 12 cm ($n = 1$) while six provided more than one answer: varices + HVPG > 12 ($n = 4$), varices + HVPG > 10 ($n = 1$) and one considered any of the four possible answers as viable. HVPG measurements alone (cutoff at 10 or 12 mmHg) was what most of the respondents (13/28 or 46%) considered the defining point of CSPH, followed by varices alone (8/28 or 29%) and varices or HVPG (cutoff at 10 or 12 mmHg; 5/28 or 18%).

1 What do you consider a 'clinically significant' portal hypertension (CSPH)?
(a) presence of oesophageal and/or gastric varices by endoscopy
(b) presence of oesophageal and/or gastric varices by EUS
(c) HVPG ≥ 12 mmHg
(d) HVPG ≥ 10 mmHg
(e) other, specify _____

2 Why?

3 In your opinion, when should a patient with cirrhosis be first screened for the presence of CSPH?
(a) at the time of diagnosis of cirrhosis
(b) when noninvasive parameters suggest the presence of CSPH
(c) when the patient presents with upper gastrointestinal haemorrhage
(e) other, specify _____

4 If you answered (b), what noninvasive parameters do you consider suggestive of the presence of CSPH (several answers allowed) If you did not answer (b), skip to next question.
(a) low platelet count
(b) splenomegaly on physical exam
(c) splenomegaly on imaging studies
(d) low albumin
(e) telangiectases
(f) enlarged portal vein on Doppler-ultrasound
(g) decreased portal flow on Doppler-ultrasound
(h) other Doppler abnormalities, specify _____
(i) other, specify _____

5 In patients *without* CSPH, when would you repeat the screening procedure?
(a) every year
(b) every two years
(c) not unless the patient develops a parameter suggestive of CSPH
(d) not unless the patient presents with GI haemorrhage
(e) other, specify _____

6 In patients with small varices, do you perform repeat endoscopies to screen for the development of large varices?
(a) yes
(b) no

7 If you answered yes, how often do you screen for the development of large varices? If you answered no, skip to next question.
(a) every year
(b) every two years
(c) not unless the patient presents with GI haemorrhage
(c) other, specify _____

7b If you answered no to question 6, please specify why not: _____

8 In your opinion, which are the most important risk factors for haemorrhage from gastro-oesophageal varices. Please list only the risk factor(s) that you use in your clinical practice when selecting patients for prophylactic therapy.

Fig. 6 Questionnaire used to draw expert opinions.

9 Do you think that monitoring treatment effect is clinically important in the prevention of variceal bleeding/rebleeding?
(a) yes
(b) no
9b Why?
10 If yes, what would you monitor?
(a) endoscopy
(b) HVPG
(c) Doppler parameters. Specify _____
11 How many HVPG measurements are performed in your centre each year?
12 In your centre, who performs HVPG measurements:
(a) radiologist
(b) hepatologist
(c) radiologist plus hepatologist
(d) other, specify _____
13 Do you keep HVPG tracings for future analysis?
(a) yes
(b) no
(c) tracings not performed, results obtained from monitor readings.

Fig. 6 (*continued*)

Table 10 Criteria used to assess the validity of the reviewed studies.

Criteria	Studies about prognosis	Studies about a diagnostic test
Major	• Representative sample of patients assembled at a common point in the course of their disease • Patient follow-up sufficiently long and complete	• Clear description of an appropriate study setting • Assessment of a sample of patients in whom the disease is suspected (but not known) to be present • Comparison with a gold standard
Minor	• Objective outcome criteria applied in a 'blind' fashion • Adjustment for important prognostic factors • Validation in an independent group of 'test-set' patients	• Independent interpretation of the test and gold-standard • Demonstration of reproducibility of test results

The clinical significance of the parameter the respondents chose was related to the risk for development of complications of portal hypertension ($n = 11$), development of variceal haemorrhage ($n = 10$), development of varices ($n = 4$) and risk of death ($n = 2$).

'Clinically significant' therefore implies the identification of a group of patients with cirrhosis at a high risk of developing complications of portal hypertension that would be candidates for prophylactic therapy.

The literature evidence is summarized in the following section.

Measurement of hepatic venous pressure gradient (HVPG)

HVPG and varices. Initial cross-sectional studies indicated that all cirrhotic patients with varices have a minimal threshold level of either 10 mmHg [6] or 12 mmHg [(7], while a significant proportion of patients without varices (up to 40%) have an HVPG < 12 mmHg. Subsequent studies that have included patients with varices (without haemorrhage at time of inclusion) have confirmed the existence of this threshold level [8–9]. The development and growth of varices at different HVPG levels above this threshold or at different degrees of change in HVPG over time is as yet unknown. The HVPG has a tendency to be higher in patients with large varices than in those with small varices [8]. Also, a significant reduction in variceal size has been shown to occur in patients in whom HVPG is reduced under 12 mmHg [8] or in patients in whom HVPG decreases by > 15% [9].

HVPG and variceal haemorrhage. Cross-sectional studies have shown that patients with variceal haemorrhage have a minimal threshold level of either 10 mmHg [6] or 12 mmHg [8,10]. Of note, in the first study [6] of 45 bleeders, only two had an HVPG of 10 mmHg while the rest had an HVPG > 12 mmHg. This threshold level has been confirmed in subsequent prospective studies that have included variceal bleeders [11–15]. HVPG has been found to be an independent predictor of variceal haemorrhage. A recent study correlated the recurrence of complications of portal hypertension after placement of transjugular intrahepatic porto-systemic shunt (TIPS) with the course of porto-systemic pressure [17]. The study showed that, while at the time of TIPS placement all 122 patients had a porto-systemic pressure < 12 mmHg, all patients in whom variceal haemorrhage recurred demonstrated an increase in porto-systemic pressure to levels above 12 mmHg. More importantly, longitudinal prospective studies [8,14,18] have demonstrated that variceal haemorrhage does not occur if the HVPG is reduced to levels below 12 mmHg (Table 11). It has also been shown that if the HVPG is reduced significantly, either spontaneously (> 15% from baseline) or pharmacologically (> 20% from baseline), the risk of variceal haemorrhage is also reduced [9,18]. The reduction in risk of bleeding occurs even though varices continue to be visualized in the majority of patients.

Table 11 Studies assessing HVPG as a prognostic indicator of death.

First author	Year	*n* (total)	Variceal bleed at inclusion *n* (%)	Follow-up (months)	HVPG cutoff (mmHg)	Variceal haemorrhage		Deaths	
						Below cutoff	Above cutoff	Below cutoff	Above cutoff
Vinel	1986	89	71 (80%)	< 36	20.8			25%	56%
Gluud	1988	58	0	31	15.0			5%	50%
Tage-Jensen	1988	81	0	> 42	20.0			25%	75%
Groszmann	1990	102	0	~17	12.0*	0	13%	5%	18%
Merkel	1992	129	21 (16%)	45	16.0	14%	37%	10%	29%
Patch	1999	105	105	47	17.0	NS	NS	21%	40%
Moitinho	1999	65	65		20.0	12%	50%	20%	64%
Minana	2000	88	88	24	12.0**/↓ 20%	4%	44%	7%	19%

*HVPG after treatment with placebo or propranolol

**HVPG after treatment with EVL or propranolol

HVPG and other complications of portal hypertension. The development of ascites has also been related to a threshold level of HVPG of around 12 mmHg [19–20]. The existence of such a threshold is confirmed in a prospective study that showed that HVPG had risen above 12 mmHg in 21/23 (91%) patients in whom ascites appeared after TIPS [17].

Prognostic value of HVPG.
As seen in Table 11, HVPG at different cutoff levels has been shown to be a predictor of long term survival in cirrhotic patients without variceal haemorrhage at inclusion in the study [8,12,16,21] HVPG has also been predictive of mortality in patients with recent variceal haemorrhage in whom the cutoff level is around 20 mmHg [15,22–23].

Assessment of the presence of varices

Diagnosis of varices. All respondents to the questionnaire considered endoscopy as the only procedure to diagnose varices. No respondent chose endoscopic ultrasound. Endoscopy is a far more widely available technique than HVPG measurements.

Varices in the prediction of variceal haemorrhage. Several prospective studies show that the presence and size of oesophageal varices is an indicator of the risk of variceal hemorrhage [24–26]. Large varices are at a significantly greater risk of bleeding than small varices.

Prognostic value of the diagnosis of varices. In a recent report of prognostic studies of cirrhosis that analyzed 56 prospective studies that used multiple regression analysis to identify prognostic indicators of death, the presence of varices was evaluated in 18 studies and in five of them it was found to be a significant and independent predictor of death [27].

From the above, and after discussion with the audience, the following consensus statements were established regarding the definition of CSPH:

1 Clinically-significant portal hypertension (CSPH) is defined by an increase in portal pressure gradient to a threshold above approximately 10 mmHg.
2 The presence of varices, variceal haemorrhage, and/or ascites is indicative of the presence of CSPH.

Timing of first evaluation for the presence of portal hypertension

Seventeen of the 28 respondents indicated that patients should be screened for the presence of portal hypertension when the diagnosis of cirrhosis is made. Six answered 'when noninvasive tests suggest CSPH' and four answered either diagnosis of cirrhosis or when noninvasive tests are positive. One responded that screening should be performed at diagnosis of cirrhosis, positivity of noninvasive tests or bleeding, whichever occurs first. Therefore, overall, 21 (71%) answered that the first assessment for CSPH should be done at the time of the diagnosis of cirrhosis and 10 suggested that noninvasive tests may serve as a prescreening method.

There are no studies addressing this specific point. To achieve a consensus on the timing of first evaluation of CSPH, studies on the natural history of cirrhosis were evaluated. Varices are present in about 60% of decompensated and in 30% of compensated cirrhotic patients [21,28]. In a recent review [27], the median prevalence of varices was calculated at 60% in 16 studies reporting this information.

Thirteen experts answered that noninvasive tests may suggest the presence of CSPH: 11 indicated low platelet count, eight splenomegaly, five enlarged portal vein on ultrasound, three reduced portal flow velocity on echo-Doppler and two evidence of perisplenic or other collateral circulation on ultrasound. However, although several studies [26,29–30] indicate that noninvasive tests (particularly platelet count), may have a potential use in the screening of patients with varices, none of these tests has been so far proven accurate enough as to safely avoid endoscopy in patients who are negative for the test.

Therefore, since the prevalence of varices at the diagnosis of cirrhosis is near 60%, since noninvasive tests with sufficient accuracy to detect patients with varices are not yet available and since measurement of HVPG is not widespread and results of pre-primary prophylaxis are not yet available, the consensus on the timing of first evaluation was the following:

> All cirrhotic patients should be screened for the presence of varices at the time of the initial diagnosis of cirrhosis.

Reliability of diagnostic investigations

Hepatic venous pressure gradient (HVPG)

Of 27 respondents, 16 perform > 40 HVPG measurements per year in their centres, two perform between 20 and 40, five perform between 10 and 20 procedures, one performs between 5 and 10 and three perform < 5 per year.

Measurements are performed mostly by hepatologists ($n = 12$, all of them from European centres), followed by radiologists ($n = 10$) and in four cases by a radiologist plus a hepatologist. The majority (57%) keep a recording for future analysis, however almost half do not keep tracings or results are taken from monitor readings. At the time of the conference, a question on the type of catheter utilized for HVPG was added. Of 22 respondents, 15 use the balloon catheter, while eight routinely use a regular catheter that is wedged.

The technique of hepatic vein catheterization with measurement of the HVPG, which is the difference between wedged (WHVP) and free hepatic vein pressure (FHVP) is a safe and reproducible technique. The coefficient of variation has been calculated at $2.6 \pm 2.6\%$ [7]. The balloon catheter technique is the preferred technique because it allows for repeat measurements without having to move the catheter and the wedged pressure obtained with the balloon catheter represents a mean pressure from a larger area of the liver than the one obtained by wedging the catheter [31]. However, recent unpublished observations (Bosch, personal communication) indicate that centres that are not experienced in the method may incur errors that may render the technique unreliable, the most common being the use of readings obtained from a monitor and the use of an inappropriate scale (one used for arterial and not for venous measurements). These errors are easily correctable.

In alcoholic cirrhosis, WHVP equals portal (sinusoidal pressure) and because FHVP equals vena caval pressure, the HVPG equals porto-caval pressure gradient. In patients with a predominantly pre-sinusoidal condition (e.g. patients with a portal-based disease such as hepatitis C), HVPG may underestimate direct portal measurements [32]. However, two recent studies have been published comparing direct portohepatic measurements to HVPG measurements (using a balloon catheter) in patients with chronic hepatitis C [33–34] Both studies show a good correlation (0.80 and 0.95 respectively) between both methods and the discrepancies found (38% and 10% respectively) did not all result from WHVP subestimating portal pressure.

Endoscopic assessment of varices

As there is no gold standard test for the diagnosis of oesophageal varices (EV), the reliability of endoscopic diagnosis of EV can only be assessed indirectly—by interobserver variability or by measuring the diagnostic accuracy of EV for robust judgement criteria such as cirrhosis.

Interobserver agreement. Seven such studies have been performed in patients with cirrhosis [35], with number of studied patients ranging from 28 to 347. The presence, grade, number, size, length, colour and red signs of oesophageal varices were evaluated in these studies. For gastric varices (GV) only their

presence and grade were evaluated. Results are presented in Table 12. The best agreement was observed for red signs with $\kappa = 0.61$ to 0.70. Agreement was good for the size of EV. Agreement was poor to fair for the presence of EV and GV grade. Agreement was very poor for EV length and presence of GV. Generally the higher the size, the better the agreement.

Agreement did not vary as a function of the level of expertise of the practitioner (junior vs. senior endoscopist). Agreement was not evaluated as a function of EV classification. However, the homogeneity of results for the grade or size of EV suggests that the type of classification does not influence agreement. On the other hand, interobserver agreement within one centre was significantly greater than between different centres.

The methodological quality of these studies has recently been evaluated [35] with a quality score ranging from −10 to +35 (mean score was 12 ± 5.5).

Table 12 Interobserver agreement for oesophageal varices and gastric varices [1].

Sign	1st author (year)	Test	Results
Oesophageal varices			
Presence	Conn	DA	67%
	Calès (1989)	κ	0.40 (0.36–0.44)
	Bendtsen	κ	0.38 ± 0.16
	Calès (1990)	κ	0.59
	Calès (1993)	κ	0.52 (0.49–0.56)
Number	Theodossi	DA	40%*
Grade	Dagradi	DA	66%
	Calès (1989)	κ	0.51 (0.49–0.54)
	Bendtsen	κ	0.52 ± 0.17†
	Calès (1990)	κ	0.59
	Theodossi	κ	0.37
	ILCP	κ	0.50
Length	Calès (1989)	κ	0.20 (0.16–0.24)
	Calès (1990)	κ	0.37
Red signs	Calès (1989)	κ	0.61 (0.57–0.65)
	Calès (1990)	κ	0.58
	Calès (1993)	κ	0.71 (0.66–0.77)
Gastric varices			
Presence	Calès (1989)	κ	0.35 (0.31–0.39)
	Calès (1990)	κ	0.60
	Calès (1993)	κ	0.25 (0.21–0.29)
Grade	Calès (1989)	κ	0.29 (0.26–0.32)

* ± 1 varix

† VO grade 0,1/2,3

DA, diagnostic accuracy; κ, kappa index.

Results of the Baveno I meeting have suggested that the accuracy of EV classification should be evaluated according to grade (morphological description) or size (in mm) [36].

In a recent study [37], this data was recorded but was not published. It is now reported in Table 13. Agreement was compared between the evaluation made by the observer *in vivo* and the evaluation of four experts that analysed video recordings of the procedure (gold standard). Good agreement was found for both methods.

Diagnostic accuracy of EV. The diagnostic accuracy of EV for cirrhosis has only been evaluated in three studies. In one recent study, EV were evaluated together with other endoscopic signs. EV had a high independent diagnostic accuracy—from 77 to 96%—depending on the control group and the clinical setting [38]. In another recent study of 63 variables evaluated for the noninvasive diagnosis of cirrhosis, EV were the second independent variable for the diagnosis of cirrhosis with a diagnostic accuracy of 80% [39].

The consensus statements on the reliability of HVPG and endoscopy for CSPH were the following:

1 Reliability of both HVPG measurement and endoscopic assessment of oesophageal varices for the diagnosis of CSPH is satisfactory.
2 However, specific simple guidelines may further improve their reliability.

Table 13 Agreement between two modes of endoscopic evaluation of oesophageal varice size during a clinical trial on preprimary prophylaxis (3).

	In vivo (1 investigator)	On video (4 experts)	Agreement
Oesophageal varices grade (%):			
• inclusion: grade 1	61	57	κ: 0.66
• last visit: grade 2	28	29	κ: 0.60
Oesophageal varice size (mm)*:			
• inclusion	2.8 ± 1.0	3.2 ± 1.0	r: 0.51 (0.62)†
• last visit	4.05 ± 1.9	4.6 ± 1.7	r: 0.31 (0.77)†

* in patients with oesophageal varices
† the figures in brackets take into account patients without oesophageal varices (variceal size = 0 mm)
κ, kappa index; r, intraclass correlation coefficient

Reliability and accuracy of noninvasive investigations

The screening of oesophageal varices is recommended both for prognosis and for identifying patients candidate to the prophylaxis of bleeding [39–42]. Recently, numerous techniques have been developed for the noninvasive diagnosis of portal hypertension [43–44]. The need to predict or diagnose the presence of CSPH noninvasively is important in order to be able to prescreen patients who will then require an invasive procedure. Until results of studies on preprimary prophylaxis are available, patients with large EV are the ones that require primary prevention. Therefore, the noninvasive diagnosis of EV, especially large sized EV, is clinically relevant.

Clinical parameters

The noninvasive diagnosis of EV has been studied mainly in cirrhosis (Table 14). A distinction must be made between studies evaluating the development of EV and those evaluating the diagnosis of EV. The former are longitudinal studies that evaluate risk factors for the development or growth of EV [40,42,45,46]; the latter are cross-sectional studies that assess markers for the presence of EV. In this last category, markers can be direct, such as radiologic studies [47], e.g. barium swallow [48] or indirect, such as the ones listed in Table 14 [30,44,49–53]. Most of these are preliminary results and markers are based on physical exam findings, laboratory values and/or Doppler ultrasound parameters. We focused on the three multivariate analyses performed in cirrhotic patients [30,44,52].

In the study by Pilette *et al.* [44], three markers were found to be independent predictors of the presence of *large* EV, which were, in a decreasing order of importance: platelet count, prothrombin index and spider naevi. Platelet count was also found to be an independent marker of the presence of large varices [52] or of CSPH [30] in the other two multivariate analyses. The ROC curve in the Pilette study showed that a platelet count fixed at 160 000 was the best cut-off for the diagnostic accuracy of large EV. The ROC curve also showed that the presence of large EV is improbable in cirrhotic patients with a platelet count $\geq 260\,000$ (negative predictive value $\geq 91\%$). In fact, in our questionnaire, 11 out of 13 respondents indicated a low platelet count as a marker of CSPH (i.e. the highest rating level). It is of interest that in patients with primary biliary cirrhosis, the 5-year incidence of bleeding has been shown to be twice as high in those with a platelet count $< 150 \times 10^9$ compared to patients with a platelet count above this level [29]. However, it has also been shown that, in cirrhotic patients with a platelet count $\leq 140 \times 10^9$/L and a portal vein diameter ≥ 13 mm the prevalence of medium or large sized oesophageal varices is only 8% [21].

Table 14 Diagnostic signs of oesophageal varices in the literature.

1st author [ref]	Year	Liver disease	*n* patients	*n* variables	Variable type	Univariate analysis	Multivariate analysis	Oesophageal varices (%)
Lavergne [49]	1997	Cirrhosis?	52	12	Clinics, US blood tests	Ascites	–	79
Zeijen [50]	1994	CLD	32	–	Blood tests, US Doppler	Cholinesterase spleen length	–	28
Gorka [51]	1997	Cirrhosis HCV	50	5	US Doppler	Hepatic vein waveform, portal vein diameter, congestion index	–	86
Chalasani [52]	1998	Cirrhosis preliver transplantation	346	–	Clinics, blood tests	–	Splenomegaly, platelet count NASH	–
Garcia-Tsao [30]	1997	Compensated cirrhosis	180	15	Clinics, blood tests	Age, sex, Child, spider naevi, bili, alb, PT, Hb, WBC, platelet	Spider naevi, alb, platelet	16
Khishimoto [53]	1998	Cirrhosis, idiopathic PHT	47	3	US Doppler	Oesophageal wall	–	64
Pilette [44]	1999	1. CLD 2. Cirrhosis	1. 207 2. 116	65	Clinics, Blood tests, US Doppler	1. $n = 49$ 2. $n = 7$	1. Liver surface 2. Platelet count, prothrombin index, spider naevi	1. 45 2. 72

CLD, chronic liver disease; US, ultrasonography; –, not available; PHT, portal hypertension

Spider naevi were also shown to be an independent diagnostic factor for large EV in one of the two other studies with multivariate analysis [30]. This factor has already been shown to be related to EV, large EV [54, 55] or variceal bleeding [55].

Finalization of preliminary studies and future studies should be assessed before any of these tests can be recommended either for the diagnosis of CSPH or for the diagnosis of large varices.

Doppler-ultrasound

Ten out of 28 respondents indicated that one or more non-invasive tests may be suggestive of CSPH. Overall, ultrasonographic changes were mentioned ten times: portal vein enlargement ($n = 5$), portal flow reduction ($n = 3$), collateral circulation or ascites ($n = 2$).

An increased diameter of the portal vessels, in suspended expiration, has been reported to be suggestive of portal hypertension [56–58]. A portal vein diameter > 14 mm or a splenic and superior mesenteric vein diameters > 10 mm had a specificity of near 95% and a sensitivity of 50% in these studies [56–58]. Splenic and superior mesenteric veins have reduced respiratory variations in the presence of cirrhosis. A reduction of < 20% from deep expiration to deep inspiration, was reported to have a sensitivity of near 80% and specificity of near 100% to detect cirrhosis [56–58]. A portal vein caliber ≥ 13 mm together with respiratory variations < 50% in splenic or mesenteric veins was reported to have a sensitivity of 50% and specificity of 92% in detecting patients with large varices [59]. This test would thereby prevent the performance of 50% of endoscopies when screening cirrhotic patients for large oesophageal varices.

The visualization of ectatic collateral veins (umbilical/paraumbilical vein, left gastric vein, short gastric veins, spleno-renal anastomoses) in cirrhotic patients has been reported to have 80% sensitivity and 100% specificity to detect patients with HVPG ≥ 10 mmHg [60]. Collateral veins may be identified more easily by colour-Doppler and, when present, a hepatofugal flow can be demonstrated [60–61]. Inversion of flow in the portal vein, or in one of its branches, is rare (< 8% of patients) but, if present, it is highly related with the presence of oesophageal varices [62]. Hepatofugal flow in left coronary vein and in gastric veins may also be related to the presence of varices. No data on sensitivity or specificity of these Doppler findings for the presence of varices or given values of HVPG are available.

The mean velocity of portal blood flow is significantly reduced in cirrhotic patients with portal hypertension, while portal blood flow volume may be in the normal range. Normal values however show a wide range (12–16 cm/sec), perhaps as a result of equipment variability [63–67]. Although this high

variability hampers their generalizability, with each specific equipment cut-off values for portal blood flow velocity may be set allowing high sensitivity and specificity in the diagnosis of cirrhosis [65,67–68]. Furthermore, a significant correlation between portal blood flow velocity and HVPG has been recently found in patients without patent paraumbilical veins [69]. This finding might anticipate a satisfactory accuracy of this parameter in detecting patients with CSPH. It is also of interest that hyperdynamic circulation may be detected by transit-time analysis of an ultrasound contrast agent [70]: this test has been reported to be highly specific for identifying cirrhotic patients although a thorough evaluation of its sensitivity and specificity is not yet available.

Other Doppler flowmetry parameters reported to be related to portal pressure or bleeding risk are the congestion index (the ratio between the sectional area of the portal vein and the blood flow velocity), the reduction of postprandial portal hyperemia and hepatic and splenic arterial indexes [71–76]. However no satisfactory assessments of sensitivity and specificity to detect patients with varices or with a given value of HVPG, of any of these parameters have been reported.

Reliability of US parameters, mainly of Doppler parameters, is strictly related to operators' experience. Interobserver and interequipment variability in measuring vessel caliber as well as in identifying the direction of blood flow is usually < 10%. By contrast the assessment of blood flow velocity and volume is not reliable because of low interobserver and interequipment reproducibility. Therefore adequate training programs should be used at every centre to reduce the interobserver errors and the normal range of Doppler quantitative parameters should be established for each specific equipment [77–78].

Other investigations

Variceal pressure (VP)

Previous studies have identified tension in the wall of the varix as the decisive factor determining variceal rupture [31,78–80]. According to Frank's modification of Laplace's law [80], variceal wall tension is directly proportional to transmural variceal pressure (the gradient between variceal and intraoesophageal pressures) and the radius of the varix, and inversely proportional to the thickness of the variceal wall. Therefore, the measurement of variceal pressure (VP) is thought to closely correlate with the risk of variceal bleeding.

Different methods have been used to measure VP. The 'gold standard' is the measurement of intravariceal pressure by direct puncture of the varix with a thin needle. However this method carries a high risk of bleeding and ethically can only be used in patients undergoing sclerotherapy after the procedure [81]. For this reason, different noninvasive methods have been developed.

In 1982, Mosimann and coworkers reported their experience measuring VP by means of a pneumatic pressure gauge fixed at the tip of an endoscope [82]. The gauge consists of a small chamber covered by a thin elastic membrane continuously perfused with air by a minicompressor. Measurement of VP is based on the assumption that when the gauge is applied to the varix, the pressure needed to perfuse the gauge equals the pressure inside the varix [82]. Transmural VP results from the difference between this pressure and the zero pressure (which is the pressure recorded while the gauge is free in the oesophageal lumen). Seventy-eight patients have been evaluated using this technique in five studies [82–86], in one of them it was compared to direct intravariceal pressure measurements, finding an absolute concordance in five of seven patients [86]. However, Polio *et al.* correlated measurements obtained with a modified version of this initial gauge (measuring surface: 7 mm in diameter) applied to a canine mesenteric vein with the intravessel pressure measured by direct catheterization and found substantial variability, particularly in small vessels [87]. The same authors provided accurate and reproducible measurements of rabbit mesenteric vessel pressure using a small gauge (measuring surface: 5.5 mm in diameter) which closely correlated with intravessel pressure ($r = 0.99$) [88].

Bosch and coworkers modified the technique by using constant perfusion of the gauge with nitrogen [89]. With this technique, they found a good correlation both *in vitro* (with an artificial varix system) and *in vivo* (by measuring intravariceal pressure) [89]. The same technique, but with a small gauge (measuring surface: 2 mm in diameter), has been used in several studies by these [82,89,90–94] and other investigators [95–100]. In 26 cases, transmural variceal pressure measured by this nitrogen-perfused gauge was compared with intravariceal pressure; both measurements being closely correlated ($r > 0.91$) [89,98]. In addition, in double-blind studies, placebo caused little variations in variceal pressure following either acute (variation ranging from 0 to 4.3%) [89,90–93,97] or chronic administration (from 1 to 6%) [98,99].

Manometry with an endoscopic balloon technique has been introduced to measure variceal pressure [101–104]. However, few authors use this technique which relies on the visual appearance of the varices, subject to observer bias. For these reasons, it is still considered experimental.

Both in cirrhotic and in noncirrhotic patients, VP measurement with the noninvasive gauge has been found to be predictive of variceal hemorrhage [100,105–107]. In cirrhotic patients, the level of VP appeared to provide further prognostic information in addition to the one provided by the NIEC index [24].

However, and even though there is a positive correlation, these studies have shown that VP is not equivalent to portal pressure. The gradient between both measurements is thought to be due to variable resistance of the collaterals

communicating the portal vein and the varices [79]. In addition, there are some patients in whom variceal pressure measurements are not feasible (about 25% of initially enrolled patients in a recent study) [94], mainly due to technical difficulties involving small varices. On the other hand, VP measurements are superior to HVPG measurements in patients with prehepatic or presinusoidal portal hypertension since these patients have a normal HVPG.

Consequently, in cirrhosis measurements of VP should be considered complementary rather than a substitute for HVPG measurements [94].

Endoscopic ultrasound (EUS)

Besides being able to visualize oesophageal and gastric varices, perioesophageal and perigastric collateral veins, and submucosal gastric venules, EUS enables the visualization of the portal venous system and azygos vein [108–109]. However endoscopy is still considered the most important technique in the diagnosis and grading of oesophageal varices. The only clinically relevant use for EUS is in the detection of fundal varices. The presence of red colour signs, a prognostic factor for bleeding [110], can not be evaluated with EUS.

EUS could potentially contribute to the prediction of variceal haemorrhage by being able to evaluate two of the components of variceal tension, wall thickness and vessel diameter. However, such studies have not been performed yet.

EUS performed before sclerotherapy and after variceal eradication, can provide important information on the status of the peri-esophageal collateral veins, gastric varices and visible portal system. This may help understand factors involved in the failure to achieve eradication [111–112]. The visualization of perforating veins below the gastro-oesophageal junction seems useful in predicting the effectiveness of sclerotherapy [113].

Recently Leung *et al.* [114] reported that the sensitivity of EUS in detecting oesophageal varices can be greatly improved by using a miniature ultrasonic probe with water infusion. Moreover, in their experience the presence of large paraoesophageal varices after sclerotherapy or banding was associated with higher variceal recurrence and rebleeding. They concluded that the main clinical role of EUS is in the prediction of variceal rebleeding.

Liu *et al.* [115] using a 20-MHz transnasal probe detected oesophageal varices and correctly measured their size in 79% of patients, versus 94% for endoscopy. They suggest the use of this technique as a supplement to endoscopy. Kishimoto *et al.* [116] proposed the use of ultrasonic miniprobes to monitor the effects of endoscopic variceal ligation, and their observations were similar to those reported by Liu *et al.*

Currently there is no evidence to support the routine use of EUS, a more complex and expensive technique, in patients with cirrhosis and portal hyper-

tension. Even though it may be useful in detecting variceal recurrence or haemorrhage after endoscopic treatment, its use has not modified the number or timing of sclerotherapy/ligation sessions [117].

Finally, colour Doppler endosonography which allows the visualization of the intra-abdominal vasculature has very limited clinical value and can be considered only when transabdominal ultrasound is nondiagnostic in patients with suspected thrombosis of the splenic vein, portal vein or portosystemic shunt [118].

EUS in portal hypertension is a fascinating technique that is still looking for a practical application [119].

In conclusion, none of the noninvasive tests mentioned in this section can currently replace endoscopy and measurements of HVPG, supporting the following consensus statement:

> The accuracy of noninvasive tests for the diagnosis of CSPH should be further assessed before its use can be recommended in clinical practice.

Timing for subsequent evaluations and goals

Patients without varices on initial endoscopy

Among the 28 respondents, 17 answered that the screening procedure should be repeated every two years, seven 'every year' and four 'when the patient develops a parameter suggestive of CSPH'.

Since the aim of a second evaluation in patients without varices when first seen is to detect varices when they develop, the best timing to do this should be drawn from studies of the incidence of oesophageal varices. There are only two large studies of the natural history of cirrhosis addressing this point, including 532 [120] and 1649 patients [121], respectively. The incidence of varices was very similar in the two studies and was near 5% per year. This is, at present, the best available estimate of the incidence of oesophageal varices. Based on this estimate and on the likelihood that newly appearing varices are small if seen within a relatively short interval, it might be reasonable to repeat endoscopy after two to three years in patients without varices at the first endoscopy. At this time, there should be 10–15% probability of development of new varices. Since there is no scientific evidence that other noninvasive parameters may accurately suggest the development of oesophageal varices, the consensus on this issue was the following:

1 In compensated cirrhotic patients without varices, endoscopy should be repeated at 2–3 year intervals to evaluate the development of varices.
2 Further studies of the natural course of cirrhosis should confirm the present estimate of the incidence of oesophago-gastric varices.

Patients with small varices on initial endoscopy

All respondents agreed that an endoscopy should be repeated in patients with small varices in order to assess the development of large varices. Fifteen indicated that this endoscopy should be repeated in one year, while 11 considered a two-year interval as reasonable. One answered that the timing for a new evaluation depends on the rapidity of the disease progression and one did not answer.

The largely homogeneous opinion of the experts is based on the fact that 24 of them indicated that variceal size is the main indicator of the risk of bleeding, followed by red signs ($n = 18$), both endoscopic parameters. Other indicators of bleeding risk most frequently used in clinical practice by the experts are Child (–Pugh) class ($n = 9$), HVPG ($n = 3$) and variceal pressure ($n = 2$).

Studies assessing the interval for progression from small to large varices are controversial and data are not solid. There are five such studies [26,40,45,123–124], that show variable rates of progression of varices ranging from 8% [26] to 30% per year [40]. If we take the median value of these estimates as an acceptable one, then we could expect to find progression of varices in approximately 12% patients per year in the first two years following endoscopic diagnosis of varices.

Based on the above, the consensus reached at the conference on this issue was as follows:

1 In compensated cirrhotic patients with small oesophageal varices, endoscopy should be repeated at 1–2 year intervals to evaluate the progression of varices.
2 Studies of the progression of variceal size from small to large should be encouraged to better define this interval.
3 Once large varices are detected, there is no indication for subsequent evaluations.

Treatment monitoring

Twenty-four respondents consider monitoring treatment effect as clinically important in the prevention of variceal bleeding or rebleeding. The aim of

monitoring treatment is to reassess the bleeding risk and/or to modify therapy ($n = 18$), for research purposes ($n = 1$) and not specified ($n = 5$). Three respondents considered that monitoring treatment was not worthwhile and one did not answer.

As mentioned on p. 40 (Measurement of HVPG), prospective cohort studies and clinical trials have shown that risk of bleeding (or rebleeding) is virtually abolished when the HVPG is reduced under 12 mmHg and is significantly reduced when it is reduced by > 20% of the baseline value [8–9,14,18,125]. Failure to reach an adequate treatment response, as defined by achievement of these parameters, might therefore indicate the need for a different therapy. Although the efficacy of such haemodynamic monitoring has not been directly proven in an RCT, efficacy is predictable in patients treated for the prevention of rebleeding, whose baseline risk of rebleeding is 60% in one year. However, efficacy is uncertain in patients treated for prevention of first bleeding, whose baseline risk is much lower being in the order of 15% per year in the presence of large varices.

Doppler ultrasonography is useful in estimating short-term changes in flow. Noninvasive monitoring of propranolol treatment by assessing variations of the femoral artery blood flow (FBF) has been suggested [126]: a reduction of FBF of < 20% with respect to baseline value before propranolol treatment, predict lack of HVPG reduction ≥ 20% (and hence unsatisfactory haemodynamic response to propranolol) in 94% of patients. However, a long-term study comparing HVPG measurements and duplex-Doppler parameters (portal blood flow and hepatic artery pulsatility index) before and after treatment with nadolol or nadolol plus isosorbide-5-mononitrate [127] failed to show any correlation. Therefore, although Doppler ultrasonography might be promising, its accuracy in monitoring treatment effects should be confirmed before it is introduced in clinical practice. Moreover, the applicability of such a monitoring test is limited by marked interequipment variability and further studies would be necessary to confirm these results.

Changes in variceal pressure have also been used to monitor treatment effects. Variceal pressure has been shown to decrease after treatment with beta-blockers both in cirrhotic and noncirrhotic patients [98,106] and in patients on propranolol that receive spironolactone [99]. A recent study [107] showed that the risk of variceal bleeding was markedly reduced when VP had decreased below 14 mmHg (9% bleeders against 39% if VP did not drop < 14 mmHg), indicating that noninvasive measurement of VP may be a method of monitoring treatment response. However, as mentioned previously, there is variability in the measurements particularly in patients with small varices in whom the study is often not feasible.

Based on the above, the following consensus statements were reached in the area of treatment monitoring:

1 HVPG is the only parameter presently suitable to monitor pharmacological treatment.
2 Variceal pressure and Doppler-ultrasound seem promising but, due to interequipment and interobserver variability, their use in clinical practice can not be recommended.
3 Efficacy of treatment adjustments based on monitoring should be further investigated.

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Baveno III Consensus Statements: Diagnosis of Portal Hypertension: How and When

Gennaro D'Amico, Guadalupe Garcia-Tsao, Paul Calès, Angels Escorsell, Frederik Nevens, Renzo Cestari, Giancarlo Caletti and Marco Zoli

1 Clinically significant portal hypertension is defined by an increase in portal pressure gradient to a threshold above approximately 10 mmHg.

2 The presence of varices, variceal haemorrhage and/or ascites is indicative of the presence of CSPH.

3 All cirrhotic patients should be screened for the presence of varices at the time of the initial diagnosis of cirrhosis.

4 Reliability of both HVPG measurement and endoscopic assessment of oesophageal varices for the diagnosis of CSPH is satisfactory.

5 However, specific, simple guidelines might further improve reliability.

6 The accuracy of noninvasive tests for the diagnosis of CSPH should be further assessed before their use can be recommended in clinical practice.

7 In compensated patients without varices, endoscopy should be repeated at 2–3 year intervals to evaluate the development of varices.

8 Further studies of the natural course of cirrhosis should confirm the present estimate of the incidence of oesophago-gastric varices.

9 In compensated patients with small varices, endoscopy should be repeated at 1–2 year intervals to evaluate progression of varices.

10 Studies of the progression of variceal size from small to large should be encouraged to better define this interval.

11 There is no indication for subsequent evaluations once large varices are detected.

12 HVPG is the only parameter presently suitable to monitor pharmacological treatment.

13 Variceal pressure and Doppler-ultrasound seem promising but, due to interequipment and interobserver variability, their use in clinical practice can not be recommended.

14 Efficacy of treatment adjustments based on monitoring should be further investigated.

SESSION 3A

Portal Hypertensive Gastropathy

Massimo Primignani, Luca Carpinelli, Shiv K. Sarin and Patrick S. Kamath

INTRODUCTION

In recent years, portal hypertensive gastropathy (PHG) has been recognized as a potential source of gastrointestinal bleeding in patients with cirrhosis and portal hypertension [1,2]. However, attempts to assess the importance of this entity as a source of bleeding and the severity of bleeding that it may cause have given conflicting results [2,3]. The major controversies concern the incidence of PHG, ranging between 7% and 98% in the available studies [2,3,4–9], the proportion of bleeds that can be attributable to PHG (range 4–40%), the probability of bleeding even from mild forms of PHG (range 0–15%) [2,3] and the evolution of PHG after endoscopic sclerotherapy of oesophageal varices [3,6,10]. In addition, there are scanty data on the mortality rates of patients bleeding from PHG in comparison with those bleeding from oesophageal or gastric varices.

Possible sources of disagreement between studies include: differences in patients selection, absence of uniform criteria to define the elementary endoscopic lesions of PHG, absence of a universally accepted classification system, and paucity of data regarding the reproducibility of the existing classifications.

CLASSIFICATION OF PHG

The NIEC classification

In order to overcome these limitations which hamper a proper evaluation of the clinical significance of PHG, a thorough classification of PHG, based on the recognition of elementary gastric lesions, was recently developed by the New Italian Endoscopic Club (NIEC) (Plate 1, facing p. 78).

These elementary lesions are: (1) Mosaic-like pattern (MLP), defined as the presence of small, polygonal areas surrounded by a whitish-yellow depressed border. The mosaic is defined as mild when the areola is uniformly

pink, moderate if the centre is red, and severe if the areola is uniformly red. (2) Red-point lesions (RPLs) are small, flat, red point-like lesions < 1 mm in diameter. (3) Cherry-red spots are round, red lesions > 2 mm in diameter slightly protruding into the lumen of the stomach. (4) Black-brown spots (BBSs) are irregularly shaped flat spots, black or brown, persistently present after washing, and caused by intramucosal haemorrhage.

The degree of agreement in the assessment of these lesions was evaluated and a fair to good degree of beyond chance agreement was obtained [11].

At a previous International Consensus Conference [12], it was decided to define PHG as mild when only MLP of any degree was present, and severe when RPLs, CRSs, or BBSs were present. This decision was based on the common experience of the participants, but it was agreed that the definition was only tentative and needed prospective evaluation. Moreover, since RPLs and CRSs were found to have overlapping features it was felt useful to classify altogether these lesions as Red Markings (RM), while BBSs were considered as evidence of an old intramucosal bleed and not different from the RM.

Gastric (antral) vascular ectasia (GAVE/GVE)

Another lesion described in portal hypertensive patients is gastric vascular ectasia (GVE). This is considered as a distinct clinical, endoscopic and histopathologic entity and has been reported in association with scleroderma, atrophic gastritis as well as cirrhosis of the liver. This lesion is characterized by aggregates of red spots, arranged in a linear pattern in the antrum of the stomach (in this case the term gastric antral vascular ectasia [GAVE] or 'watermelon stomach', is used) [13]. The ectatic red spots may be more diffuse and involve the proximal antrum as well when they are often termed as the 'diffuse' variety of GVE.

Whereas the typical antral 'watermelon' appearance, although rare, is an easily recognized condition (Plate 2, facing p. 78), the diffuse spots often defined as GVE do not appear to be endoscopically different from the RM of the NIEC classification (Plate 3, facing p. 78).

A criterion proposed by the authors who distinguish GVE from PHG is based on the presence of a background mosaic mucosa: when red spots are present within the mosaic mucosa, the term most often used to describe these changes is PHG. On the other hand, if the background mucosa has no mosaic appearance, the term proposed to describe these spots is GVE [14]. Thus it would appear that PHG can be diagnosed only if the MLP lesion is the underlying lesion, otherwise the diagnosis is GVE.

However, if one looks at the elementary lesions described in the NIEC classification and the most frequent sites where these lesions are found over the gastric mucosa, one can observe that MLP most frequently occurs in the

fundal-body area, while red points are ubiquitous and cherry-red spots are more frequently seen in the proximal stomach. Hence MLP and RM rarely coexist in the antrum, although in many instances they are both found in the same patient (Plate 4, facing p. 78).

In these cases it seems more appropriate to classify the RM as a feature of PHG, even if RM are not superimposed on MLP, rather than as a separate entity (G[A]VE), otherwise one should state that almost all cirrhotic patients with RM in the antrum do have G(A)VE, which is probably incorrect.

This discrepancy of interpretation can explain the different reported prevalence of G(A)VE in cirrhotics.

Such disagreement and confusion on PHG and GVE is reflected by the answers of the panelists of the Baveno III workshop to the question whether GAVE is to be considered as a feature of PHG, since most of them answered that it was not, but a consistent part (more than one third) answered that it was. It is noteworthy that those who do not classify G(A)VE as a feature of PHG state that G(A)VE is very rarely seen in portal hypertensive patients, while those who classify G(A)VE as a feature of PHG observe it in up to 50% of patients with PHG. This disagreement is clearly related to a different interpretation of RM not superimposed to MLP lesions, as GVE or PHG.

Further confusion ensues from the fact that, at the previous Baveno II Consensus Workshop, it was agreed to consider GAVE (GVE was not discussed) as a part of the PHG spectrum of lesions and a scoring system was also devised in order to tentatively classify PHG according to its severity.

However, the confusion in terminology between GVE and PHG causes this classification to be misleading, since, first, we do not know how to classify the lesion recently described and termed GVE, whether as RM or as GAVE. Secondly, in most instances, confluent RM (frequently seen in the antrum) and GAVE are mutually exclusive; thus a patient with GAVE and no other lesions would have assigned a score indicating mild PHG, which is obviously wrong. Finally, we have no data to state that a scoring system to classify PHG is able to identify patients with an increasing risk of bleeding from PHG.

Moreover, in recent years evidence has accumulated that GAVE/GVE is a different clinical entity, with distinct histopathological features and, probably, a distinct pathophysiology. The relationship of these lesions to portal hypertension is also uncertain, since they can occur also in the absence of portal hypertension and, in portal hypertensive patients, they do not seem to respond to measures adopted to decrease portal pressure [15].

Therefore, while further studies are needed to clarify the pathophysiology of PHG and GAVE, it is important to identify criteria to differentiate between GVE and severe PHG since PHG, but not GVE, seems to respond favourably to a decrease in portal pressure. The endoscopic criterion, based on the absence of the MLP in the background mucosa in GVE, as opposed to its presence

in PHG, for the reasons stated above, is inconsistent. On histology, the presence of ectatic blood vessels with fibrinous thrombi should be more suggestive of GVE [16]. Further studies are awaited to clarify whether GVE and RM are really different lesions in terms of pathophysiology, relationship with portal hypertension and response to portal pressure decreasing treatments. This point holds crucial clinical implications.

At the present time, due to these problems, the Baveno II classification of PHG should be abandoned and we could rely on the NIEC classification of PHG. This classification, as stated above, does not include GAVE, while GVE is not recognized as different from RM.

Given its good reproducibility, the NIEC classification was used to evaluate the prevalence of PHG in patients with cirrhosis of the liver and to investigate the natural history of PHG [17]. This study, and its implication in modifying the NIEC classification, are now discussed.

NATURAL HISTORY OF PORTAL HYPERTENSIVE GASTROPATHY

Patient population

Three-hundred and seventy three patients were enrolled in the study; 260 were men. Mean age was 62.8 ± 23.8 years; 192 patients had Child–Pugh class A disease, 142 had class B, and 39 had class C.

This population included 74 patients with a new diagnosis of cirrhosis (group 1: 89%, 11% and 0% were Child–Pugh class A, B and C respectively); 114 patients with previously diagnosed cirrhosis and no prior haemorrhage in periodic follow-up to evaluate the risk of first bleeding (group 2: Child–Pugh classes: 39%, 45% and 16%); and 185 patients currently ($n = 38$) or formerly ($n = 147$) treated with sclerotherapy to prevent rebleeding (group 3: Child–Pugh classes: 44%, 45% and 11%). The differences in Child–Pugh class distribution between group 1 and the other two groups are statistically significant

Cause of cirrhosis of the liver was alcohol in 38.1% of the patients, HBV in 23.9%, HCV in 21.8%, HBV + HCV in 11.1%, primary biliary cirrhosis in 1.7%, cryptogenic in 9.6%.

Correlation between PHG and other endoscopic and clinical features

Prevalence of PHG

Overall PHG was observed in 80.1% of the patients. It was mild in 34% and severe in 46.1%, as classified according to the NIEC (see above, NIEC Clas-

sification). Prevalence of PHG was 56% in group 1, 75% in group 2, 91% in group 3 (χ^2 for trend 34.249; df = 1; $P < 0.0001$).

The prevalence of PHG appears to be relatively low in patients with newly diagnosed cirrhosis, higher in patients with a previous diagnosis of cirrhosis and no prior bleeding, and even higher in patients with a previous variceal bleed, with current of prior sclerotherapy. This suggests that a correlation exists between duration of the disease and development of PHG.

Prevalence and extent of PHG elementary lesions

The prevalence of elementary PHG lesions and the distribution of PHG over the gastric mucosa are shown in Fig. 7. In many patients more than one lesion was present. None of the patients had GAVE.

Correlation with clinical features

Child–Pugh class. The overall prevalence of PHG was higher in patients with Child–Pugh class B than in patients with class A or class C (89%, 74% and 75% respectively).

This suggests that the correlation between PHG and the severity of liver dysfunction is weak.

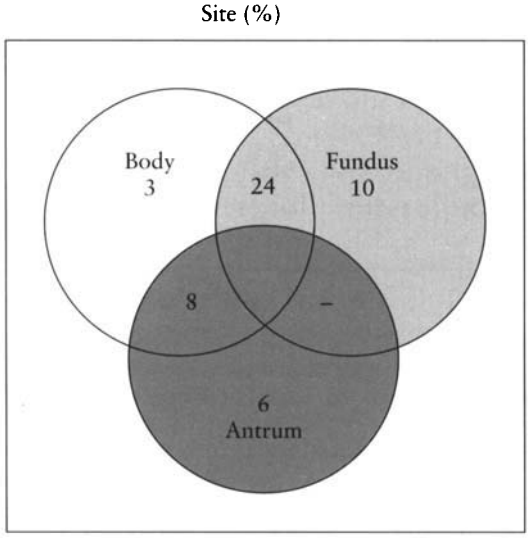

Fig. 7 Observed portal hypertensive gastropathy (PHG) lesions. The distribution of PHG over the gastric mucosa and the prevalence of elementary PHG lesions are shown. In many patients more than one lesion was present. MLP, mosaic-like pattern; RPL, red-point lesions; CRS, cherry-red spots; BBS, black-brown spots. Data from [16].

Oesophageal varices. Among the 188 patients who had not previously undergone variceal sclerotherapy, the prevalence of PHG was higher among those with oesophageal varices (76.9% of 104) than in those without (60.7% of 84; χ^2 12.1; df = 1; $P \cong 0.007$). As the size of oesophageal varices increased, overall PHG prevalence also significantly increased (χ^2 for trend 13.2; df = 1; $P < 0.0003$, see Table 15).

Oesophageal varices sclerotherapy. Of 289 patients with oesophageal varices, those treated with sclerotherapy showed a significantly higher prevalence of PHG than untreated patients (χ^2 [never treated vs. other categories] 11.03; df = 2; $P = 0.004$; see Table 16).

A higher prevalence of PHG is observed among patients with large varices and those with ongoing or previous variceal sclerotherapy. Whether this increased prevalence is a direct consequence of a more severe portal hypertension or of the endoscopic treatment, or whether these two factors are confounders of the longer duration of liver disease, remains unsettled.

Gastric varices. Prevalence of PHG was higher in patients with gastric varices (98.6% of 69) than in those without (76% of 304; two-tailed Fisher test: $P < 0.001$).

Table 15 Portal hypertensive gastropathy PHG varied with the presence/absence and size of oesophageal varices.

Oesophageal varices	PHG absent (%)	PHG present (%)
Absent ($n = 84$)	39.3	60.7
Present ($n = 104$)	23.1	76.9
Small, F1 ($n = 61$)	32.8	67.2
Medium, F2 ($n = 37$)	10.8	89.2
Large, F3 ($n = 6$)	–	100

Table 16 Patients with oesophageal varices treated with sclerotherapy showed a significantly higher prevalence of portal hypertensive gastropathy PHG than untreated patients.

EVS status	PHG absent (%)	PHG present (%)
No EVS ($n = 104$)	23.1	76.9
Ongoing EVS at enrolment ($n = 38$)	13.2	86.8
Previous EVS ($n = 147$)	8.2	91.8

EVS, endoscopic variceal sclerotherapy

Natural history of PHG

Evolution of PHG with time

Three-hundred and fifteen patients were followed up regularly for a mean of 539 ± 253 days, with a mean of 3.6 ± 1.3 endoscopies per patient. Of these, 54 belonged to group 1, 101 to group 2, and 160 to group 3. In 25% of the patients, endoscopic appearance of PHG fluctuated with time, with transition from none to mild or from mild to severe and vice-versa, on sequential endoscopies. PHG features were stable throughout follow-up in 29% (absent in 6%, mild in 11% and severe in 12%), showed a steady deterioration in 23% and a sustained improvement in 23%.

The fact that PHG not only can appear *de novo* or progress from mild to severe with time, but can also revert from severe to mild, and even disappear completely, is an interesting and previously unreported finding of this study. This observation suggests that PHG is a dynamic condition, whose pathophysiology probably depends not only on portal hypertension but also on other and not yet clarified factors fluctuating with time.

The evolution of PHG with time was similar in patients in group 1, 2 and 3. The observations that PHG may either worsen or improve in similar degree in patients treated and not treated by sclerotherapy, adds support to the hypothesis that sclerotherapy *per se* may not be responsible for the worsening of PHG observed in some studies [3,6], but not in others [18].

Moreover, no correlation was found between the evolution of PHG with time and other variables: extent of gastropathy at enrolment, continued alcohol intake in alcoholics, treatment with H_2-receptor antagonists, changes in size of oesophageal varices or in Child–Pugh class during follow-up.

The influence of beta-blocker treatment on the evolution of PHG could not be evaluated due to the small number of patients taking beta-blockers.

Definition of endpoints

The criteria adopted to define acute and chronic bleeding from PHG are those proposed at the Baveno II International Consensus Workshop [19]: acute bleeding was defined as the presence of haematemesis or melaena associated with endoscopic evidence of an actively bleeding lesion. Chronic bleeding was considered to have occurred if a drop of 2 g/dL or more took place between two consecutive controls 6 months apart, provided the patient had not acutely bled in the meantime and was not taking NSAIDs.

Acute bleeding

During follow up 31 patients (9.8%) bled acutely from the upper GI tract. No patient in group 1 bled.

Twenty-three bleeding episodes were from varices, either oesophageal or gastric, and only eight were from PHG.

Overall bleeding from PHG occurred in 2.5% of patients and accounted for 25.8% of all bleeds. The proportion of acute bleedings due to PHG in this study is similar to that observed by others [2,4], but differs from the findings of another study [3], which attributes 40% of all acute bleeds to PHG. This difference may depend on stricter criteria adopted in this study to define PHG acute bleeding (i.e. site of bleeding clearly identified at emergency endoscopy).

The site of PHG bleeding was the whole stomach in four patients, the antrum in two, and the fundus in two.

The endoscopic appearance of PHG and oesophageal varices at the time of bleeding are shown in Table 17.

Table 17 Endoscopic appearance of PHG and status of oesophageal varices at the time of bleeding.

Patient	Fundus	Body	Antrum	Site of bleeding	Size of oesophageal varices
1	Severe MLP, RPL	Severe MLP	Severe MLP	Whole stomach	Small
2	Severe MLP	Severe MLP	Severe MLP	Whole stomach	Absent
3	Moderate MLP	Moderate MLP	RPL	Whole stomach	Small (previous EVS)
4	Evaluation impossible for diffuse bleed			Whole stomach	Medium
5	RPL, BBS	Severe MLP	–	Fundus	Small (previous EVS)
6	Severe MLP, BBS	Moderate MLP	Moderate MLP	Fundus	Small
7	Moderate MLP	Moderate MLP	RPL, BBS	Antrum	Small
8	–	–	Severe MLP	Antrum	Medium (previous EVS)

MLP, mosaic-like pattern; RPL, red-point lesions; BBS, black-brown spots; EVS, endoscopic variceal sclerotherapy

Of the eight patients who bled, two had PHG classified as mild according to the NIEC classification (severe MLP alone was present in both cases). At the moment of bleeding, the PHG pattern had worsened in comparison with the previous control in three patients, appeared *de novo* in two, and was persistently severe in two. None of the patients had a recent consumption of NSAIDs. Two patients (number 7 and 8 in the table) were taking beta-blockers.

In terms of elementary lesions associated with bleeding, RPLs or BBSs were found in five of the seven patients in whom an adequate endoscopic assessment of the gastric mucosa was feasible. As agreed in the 1992 Consensus Conference [11], these two types of lesions are characteristic of 'severe' PHG. In the remaining two patients, only severe MLP was present, which is characteristic of 'mild' PHG. Thus, one should conclude that 'mild' gastropathy can also bleed acutely. However, it must be remembered that the distinction between severe and mild PHG was tentative and purely descriptive. In view of the data of this study (three patients [2, 3 and 8] with moderate and severe MLP had acute bleeding from the sites involved by these lesions), one should change the classification, and moderate MLP and severe MLP (in which the areola is centrally or uniformly red) should be considered as a feature of severe PHG. The final modified NIEC classification is presented in the descriptions accompanying Plate 1, facing p. 78.

Chronic bleeding

At enrolment, haemoglobin levels were similar in patients with or without PHG, either mild or severe, within each Child–Pugh class. A total of 284 patients could be evaluated for chronic bleeding during follow-up, i.e. 315 minus the 31 who bled acutely. Evidence of chronic bleeding (i.e. a decrease of 2 g/dL or more between two consecutive controls 6 months apart) was observed in 34 patients, in the absence of NSAIDs consumption.

The incidence of chronic bleeding was 0% in group 1, 20% in group 2 and 11.4% in group 3. The differences between group 1 and 2 and between group 1 and 3 were statistically significant, whereas group 2 and 3 did not differ significantly. The observation that none of the patients with a 'new' diagnosis of cirrhosis at enrolment bled acutely nor chronically during 18 months of follow-up, confirms that bleeding, both from varices and from PHG, is not an early phenomenon in the course of the disease.

Chronic bleeding only occurred in patients who had PHG at enrolment or in whom PHG developed during follow-up, irrespective of the grade of PHG. None of the patients persistently without PHG had evidence of chronic bleeding during follow-up.

The following variables were evaluated as potential predictors for chronic bleeding by Cox's proportional hazard model: PHG as a whole; extent of

PHG; presence and grading of elementary lesions; size and red colour signs of oesophageal varices; Child–Pugh score; persistent alcohol consumption; ascites; encephalopathy; beta-blocker treatment. None of the variables tested was significantly related to the risk of chronic bleeding.

The lack of significance of beta-blocker treatment should be interpreted with caution given the small number of patients treated and the observational nature of the study, which excludes a treatment indication and schedule common to all patients. This point, as well as the influence of beta-blocker treatment on PHG evolution with time, may be studied only with properly designed randomized clinical trials.

Mortality rates

Thirty-eight patients died during follow-up, ten as a consequence of acute bleeding (nine of oesophageal varices, one of PHG). Bleeding mortality rates were lower for PHG than for oesophageal varices (1 of 8 [12.5%] vs. 9 of 20 [39.1%]), but the difference failed to reach statistical significance. Twenty-eight patients died without bleeding.

In terms of bleeding-related mortality rates, only one of eight (12.5%) patient bleeding from PHG died of uncontrolled bleeding, compared to 9 of 23 (39.1%) of those bleeding from varices Although the difference is not statistically significant, these data suggest that bleeding from PHG is far less severe than variceal bleeding.

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SESSION 3B

Gastric Varices

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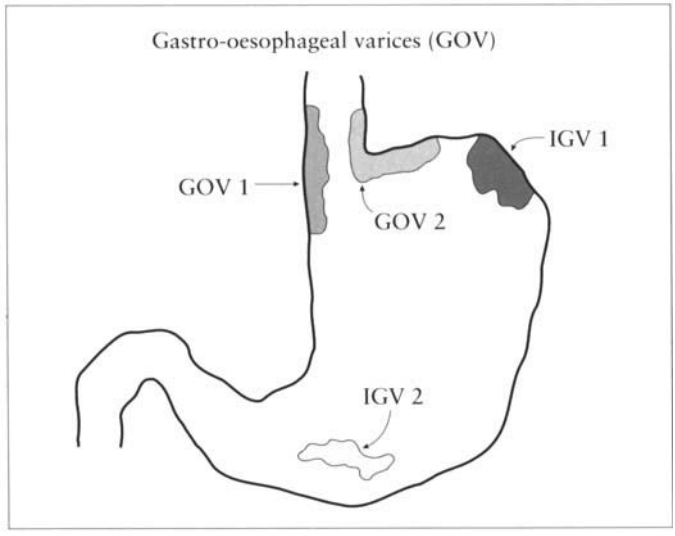
CLASSIFICATION

While every varix present in the stomach could be called a gastric varix (GV), the source of origin, the clinical course and the frequency of bleeding is quite different in many of them [1–3]. We had previously proposed a simple classification based on the location of gastric varices and their relationship with oesophageal varices (Fig. 8, Plate 5, facing p. 78) [3].

A recent survey of international experts for the Baveno III conference revealed that majority of the centres find this classification to be useful (Table 18). According to this classification, there are four main subsets of GV with distinct pathogenesis, natural history and management approach. One subset called the gastro-oesophageal varices type I (GOV1) or cardiac or junc-

Based on location



Based on presentation primary vs. secondary

Fig. 8 Sarin's classification of gastric varices.

tional varices, is basically an inferior extension of oesophageal varices, extending 20–50 mm below the gastro-oesophageal junction. The two subsets of GV, gastro-oesophageal varices type 2 (GOV2) and isolated gastric varices type 1 (IGV1) have been referred to as fundal varices by many authors. This group constitutes varices located in the fundus with (GOV2) or without (IGV1) associated oesophageal varices. The fourth subset is of GV which appear in the body, antrum, pylorus or even upper duodenum in a patient with portal hypertension. These are termed as isolated gastric varices type 2 (IGV2) or ectopic GV. The varices are further divided depending on the time of appearance as: primary (present at the time of initial presentation) or secondary (presenting after the obliteration of oesophageal varices) [3].

PREVALENCE OF GASTRIC VARICES

The prevalence of gastric varices in patients with portal hypertension has been observed to be around 25% with reports ranging from 7 to 57% [1–4]. A recent international survey revealed the frequency of GV to range from 5% to 33% (Table 18). Gastric varices are significantly more common in cirrhotic patients with a history of variceal bleeding than in those who have not bled (37% vs. 14%). This perhaps indicates that GV develop at a more advanced stage of portal hypertension. On the other hand, gastric varices (specially

Table 18 Report on international survey on classification, prevalence and profile of gastric varices (Baveno III).

Question	Number (%)
GV classification	
Total respondents	20
Classification used*	
Sarin	10 (50)
Fundal vs. Cardial	5 (25)
NIEC	4 (20)
Hashizume	2 (10)
Prevalence of GV	20% (n = 4407)†
GOV1	67%
GOV2	23%
IGV1	6%
IGV2	3%
Incidence of bleeding	< 20%
Type of GV that most frequently bleed	Fundal

* Some people have used more than one classification

† n = total number of patients with portal hypertension

IGV1) are more common in patients with portal vein thrombosis than in patients with cirrhosis or non cirrhotic portal hypertension (Fig. 9) [3]. The prevalence of different types of GV has been studied by various workers. The GOV1 have been observed to be the commonest type of GV (Table 18).

In our experience of 1424 patients with portal hypertension, the prevalence of gastric varices were seen in 415 (29%) patients. Seventy percent of the latter had GOV1, 21% had GOV2, while IGV1 and IGV2 constituted 6.7% and 1.4%, respectively (Fig. 10). GOV1 are more often associated with large oesophageal varices than GOV2 (95% vs. 83%, $p < 0.05$). An increase in the patients with IGV1 from our previous data could be due to a referral bias and inclusion of more patients with portal vein thrombosis.

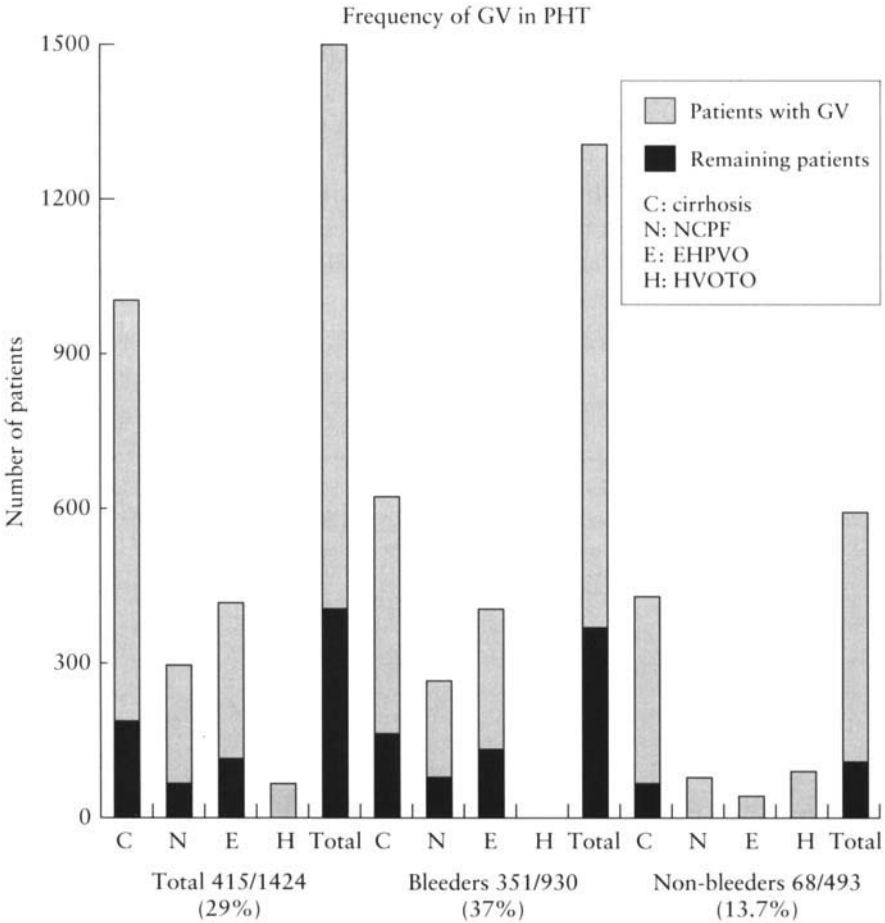


Fig. 9 Prevalence of GV in cirrhosis, non-cirrhotic portal fibrosis (NCPF), extra-hepatic portal vein obstruction (EHPVO) and hepatic venous outflow tract obstruction (HVOTO).

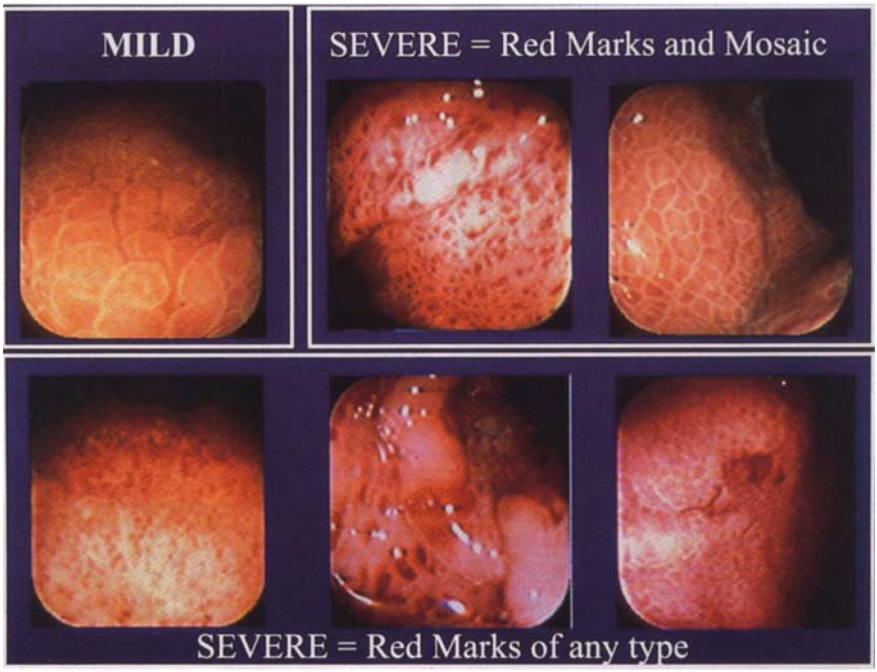


Plate 1 The NIEC classification of portal hypertensive gastropathy (PHG), modified according to the natural history study data from Primignani *et al.* [17]. Top row (left to right): mild mosaic-like pattern (MLP), moderate MLP, severe MLP; bottom row (left to right): red-point lesions, cherry-red spots, black-brown spots. The original, tentative, classification defined as 'mild' PHG the presence of mosaic-like pattern of any degree, as 'severe' PHG the presence of any of the red signs depicted in the bottom row.

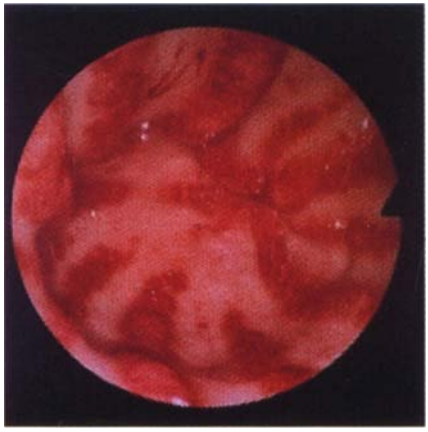


Plate 2 Gastric antral vascular ectasia (GAVE). This lesion is characterized by aggregates of red spots, arranged in a linear pattern in the antrum of the stomach.

[facing p. 78]

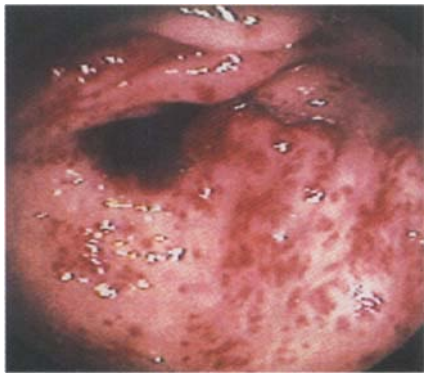
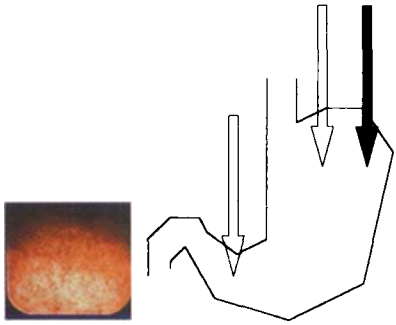
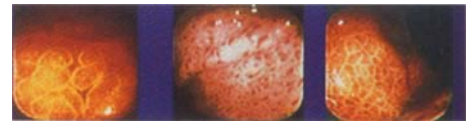


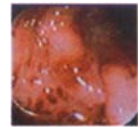
Plate 3 Gastric vascular ectasia (GVE) or severe portal hypertensive gastropathy (PHG)? Whereas the typical antral 'watermelon' appearance, although rare, is an easily recognized condition, these diffuse spots, which may be defined as GVE, do not appear to be endoscopically different from the RM of the NIEC classification (Plate 1).





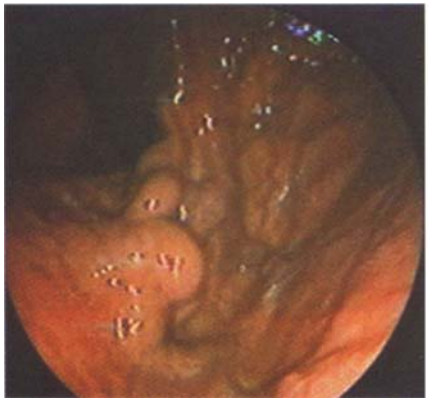
MLP: 72% fundus/body, 1% antrum, 27% whole stomach

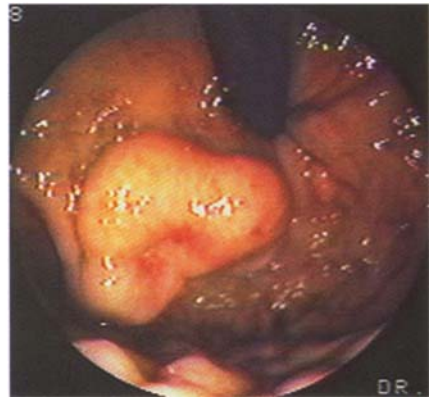
RPL: 33% antrum, 30% fundus/body, 37% whole stomach



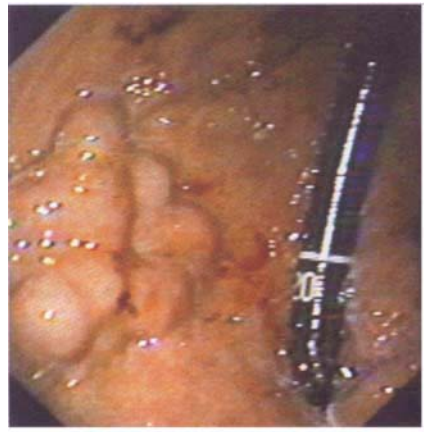
CRS: 80% fundus/body, 7% antrum 13% whole stomach

Plate 4 Prevalence of portal hypertensive gastropathy (PHG) elementary lesions in the stomach. Red-point lesions are ubiquitous in the stomach (hollow arrows). Mosaic-like pattern and cherry-red spots are mostly found in the fundus and body of the stomach (solid arrow). Data from Carpinelli *et al.* [11].





(a)



(b)

Plate 5 (a) Gastro-oesophageal varix type 1 (GOVI) and type 2 (GOV2). (b) Isolated gastric varix type 1 (IGVI).

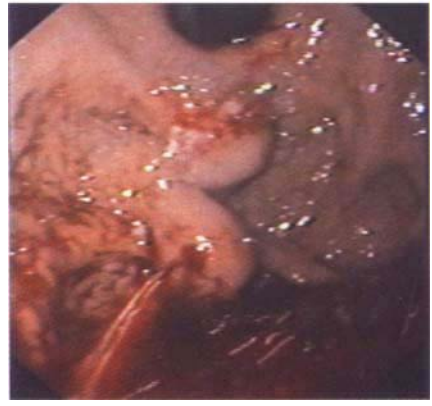
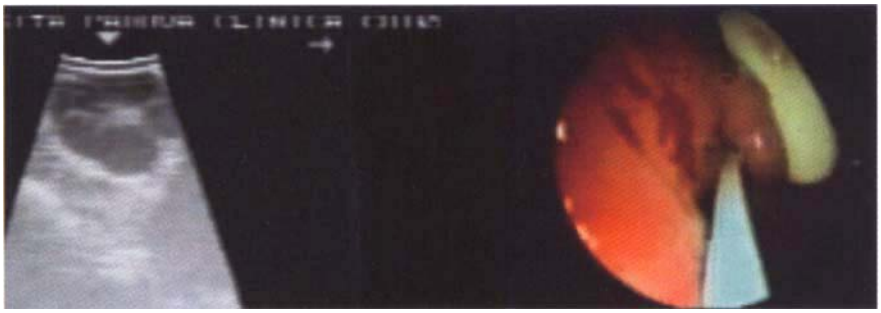


Plate 6 Active bleeding from GV (Picture courtesy Dr Battaglia).

(a)



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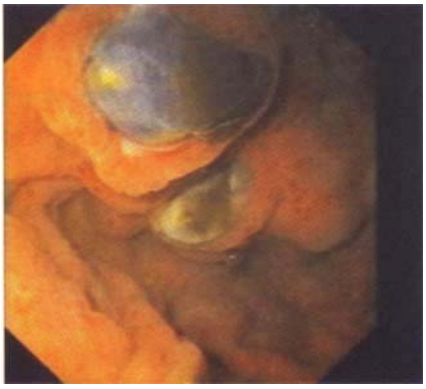

Plate 7 (a) Injection of glue under endoscopic ultrasound (EUS) guidance. (b) Glue cast after three weeks of injection (Pictures courtesy Dr Battaglia).

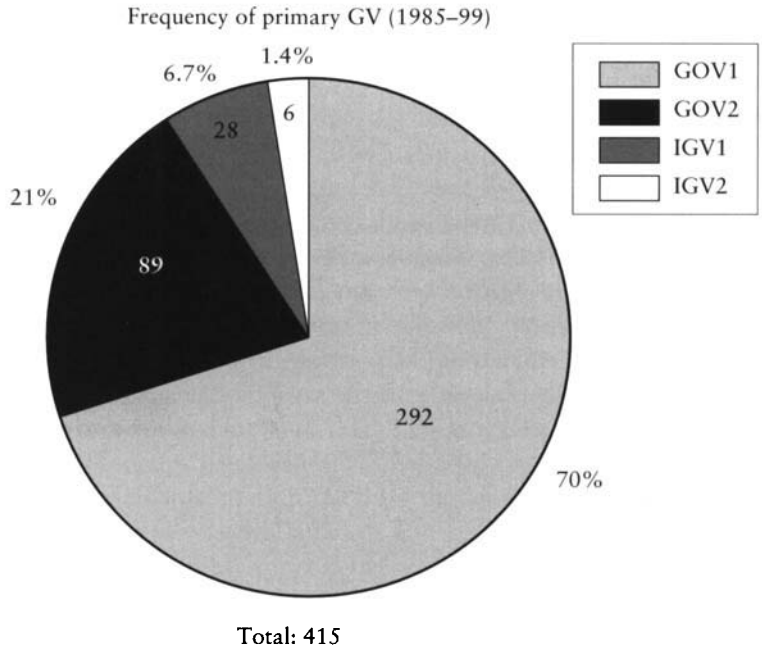

Fig. 10 Frequency of different types of primary gastric varices.

BLEEDING FROM GASTRIC VARICES

Definition

Bleeding should be considered to have arisen from GV if, (a) an active spurt or ooze is seen from the GV (Plate 6, facing p. 78), (b) an adherent clot or blackish ulcer is seen on the GV, or (c) in the presence of distinct large GV and absence of oesophageal varices, no other source of bleeding is detectable.

Incidence

There are conflicting reports on how often and how severely GV bleed. The incidence of bleeding from GV has been reported to be between 3 and 30%. It is generally believed that GV bleed less frequently than oesophageal varices. The data however, is controversial in this regard. Korula *et al.* calculated the number of bleeding episodes from the oesophageal and gastric varices. In their series, patients with fundal (4.8 ± 2.9) and junctional GV (2.2 ± 2.2) had a higher number of bleeding episodes than patients with varices (0.7 ± 1.1) [5]. We have earlier shown that the mean number of bleeding episodes in patients with gastric and oesophageal varices was comparable (2.14 ± 1.03

vs. 2.3 ± 1.8) [3]. The bleeding risk factor per year (total number of bleeding episodes/time interval between the first and the last bleed) for oesophageal varices was higher than for GV (4.3 ± 0.4 vs. 2.0 ± 0.6, $p < 0.01$) [3].

Several authors have reported a high incidence of haemorrhage from fundal (GOV2 and IGV1) varices [2,3]. We have documented an incidence of haemorrhage of 55% in GOV2 and 78% in IGV1, both representing fundal varices [3]. Kim *et al.* in a prospective study of 117 patients with fundal varices have documented cumulative bleeding rates at one, three, and five years of 16%, 36%, and 44%, respectively. The incidence of haemorrhage from high risk oesophageal varices has been shown to be 19–40% with similar follow-up period. Thus, the incidence of haemorrhage from fundal varices appears to be similar to that from moderate to large oesophageal varices. In the recent survey, nearly all the experts reported that fundal varices (GOV2 and IGV1) bleed more frequently than other types of GV (Table 18).

Risk factors for GV bleed

A recent multivariate analysis revealed (a) the size of GV (b) the Child's status, and (c) the presence of red spots on the GV to be independent predictors of haemorrhage (Table 19) [6]. Hashizume *et al.* also found the size of GV to be related to the risk of bleeding [2]. Large fundal varices have greater flow and/or wall tension and thus, result in a higher incidence of bleeding. The red colour signs, which correspond to the dilated, blood-filled channels lying within and beneath the mucosal epithelium are also a known risk factor for haemorrhage from oesophageal varices. However, the vascular structure of the stomach is not the same as that of the oesophagus and gastric varices usually lie in the gastric submucosa thus, a red colour sign is seldom found in patients with gastric varices.

Table 19 Risk factors for haemorrhage from fundal varices [6].

Factor	Risk ratio
Size of fundal varices	2.18 (1.21–3.93)*
	4.75 (1.45–15.5)†
Child's status	1.70 (1.11–2.59)‡
	2.88 (1.21–3.93)¶
Red spot present	2.06 (1.01–4.19)§

* Small vs. medium
† small vs. large
‡ Class A vs. class B
¶ Class A vs. class C
§ Absent vs. present

Influence of oesophageal variceal sclerotherapy or ligation on the fate of coexisting gastric varices

We have studied the natural history of GV in patients who have undergone sclerotherapy or variceal ligation for oesophageal varices. The outcome of different types of varices was observed to be as follows:

1 GOV1: One hundred and twenty three patients with GOV1, who had presented with oesophageal variceal bleeding underwent endoscopic sclerotherapy. GOV1 disappeared after sclerotherapy in 58% patients; concurrently in nearly three-quarters of the patients;and within 6 months of the obliteration of the oesophageal varices in the remaining patients. Similarly, GOV1 disappeared in 35 of the 50 (70%) patients who underwent endoscopic variceal ligation [8]. Both these methods therefore, are effective treatment for GOV1 [7,8]. The reason for regression of GOV1 could be the flow of the sclerosant towards stomach or formation of a thrombus at the gastro-oesophageal junction which could propagate caudally.

2 GOV2: Oesophageal variceal obliteration by sclerotherapy or ligation only marginally influenced the outcome of GOV2. Of the 81 patients of GOV2 seen at our centre, the varices were obliterated concurrently or within 6 months in 27% of patients who had received sclerotherapy and in 36% of those who received ligation EVL [8].

3 Development of secondary gastric varices: Gastric varices have been reported to develop after obliteration of oesophageal varices. Such gastric varices are termed secondary gastric varices. They could develop at any site and could thus be of GOV or IGV type. The reported frequency of secondary GV varies from 9.7 to 15.3% [1–3,5]. While in some series GOV1 have been reported to develop more frequently than GOV2 (11.2% vs. 4.1%) [2], (9.6% vs. 0.5%) [1], in our experience [3] GOV2 develop more frequently than GOV1 (11.4% vs. 2.6%) after oesophageal variceal eradication. The frequency of bleeding from secondary GV has been reported to be higher than with primary GV. Over a follow-up period of 16.1 and 12.6 months, the bleeding incidence in secondary GOV1 and GOV2 was 37% and 100%, respectively [5]. These observations raise an important issue, should secondary gastric varices be treated prophylactically? There is a need to evaluate both pharmacotherapy and endoscopic therapy in this regard.

MANAGEMENT OF GASTRIC VARICEAL BLEED

Most of the reported series of endoscopic treatment of GV bleed have either included small number of cases or have included retrospective data. Hence, despite nearly two decades of active interest the management of bleeding gastric varices remains controversial and largely empirical.

Intervention groups

Primary prophylaxis of GV bleeding

The rationale of primary prophylaxis for gastric variceal bleed has not been evaluated so far. A few studies using large variceal size and the presence of red colour signs have evaluated prophylactic treatment on a small number of cases. In our experience, the profile of bleeding in patients in whom GOV1 disappear within 6 months of eradication of oesophageal varices was quite different from that in patients in whom GOV1 persisted [3,4]. Bleeding was significantly more common and bleed related mortality was also higher in the latter group. We therefore, recommend prophylactic therapy for the group of patients in whom GOV1 persist beyond 6 months of obliteration of oesophageal varices by sclerotherapy or ligation. Prophylactic treatment of high risk GOV2 or IGV1 varices should be attempted only if the current treatment methods could be made more safe and effective. At present, there is no data to justify prophylactic treatment of such gastric varices. Prospective controlled studies are required to address this issue.

Acute GV bleeding

Presence of endoscopic evidence of acute GV bleed or stigmata of recent bleed on GV are definite indications for active intervention. Sometimes however, it is not possible to determine whether a patient with oesophago-gastric varices is bleeding from oesophageal or gastric varices. In such a situation, opinions differ whether oesophageal or gastric varices should be treated first. Most people however, prefer to inject and obliterate only the oesophageal varices (Table 20). The treatment goals are the same as for oesophageal varices; control of acute bleed and prevention of rebleeding. The patients need to be treated according to the type of varix and the expertise available (Fig. 11). The details of the different intervention strategies are given below.

Intervention strategies

The various treatment modalities employed for the control of GV bleeding include the following.

Balloon tamponade

Two types of balloons are available for the control of bleeding from GV, namely the Sengstaken–Blakemore tube and the Linton–Nicholas tube. The latter

Table 20 International survey on management of gastric varices.

Question	Number of respondents ($n = 20$)
Emergency treatment of GV bleed*	
Sclerotherapy	9
Glue	5
Drugs	1
TIPS	1
Band ligation	0
Elective treatment of GV bleed*	
TIPS	1
DSRS	1
Drugs (Beta-blockers)	4
If both OV and GV are seen and the site of bleeding is uncertain, treat	
GV only	8
OV only	3
GV after OV obliteration	2
Both OV and GV	1
Goal of therapy	
Control of bleed and prevention of rebleed	11
Control of bleed and GV eradication	9

* Not all respondents gave answers
TIPS, transjugular intrahepatic portosystemic shunt; DSRS, distal splenorenal shunt; OV, oesophageal varices; GV, gastric varices

tube has a single large gastric balloon with a capacity of 600 ml and is helpful in controlling acute GV bleeding.

Vasoactive agents

There is limited information on the role of drugs in the control of acute bleeding from GV. In an international survey though, many workers have reported use of vasoactive agents in acute bleeding as well as for secondary prophylaxis (Table 20), but no published studies of pharmacotherapy in the treatment of gastric varices are available.

Gastric variceal sclerotherapy (GVS)

The early reports of GVS were disappointing and were accompanied by a high incidence of rebleeding. However, over the years, with increase in the expertise and with the use of various novel agents, GVS has achieved fair amount of success.

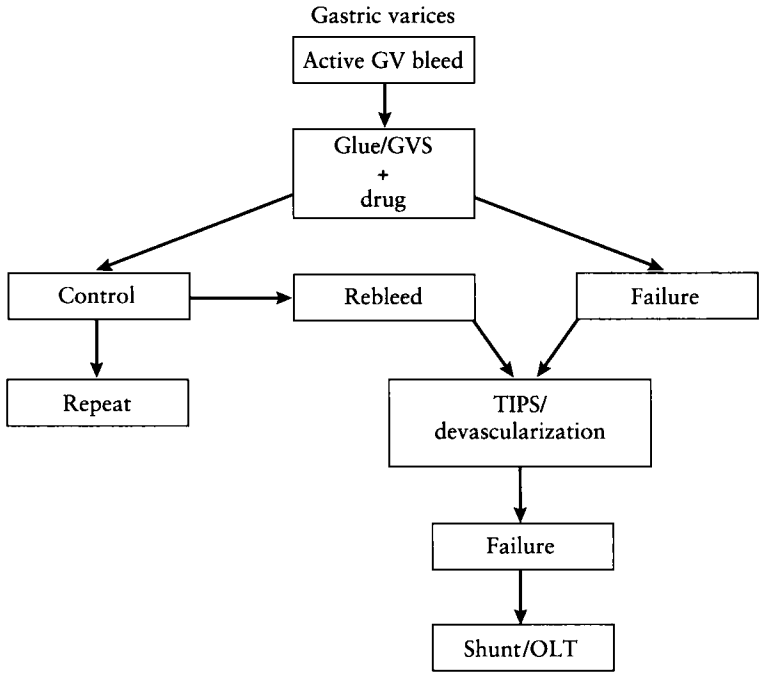

Fig. 11 Management algorithm for acute GV bleed.

Sclerosants. An ideal sclerosant for GVS should cause thrombosis with minimum tissue necrosis. It is also desirable that the sclerosant should act instantaneously at the site of injection. Sodium tetradecyl sulphate, absolute alcohol, ethanolamine oleate, hypertonic glucose, and thrombin have been successfully used by different workers.

Technique. GVS can be done with a flexible endoscope using either a straight-end-on technique or by retroflexion (i.e. by retroverting the endoscope at the incisura angularis) for better visualization of the fundus. The former technique is employed for lesser curve varices (GOV1) and the latter is used for fundal varices. We prefer using a 5–6 mm long needle and a transparent Teflon injector. Different modes of injection including paravariceal, intravariceal or preferably a combination of the two methods can be employed for GVS.

Emergency GVS. This is technically difficult especially in patients with fundal varices, in whom proper visualization of the varices becomes difficult due to pooling of blood. Putting the patient in right lateral decubitus and reverse Trendelenberg position may improve visualization. A double channel therapeutic endoscope is preferred by some endoscopists.

Elective GVS. This technique is relatively easy due to proper visualization of varices in the blood free field. GOV1 can often (80%) be obliterated with a single session of GVS. The GOV2 and IGV1 however, require three or more sessions for complete obliteration. It is during this period that the risk of rebleeding from GV is quite high.

Results. GVS is able to achieve immediate haemostasis in 40–100% of cases in actively bleeding patients (Table 21) [9–16]. Two studies have shown equal efficacy of emergency GVS for GOV1 and GOV2 [13,15] while studies by Oho *et al.* [12] and Gimson *et al.* [11] have shown higher success for GOV1 as compared to GOV2. Chiu *et al.* have done emergency sclerotherapy in 27 patients with isolated gastric varices with a success rate of 67% and rebleed rate of 18% at 48 hours [14].

Table 21 Gastric variceal sclerotherapy in active gastric variceal bleed.

Author (year)	Agent	*n*	Success (%)	Rebleed (%)	Complications
Trudeau (1986)	STD	9	100	90	Ulcer 89%
Bretagne (1986)	Polidocanol 1.5%	10	60	63	–
Gimson (1991)	EO/Glue	41	40 GOV1 = 54 GOV2 = 26	16	Ulcers 29% Perforation (1)
Oho (1995)	EO 5%	24	67 GOV1 = 85 GOV2 = 50	25 20 33	–
Chang (1996)	STD 1.5%	25	80 GOV1 = 80 GOV2 = 80	70	Ulcers 30%
Chang (1996)	GW 50%	26	92 GOV1 = 92 GOV2 = 92	30	Ulcers 30%
Chiu (1997)	STD 1.5%	27	66.7 IGV1	–	–
Sarin (1997)	AA 95%	18	67 GOV1 = 67 GOV2 = 67	34	Ulcers 100%
Ogawa (1999)	EO 5%	21	81	100	–

STD, sodium tetradecyl sulphate; EO, ethanolamine oleate; GW, glucose water; AA, absolute alcohol

The major problem with GVS is early rebleeding, usually after the first or second treatment session, i.e. before the varices can be completely obliterated. The major cause is early appearance of deep submucosal ulcerations on incompletely obliterated varices. These ulcers are quite unlike oesophageal variceal ulcers which are often mucosal and heal spontaneously. Another reason for the limited success of GVS could be difficulty in formation of thrombus because of rapid blood flow and presence of large spontaneous shunts in patients with gastric varices. The frequency of ulcers after GVS is reported to be between 30 and 100%. Approximately 50% of post-GVS bleeds are from these ulcers [9,13]. Chang *et al.* have shown a higher rebleeding rate with sodium tetradecyl sulphate (STD) as compared to 50% glucose water (70% vs. 30%). They observed a delayed ulcer healing in STD group (13 ± 5 days vs. 6 ± 2 days.) [13]. Once rebleeding occurs it is difficult to control with GVS, the success rate being only 9–44% [9,12–14].

Variceal eradication can be achieved in 17–81% of patients using repeated GVS (Table 22). Variceal obliteration is achieved more frequently in patients with GOV1 (99.4%) than in those with GOV2 (70.4%) and IGV1 (41%), and rebleeding is seen in 5.5%, 19%, and 53%, respectively in the three types of gastric varices [15]. The recurrence rate of gastric varices varies from 0 to 25%.

Gastric variceal obturation

Endoscopic obturation of oesophago-gastric varices with the tissue adhesive butyl cyanoacrylate was first reported by Gotlib *et al.* in 1981 [17]. The tissue

Table 22 Gastric variceal sclerotherapy in secondary prophylaxis of gastric variceal bleed.

Author (year)	Agent	*n*	Obliteration (%)	Rebleed (%)	Recurrence (%)	Follow-up (months)
Yassin (1985)	–	35	17.1	37	–	–
Sarin (1988)	AA 95%	32	38	16	–	–
Gimson (1991)	EO/Glue	31	32.3	16	–	–
Chang (1996)	STD 1.5%	25	32	70	25	52 ± 37
Chang (1996)	GW 50%	26	81	30	4.8	57 ± 32
Sarin (1997)	AA 95%	60	72	23 GOV1 94 GOV2 70	0	24 ± 23

AA, absolute alcohol; EO, ethanolamine oleate; GW, glucose water; STD, sodium tetradecyl sulphate

adhesive or 'superglue' as it is called, can be injected using the standard endoscope and injector. Some endoscopists prefer using endoscopic ultrasound for better monitoring (Plate 7a, facing p. 78). The glue hardens instantly on contact with blood, thereby producing immediate obliteration of varices. Several weeks after the injection (2 weeks to 3 months). the overlying mucosa sloughs off and a glue cast is extruded into the lumen of gastrointestinal tract (Plate 7b, facing p. 78). Therefore, ulceration over varix appears quite late as compared to GVS which does not hinder further sessions of obturation as well as significantly reduces the risk of ulcer bleeding. Tissue adhesives therefore, nearly fulfil the requirements of an ideal sclerosing agent for gastric varices. Two agents, n-butyl-2-cyanoacrylate (Histoacryl) and isobutyl-2-cyanoacrylate (Bucrylate) have been used although, the latter agent has been removed from the European market because of concerns about carcinogenicity.

Cyanoacrylate has been used in the management of active gastric variceal bleeding and has been shown to achieve haemostasis in > 90% of patients with early rebleed rate of 0–42% [12,16–20]. It produces variceal obliteration just in one to two sessions and eradication rate has been reported to vary between 87 and 100% (Table 23).

The overall safety record of cyanoacrylate for the treatment of variceal bleeding has been good. Minor complications like pyrexia, bacteremia and dysphagia with or without stenosis occur with similar frequency as in oesophageal variceal sclerotherapy. However, isolated cases of post-injection embolization, cerebral stroke, and fatal pulmonary embolization have been reported.

Table 23 Cyanoacrylate glue injection in the management of gastric varices.

Author (year)	Total patients	Active bleed (%)	Immediate success (%)	Eradication (%)	Rebleed (%)
Gotlib (1984)	96	22	95	–	36
Ramond (1986)	49	31	93	–	42
Sohendra (1987)	138	22	100	100	10
Ramond (1989)	27	26	86	100	37
Rauws (1991)	39	69	100	100	41
Grimm (1991)	23	–	100	100	0
Oho (1995)	29	100	93 GOV1-100 GOV2-88	–	30 25 33
D'Imperio (1996)	54	41	91	87	3.7
Ogawa (1999)	17	–	100	–	5.9

Splenic infarction and formation of retrogastric abscess, portal vein embolization have also been reported. It is advisable to limit the amount of injection to less than 2 ml to avoid these complications. Damage to the endoscope is another major source of concern while using cyanoacrylate glue. Use of silicone gel or lipiodol and avoidance of suction for 10–20 seconds after injection till cyanoacrylate polymerizes are helpful precautions. Certain newer agents such as poly-n-acetyl glucosamine have been proposed to be safer.

Comparison of sclerotherapy and obturation. Three studies have compared EST using ethanolamine oleate (5%) or absolute alcohol and histoacryl injection in acute gastric variceal bleed (Table 24). Ogawa *et al.* [16] in their retrospective study reported a significantly higher haemostasis rate with histoacryl (100% vs. 81%). While six of 17 (35%) patients rebled at 2 weeks in ethanolamine oleate group, none of the patients rebled in the histoacryl group. None of the patients died of bleed in histoacryl group while five of 21 (23.8%) died in ethanolamine group. Oho *et al.* [12] in their prospective, nonrandomized study of 53 patients with acute gastric variceal bleed have reported histoacryl to be significantly more efficacious in achieving haemostasis than ethanolamine oleate (93% vs. 67%). Three patients in each group rebled at 1 month. Three patients in histoacryl group rebled 6 months after treatment from the site of polymer elimination. A randomized controlled trial done in our centre in 35 patients with isolated fundal varices showed that cyanoacrylate is more effective in achieving initial haemostasis and in achieving faster variceal obliteration. The need for emergency surgical rescue was also much less in the glue injected group [21].

The results of all these three comparative studies show that cyanoacrylate glue is more effective and is more advisable than sclerosants like ethanolamine oleate or absolute alcohol.

Table 24 Gastric variceal sclerotherapy vs. glue injection in gastric variceal bleed.

Author (year)	Agent	*n*	Control of acute bleed (%)	Rebleeding (%)	Mortality (%)	Ulcer (%)
Oho (1995)	EO	24	67	12.5	67	25
	HC	29	93	10	38	30
Ogawa (1999)	EO	21	81	35	23.8	–
	HC	17	100	0	0	–
Sarin (1998)	AA	8	62	25	25	82
	HC	9	89	22	25	65

EO, ethanolamine oleate; HC, histoacryl; AA, absolute alcohol

Gastric variceal ligation (GVL)

The development of multiband ligating devices has made endoscopic variceal band ligation technically easier to perform so that banding can be accomplished with the endoscope retroflexed in the stomach. Some studies had reported 100% haemostasis with GVL, though the number of subjects was small. In a recent prospective study, immediate haemostasis was achieved in 89% of cases with rebleeding in 18.5% [22]. Eradication of varices could also be achieved in all the patients with a median of three sessions of banding. A combination of variceal ligation and injection sclerotherapy has been used by Korean workers with success. They were able to control active bleeding in all the 11 cases and obliterate the GV in all the 32 patients [23]. These results however, await confirmation by other studies. The lower rate of recurrent bleeding with GVL can be explained by rapid obliteration of varices as compared to GVS. GVL was in fact, more effective in patients with IGV1 where sclerotherapy is not so effective. One study has compared histoacryl injection with band ligation of gastric varices in 16 patients. Both the methods were found to be equally effective in achieving haemostasis with a similar rebleed rate [24].

The major concern however limiting the use of GVL is the fear of incomplete inclusion of large GV in the band and a subsequent ulcer bleed. Therefore, many authors recommend use of a snare for ligation of gastric varices which are more than 10 mm in size.

Endoscopic snare ligation

Yoshida *et al.* reported a new technique using detachable snare for ligating GV [25]. A stainless steel snare with an inner diameter of 40 mm is tightened around the base grasping the periphery of varices with a forceps through the second channel of the double channel scope. High success rates in control of acute gastric variceal bleed and variceal eradication have been reported by them and other workers (Table 25) [25,26]. No significant ulcer related complications have been reported except perforation in two patients in one study [26].

While some experimental studies have not found band ligation of GV to be as effective [27], results of the clinical studies suggest that ligation with rubber band or snare could be an effective and safe alternative in the management of gastric variceal bleed. Prospective, randomized controlled studies are required to compare these endoscopic modalities in the treatment of gastric varices.

Balloon-occluded retrograde transvenous obliteration of gastric varices (BRTO)

Gastrorenal shunt is often present between gastric varices and left renal vein in

Table 25 Gastric variceal ligation in the management of GV bleed.

Author (year)	Modality	*n*	Active bleed (%)	Success (%)	Rebleed (%)	Obliteration (%)	Recurrence (%)	Mortality (%)
Yoshida (1994)	GVL-S	10	10	100	10	100	0	–
Takeuchi (1996)	GVL and GVL-S	45	13	83	2	94	5 0 14	4.4
Harada (1997)	GVL-S	5	100	100	20	–	–	–
Cipolletta (1998)	GVL-S	7	100	100	0	–	–	0
Yoshida (1999)	GVL-S and EIS	35	23	100	3	97	6	0
Shiha (1999)	GVL	27	7	89 GOV1–100 GOV2–80 IGV1–100	18.5	100		11

GVL, gastric variceal ligation; GVL-S, gastric variceal snare ligation

patients with fundal varices. A balloon catheter is introduced in the gastrorenal shunt via the left renal vein, and the shunt is occluded by inflating the balloon and injecting a sclerosant into gastric varices (Fig. 12). BRTO has been reported have a high initial success rate (100%) of GV obliteration and low recurrence rate [28]. It could serve as a feasible alternative to TIPS for patients with large gastrorenal shunts or hepatic encephalopathy.

Transjugular intrahepatic portosystemic shunt (TIPS)

In patients who fail on endoscopic therapy, TIPS and rescue surgery remain an alternative. In patients with advanced liver failure, ascites, encephalopathy, or actively spurting varices emergency surgery carries an overall mortality of 70–90%. TIPS can provide an effective rescue therapy in this group of patients. However, there are no controlled trials comparing the two modalities. Placement of TIPS abruptly reduces the outflow hepatic resistance, lowers

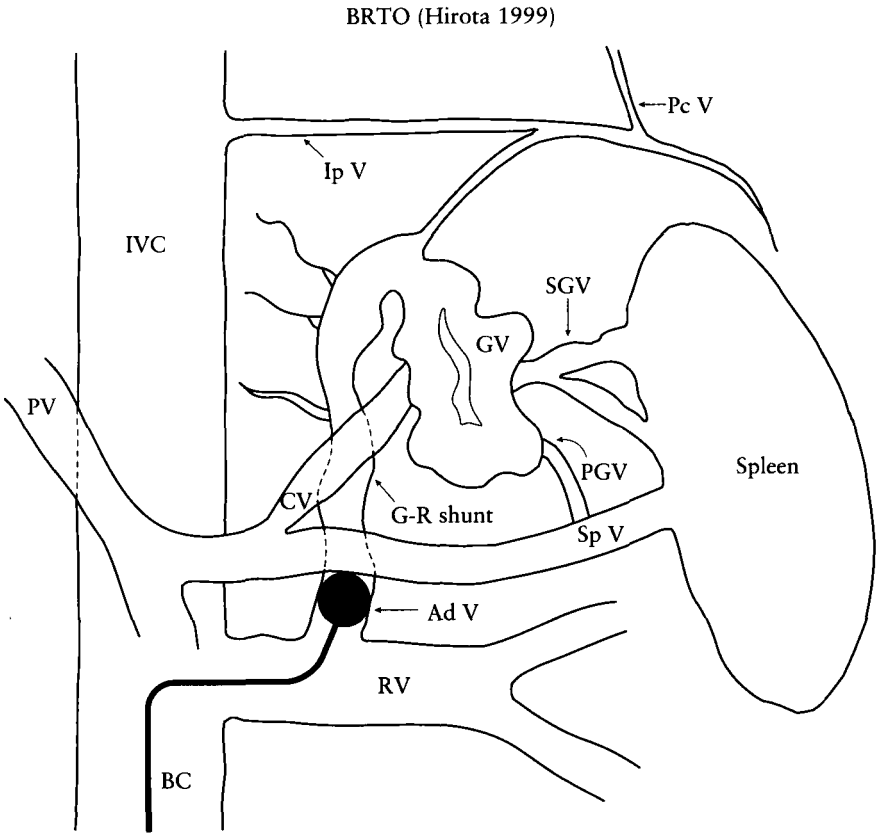

Fig. 12 Balloon-occluded retrograde transvenous obliteration of gastric varices (BRTO).

portal pressure, and diverts portal flow from gastro-oesophageal collaterals to the stent. TIPS has been shown to achieve initial control of bleeding in greater than 95% of the patients. The 30 day rebleeding rate is ~25–30% [29]. often due to stenosis or obstruction of the stent. TIPS dysfunction occurs in ~ 50–60% of patients at 6 months, requiring close monitoring and repeated interventions to keep it patent [29].

LONG-TERM FOLLOW-UP OF GV

While a number of trials have shown the long-term outcome in respect to endoscopic management of oesophageal varices, there is scanty data on the long-term follow-up after gastric variceal obliteration [15]. The recurrence rates after obliteration with sclerotherapy are much lower in patients with GV compared to oesophageal varices [15].

In conclusion, patients with active GV bleed or those who have bled in the past from GV are candidates for endoscopic intervention (Fig. 13). The agent of choice for injection of GV is acrylate glue since it achieves more rapid and effective haemostasis with high obliteration rates. Gastric variceal sclero-

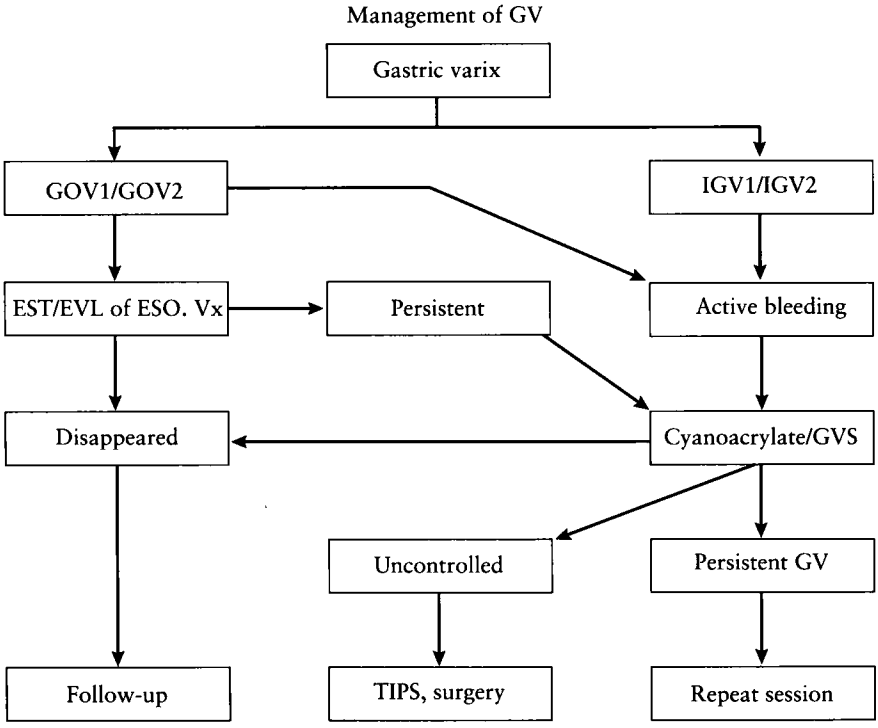

Fig. 13 Algorithm of management of gastric varices.

therapy using absolute alcohol or ethanolamine oleate is an effective alternative treatment. With both techniques, more so with sclerotherapy, attention needs to be paid to decrease the frequency of ulcers developing following injection, which cause recurrent bleed. The data on the efficacy and safety of gastric variceal ligation is preliminary and needs to be analysed prospectively in larger number of patients. Further advances in the management and outcome of GV bleeding could come only when the natural history, risk factors for bleeding and the mechanism of GV rupture are clearly defined.

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Baveno III Consensus Statements: Portal Hypertensive Gastropathy (PHG), Gastric Varices (GV)

Massimo Primignani, Shiv K. Sarin (Chairpersons), Giorgio Battaglia, Gennaro D'Amico, Patrick S. Kamath, H.C. Lin, Josep Piquè and Jean Pierre Vinel

1 Based on current data of natural history, PHG should be classified as:
(a) *Mild*: when MLP in its mild degree (without redness of the areola) is present
(b) *Severe*: when the MLP is superimposed by red signs or if any other red sign is present.

2 GAVE is a distinct clinical, endoscopic and histopathologic entity endoscopically characterized by aggregates of red spots arranged in a linear pattern or diffused lesion if confirmed by biopsy in the antrum of the stomach:
(a) GAVE can be seen in conditions other than portal hypertension.

3 The incidence of:
(a) Acute PHG bleeding is low (less than 3% at three years)
(b) Chronic bleeding is around 10–15% at three years

4 The lesions may change over time (fluctuate, worsen or improve).

5 Treatment of acute bleeding:
(a) Vasoactive drugs are anecdotally used with a high success rate (70–100%) in uncontrolled studies
(b) Emergency TIPS or shunt surgery should be regarded as rescue treatments in failures of vasoactive drugs.

6 Treatment of chronic bleeding:
(a) Beta-blockers, and if needed iron, are the first choice treatment
(b) Beta-blockers and Isosorbide-5-Mononitrate, as well as other medical treatments (i.e. long-acting somatostatin analogues), should be evaluated
(c) Treatment should be continued indefinitely
(d) TIPS or shunt surgery are rescue treatments for PHG lesions likely to respond to a portal pressure decrease
(e) The usefulness of Argon plasma coagulators should be evaluated.

7 For Gastric varices, Sarin's classification should be used:
(a) For fundal varices (GOV2 and IGV1)
(b) Consider risk factors also:
- red signs
- size
- Child class.

8 Fundal gastric varices (GOV2 + IGV1) are at the highest risk of bleeding.

9 The varices which most frequently bleed are GOV2 followed by GOV1 and IGV1.

10 Emergency therapy of bleeding gastric varices: the following hypotheses need testing by randomized controlled trials:

(a) Acrylate glue injection is effective for acute GV bleed

(b) EVS (EtOH, ethanolamine oleate) is a an alternative

(c) Vasoactive drugs could be used in combination with other treatments; banding needs evaluation

(d) TIPS and surgery are indicated as rescue therapy.

11 Long-term treatment of gastric varices: the following treatment modalities need testing by randomized controlled trials:

(a) long term glue injection

(b) TIPS

(c) shunt (for good risk patients)

(d) drug therapy.

12 The most important issues for future studies on GV are:

(a) Role of vasoactive drugs:

- in acute GV bleed
- in preventing development of secondary GV

(b) Role of prophylactic endoscopic therapies.

SESSION 4

Preprimary Prophylaxis: Can (and Should) We Prevent the Formation and Growth of Varices?

Carlo Merkel, Angels Escorsell, Cornel C. Sieber, Fa-Yauh Lee and Roberto J. Groszmann

EXPERIMENTAL DATA ON THE PREVENTION OF THE COLLATERALIZATION OF THE PORTAL BLOOD FLOW

Pathophysiological background

Portal hypertension results from increases both in resistance to portal flow and in portal venous inflow [1]. Nevertheless, portal hypertension persists even after the development of venous collaterals. This is especially exemplified in the model of prehepatic portal hypertension due to partial portal vein ligation (PVL), a model with a shunting percentage of more than 75% [2]. These findings agree with the 'forward theory' of portal hypertension, which postulates that in chronic portal hypertension arterial inflow in the splanchnic vascular area is significantly increased, and paralleled by a systemic vasodilatation and an increase in cardiac output [2]. Data by different groups over recent years have substantiated the important role of the endothelium-derived vasodilator NO as a key factor in this vasodilation [3–7]. The most recent data suggest that this increased production of NO is due to an activation of the endothelial nitric oxide synthase (eNOS) [8]. Furthermore, different vascular beds and organs in all the major rat models of portal hypertension were recently mapped and only eNOS (and not inducible nitric oxide synthase—iNOS) could be detected by both immunohistochemistry and Western blotting [9].

Modulation of the amount of shunting in the collaterals

The inhibition of NO-biosynthesis with a net vasoconstrictive effect can reverse the hyperdynamic circulation [3,4,10]. In contrast, cirrhotic liver seems to synthesize less NO when compared to normal one [11,12]. The net effect is therefore an increase in portal venous pressure, directly related to alterations in NO dynamics. An unsolved question is if the amount of portosystemic shunting is merely due to changes in portal pressure; a tentative answer resulted from a study in mice with schistosomiasis performed before the 'NO

era'. Chronic propranolol treatment in these infected mice led to a significant fall not only in portal pressure and portal venous inflow, but even more in the percentage of portal-systemic shunting [13]. These interesting data were further substantiated in cirrhotic rats, where again a significant fall in portal pressure was observed in propranolol treated animals (a fall of about 10%), with a parallel decrease in portal-systemic shunting of more than two-thirds [14]. Propranolol also decreased portosystemic shunting in PVL rats [15], but not in rats with secondary biliary cirrhosis due to bile duct ligation [16]. Similar to propranolol, clonidine, a centrally acting alpha2-adrenergic agonist, has also been shown to reduce portal pressure and portal venous inflow and to ameliorate portosystemic shunting [17]. These results suggest that increased portal pressure and/or portal venous inflow are involved in the pathophysiology of collateral vessel formation, but that additional factors may be implicated too.

The studies discussed above used radioactive microsphere methods to quantitate portal-systemic shunting [18]. Mosca *et al.* [19] developed an *in situ* collateral perfusion method to selectively explore the functional behaviour of collaterals in the rat. Using this approach, it was shown that isoproteronol-induced vasodilatation in collaterals can completely be blocked by propranolol [19]. These data confirm the existence of beta-adrenoceptors in these venous collaterals and also suggest that beta-blockers can modulate vascular tone in portal-systemic collaterals. The beneficial effect of propranolol in patients with chronic portal hypertension may therefore also be due to a selective constriction of collaterals, leading to a decrease in blood flow in gastro-oesophageal varices.

In addition, it was demonstrated in the same paper that these collaterals also dilate in response to a NO-agonist, acetylcholine. Once again, this vasodilation was completely blocked by inhibiting NO-biosynthesis. Inhibition of NO-biosynthesis was able to decrease significantly portal-systemic shunting using the same model [20]. Nevertheless, the amount of decrease in shunting was smaller than that seen with propranolol. One reason for this difference could be that in this study, a prehepatic portal-hypertensive rats model was used, which is characterized by a significantly larger shunting percentage (80% in this study) when compared to cirrhotic animals, in which only about 20% of portal-systemic shunting is observed. The same study demonstrated that chronic nitric oxide formation inhibition by N^{ω}-nitro-L-arginine ameliorates collateralization by preventing an increase in portal venous inflow without any decrease in portal pressure. This observation supports the assumption that a reduction in portal pressure is not a prerequisite to diminishing the collateralization of the portal system in chronic portal hypertension. It has also been shown that 1 day after partial PVL, there is a strong positive correlation between portal pressure and portosystemic shunting [21]. However, this cor-

relation did not exist at day 3 and 7 after PVL, suggesting that portal hypertension is an important driving force for the initial development or reopening of collaterals, but that further factors are also important in a later period after induction of portal hypertension. On the other hand, earlier studies have not found a correlation between the degree of portosystemic shunting and an increase in splanchnic blood inflow [2]. Therefore, the development of the collateral vascular venous bed seems also to depend on factors different from the degree of portal pressure and intestinal arterial blood flow. Recently, it has been demonstrated that chronic octreotide treatment, a synthetic octapeptide of natural somatostatin, can decrease portal venous inflow and pressure without modulating the degree of portosystemic collateralization [22]. Additional factors interfering with the extent of the collateralization process may be neovascularization—discussed below—or changes in the tone of tissue adjacent to vessels, as shown for metoclopramide [23].

In this respect, the role of NO synthases for the functional behaviour in venous collaterals has not been studied yet. Nevertheless, NO synthase activation has been demonstrated in oesophageal mucosa of portal hypertensive rats [24]. The same group has also described diminished basic fibroblast growth factor (bFGF) expression in the mucosa, and suggested that this mechanism may be involved in thinning of mucosal wall and eventually to the rupture of oesophageal varices [25]. It is tempting to speculate that NO biosynthesis may also be increased in the adjacent vessels or that NO released by mucosal cells may act upon vessel function (or even structure) through paracrine mechanisms.

Table 26 summarizes different studies on the pharmacological prevention of portal-systemic shunting in experimental portal hypertension. To sum it up, some of the beneficial effects of pharmacological treatment of chronic portal hypertension—e.g. with regard to restricting collateralization of the portal system and therefore preventing/ameliorating the development of gastro-oesophageal varices—may also be caused by a selective vasoconstrictive effect in the collateral vascular bed. Therefore, the effect of treatments decreasing splanchnic blood flow could be due to further mechanisms in addition to the effect of decrease in portal pressure.

Chronic portal hypertension—function versus structure

The data detailed above were concentrated on modulating vascular tone in the splanchnic vascular bed in chronic portal hypertension. Beside vascular tone, structural vascular changes also determine flow and pressure parameters. It has been known for some time that in arterial hypertension, structural vascular changes of the wall of pre-existing vessels can be observed [26]. Furthermore, chronic arterial hypertension leads to a rarefication of splanchnic

Table 26 Pharmacological prevention of portosystemic shunting in experimental portal hypertension.

Author	Animal	Drug	PP	PVI	PSS
Sarin *et al.* [13]	Mice (schistosomiasis)	Propranolol	↓	↓	↓
Colombato *et al.* [14]	Cirrhotic rats (CCl_4)	Propranolol	↓	NA	↓
Lin *et al.* [15]	PVL rats	Propranolol	↓	↓	↓
Oberti *et al.* [16]	Cirrhotic rats (bile duct ligation)	Propranolol	↔↓	↔	
Lin *et al.* [17]	PVL rats	Clonidine	↓	↓	↓
Lee *et al.* [20]	PVL rats	NNA	↔↓	↓	
Lin *et al.* [22]	PVL rats	Octreotide	↓	↓	↔
Ohta *et al.* [23]	PVL rats*	Metoclopramide	↔(LOSP↓)	NA	↓OV

PVL, partial (*total) portal vein ligation; PP, portal pressure; PVI, portal venous inflow; PSS, portosystemic shunting; LOSP, lower oesophageal sphincter pressure; OV, oesophageal varices.

arteries [27]. Theoretically, the inverse could be due in longstanding vasodilatation as observed in chronic portal hypertension. For example, chronic treatment of normotensive rats with the vasodilatator minoxidil leads to structural vascular changes in existing splanchnic arteries [28]. Controversial studies exist with regard to structural vascular changes in the gastric mucosa of chronic portal hypertensive animals [29,30]. Using a newly developed quantitative *in vivo* angiogenesis model in the rat, a significant increased angiogenesis could be observed in chronic portal-hypertensive rats [31]. This increased angiogenesis could be reverted by inhibiting NO-biosynthesis but not by chronic treatment with propranolol [31]. These results suggest that NO is an angiogenic molecule in itself [32,33]. In addition, as an increased NO-biosynthesis has been demonstrated to be responsible for the hyperdynamic circulation in chronic portal hypertension [1], NO apparently is a key molecule for the vascular changes in chronic portal hypertension. bFGF, one of the most potent angiogenic molecules, seems also to work through NO [34]. In addition, bFGF was able to significantly increase angiogenesis in normal rats, whereas it had no effect in chronic portal-hypertensive rats. It therefore appears that chronic portal hypertension in itself is a very strong angiogenic stimulus.

In this line of evidence, many data suggested that the hyperdynamic circulation in chronic portal hypertension is related to an increase in cytokine release [35,36]. These factors, including interleukins, are also established agonists of many angiogenic molecules [37]. A close interplay with cytokine release and NO biosynthesis dynamics may prove to be a key factor for functional and structural changes in chronic portal hypertensive states.

In summary, data over recent years have shown an important role of modulation of vascular tone in the venous collaterals observed in chronic portal hypertension. This vascular tone can be modified by beta-adrenergic blockers such as propranolol, still the leading class of drugs in the pharmacological treatment for the prevention of complications of chronic portal hypertension. Furthermore, the role of NO has been thoroughly studied as a key molecule on the development of the hyperdynamic circulation by many groups. NO also modulates collateral vascular tone. Finally, NO has also been shown to be an angiogenic molecule in the splanchnic arterial vascular bed. Inasmuch NO may also influence structural vascular changes within collaterals, namely its role in angiogenesis in these vessels, still remains to be explored.

CLINICAL ISSUES RELATED TO PREPRIMARY PROPHYLAXIS

Diagnostic aspects

The first important issue is related to diagnosis of portal hypertension in the initial stage of disease. In the Baveno II consensus conference it was stated that presence of portal hypertension must be searched for in all cirrhotic patients. This statement was confirmed by all the experts who answered the questionnaire. It was also stated that diagnosis of portal hypertension should be made by endoscopy and ultrasonography, but the relative value of each technique was not clearly defined.

It is agreed that the presence of oesophageal or gastric varices is enough for a diagnosis of portal hypertension, and current methodology allows to diagnose portal hypertension in the absence of varices, when a collateral circulation is seen by Doppler ultrasonography. There is no clear-cut evidence on the efficiency of DDU in recognizing portal hypertension in the absence of oesophageal varices, although it is reasonable that specificity is good (very rare false positive results), and sensitivity is limited, particularly in difficult clinical conditions. There was no consensus among experts on the ability of diagnosing portal hypertension in this clinical context, but most experts agree that the presence of collaterals other than varices is not a predictor of more severe portal hypertensive complications. In fact, some experts argue that the presence of such circulation may be protective from the development of severe complications. These opinions, however, are based on a very limited amount of clinical data (if any). In particular, available evidence is not direct, but circumstantial, and there is a tendency to a negative answer. It was shown that comparing cirrhotic patients with or without an evident collateral circulation, like a para-umbilical vein, the distribution of patients with or without varices is not different [38]. In addition, Vilgrain *et al.* [39] observed that portal pressure

is not different in patients with or without patent para-umbilical vein. However, all this information is not prospective, and does not answer the question if the collateral circulation is predictive of future development of varices or bleeding.

Although portal pressure is the driving force leading blood to pass in the collateral circulation, the role of elevated portal pressure in predicting varices formation is controversial. It was shown that portal pressure is more elevated in patients with varices than in those without [40–43], and in those with large varices compared with small varices [41,44,45], although a lack of difference has also been reported, once a threshold value is reached [43,46]. None of these studies, however, assessed prospectively the role of portal pressure measurement in predicting the future development of oesophageal varices in patients without varices at the beginning of observation. This information may arise from a long-term multicentre double-blind clinical study of cirrhotic patients without varices, prospectively assessed with portal pressure measurements, which is actually in progress [42]. Despite this insufficient evidence, three quarters of the experts agreed that portal pressure is predictive of varices formation, although more prospective clinical observations are needed to clarify this point.

Data on reproducibility of the diagnosis of low risk varices can be found in a few studies of inter-observer agreement [47–51]. In the report from the Italian Liver Cirrhosis Project [47], the agreement was good for size of varices, but not for the presence and severity of red colour signs; in two further studies, one from Scandinavia and one from France, overall agreement was fair to good for size of varices, but the discrimination was less efficient when small varices were observed. At variance, in a multicentre study of patients without varices or with small varices, Garcia-Tsao *et al.* [51] reported a 98% agreement among examiners.

Among experts there is a limited consensus on this point. A few experts stated that it is not known, or more data are needed (probably this means that the way interobserver agreement is assessed is not optimal, since videotapes and not complete procedures were assessed in most agreement studies, and this may lead to falsely uniform results). The others are equally divided into enthusiasts, sceptics, and uncertain.

Natural history of low risk varices

Once varices are formed, they are at potential risk of bleeding. Extensive clinical research was devoted to recognizing factors that predicted bleeding, and to stratify patients into classes of different risk. The Beppu's classification [52], the NIEC classification [53], the ILCP classification [47], and a semiquantitative assessment (larger or smaller than 5 mm) are the most frequently reported

methods of stratification of risk of bleeding. However, the definition of 'low risk varices' may be ambiguous. Indeed, it is the opposite of 'high risk varices', which, from an empirical point of view, means varices for which it is reasonable to prescribe a treatment. Since most clinical trial of prophylaxis were done in patients with medium or large oesophageal varices, with or without red signs, it is generally held that high risk varices are those with these endoscopic characteristics. Nearly all experts agree that low risk varices are small varices without red signs. Few experts add that other factors may be important in defining low risk (HVPG below the threshold value for bleeding of 12 mmHg, or a Child–Pugh class A).

The definition of how low is the risk of bleeding in patients with 'low risk varices' is essential for the planning of possible therapeutic strategies in these patients. Available evidence is small, but comparably larger than that on other aspects of this issue. In the NIEC study [53], if we consider low risk varices to be those in class I and II, the bleeding rate within two years was 18/139 = 13% (compared to 63/241 = 26% in the other classes), and if low risk comprises also class III, the bleeding rate was 32/202 = 16% (compared to 49/115 = 43% in the other classes). In two validation studies of the NIEC index, the risk of bleeding within 12–14 months in class I and II of the NIEC index was 3/73 (4%) and 7/144 (5%) [54,55].

In a prospective study of 344 patients without previous bleeding, Zoli *et al.* [56] observed 7/147 (5%) bleedings in two years of follow-up in patients with varices with a radius smaller than 25% of the oesophageal radius, and 22/240 (9%) bleedings in patients with less than 25% of the lumen occupied by varices. Data from further studies make it possible to distinguish the risk of bleeding between patients with small and large varices, or between patients with small and medium-sized varices: the relative risk ranges between a 30% [57] increase and a fourfold increase [58]. According to published series, it appears that bleeding risk in low risk varices is low but not negligible, and it is half or one third of that of the so called 'high-risk varices'. (See Fig. 14.)

The answers of the experts on this points were very spread out, ranging from near 0 to 12% per year. Median value, however, was 8%, which is in agreement with published series.

Spontaneous regression of oesophageal varices is another important point to be taken into account when planning a study on preprimary prophylaxis. In one study, 7/43 (16%) patients with small oesophageal varices no longer had the varices at one year's follow-up [49]. In the Vorobioff *et al.* study [59], four out of 30 patients (13%) also had regression of varices after one year's follow-up. At variance, no patient with small varices had regression of varices in the series of 166 patients observed by Zoli *et al.* [60], and 2/54 (4%) in the placebo arm of a trial of prophylaxis in patients with small varices with a follow-up of

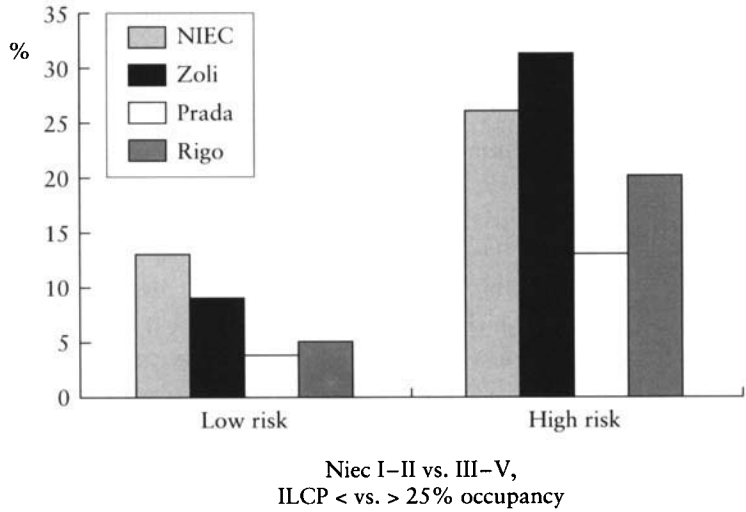

Fig. 14 Risk of first bleeding in 'low-risk varices' and in 'high-risk varices' according to some published series.

16 months [61]. The difference may be related to the difference in the prevalence of alcoholic aetiology, being the majority in the study by Calès [49] and the total number in the study by Vorobioff [59], and only 16% in the study by Zoli [60].

Experts' opinions diverge on this point, and consensus cannot be reached, estimated rates ranging from 0 to 20%. There is agreement that the most important factor in determining regression of varices is prolonged abstinence from alcohol. Few experts suggest that other factors may be important, such as decrease of activity of the underlying liver disease, obtained using interferon in chronic hepatitis, or steroids in autoimmune disease.

Considering that follow-up endoscopies should be performed every one to two years in patients with low risk varices, it is questionable how severe is the risk of bleeding is between two consecutive endoscopies. Prospectively collected data are very few, and may arise from studies of natural history, and from the placebo arms of randomized clinical trials. In the Calès *et al.* study [49] none of 43 patients with grade I varices bled between follow-up endoscopies planned at six-month intervals. In the Zoli *et al.* study [60], three out of 258 untreated patients with F1 varices without red signs bled between two endoscopies planned at an 18 month interval. In the placebo arm of our ongoing clinical trial of preprimary prophylaxis, according to the interim analysis [61] two patients out of 54 bled in an interval of 12 months between consecutive endoscopies.

Most experts agree that this risk is not clearly established, and is worth studying with adequate methodologies. Overall, this risk is considered low or very low.

Therapeutic aspects

A single study assessed the effects of sclerotherapy in patients with small oesophageal varices [62]. Not surprisingly, treatment resulted to increase significantly the rate of bleeding in this setting.

There is a single clinical trial fully published [63], and another one reported as interim analysis as an abstract [61] on the effects of beta-blockers in preprimary prophylaxis. In the former, 60 patients with small varices were treated with propranolol and compared with 67 treated with placebo; at the same time that 42 patients without varices were treated with propranolol and compared with 37 treated with a placebo. After two years of follow-up 41 patients were lost to follow-up in the treated arm, and 32 in the placebo one. Contrary to expectations, in the observed patients there was a significantly larger incidence of increase in size of varices in those treated with propranolol than in placebo. Extending the period of observation to three years, the difference was not significant any longer, but the trend was still of a negative effect. (See Fig. 15.)

At variance, in the interim analysis of a trial of 50 patients with small oesophageal varices versus 54 patients treated with a placebo there was a

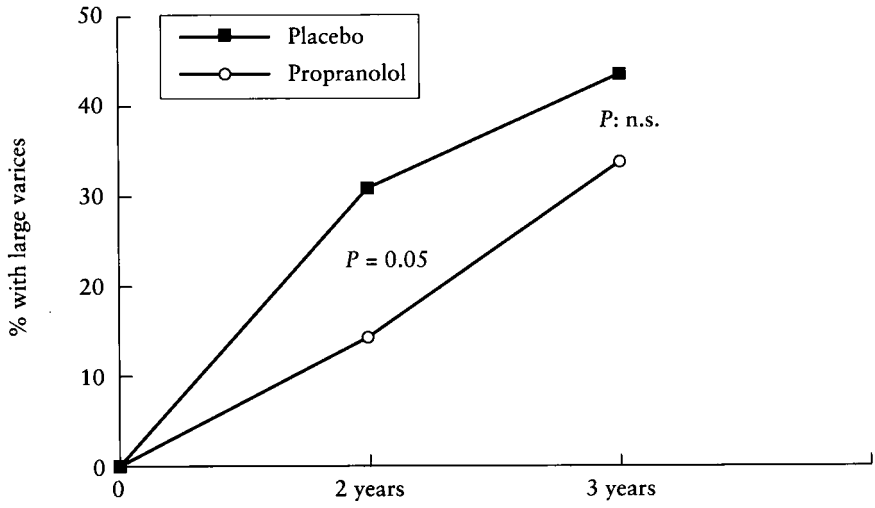

Fig. 15 Occurrence of large varices in patients treated with propranolol or placebo (Calés *et al.*) [63].

trend to a lower risk of aggravation of varices in patients treated with nadolol, and the difference reached the significance levels if bleeding from varices or aggravation was considered the end-point. Final results are expected next year. A further clinical study is in progress.

It is evident that the limited number of data and the contradictory results do not allow conclusions. There is general agreement that more clinical data are needed to define this point.

CONCLUSIONS

The problem of preprimary prophylaxis of variceal bleeding in cirrhosis is of great clinical relevance, and will become more crucial, as soon as new experimental data will be available, and ongoing clinical trials of treatment will be completed. Considering these aspects from a historical perspective, we observe that there is a progressive tendency to start earlier and earlier the treatment of patients with cirrhosis. Indeed, in 1988 Harold O. Conn, acknowledging the role of medical treatment in prophylaxis of bleeding in high risk varices, suggested that doctors should not behave like fishermen who throw back fishes smaller than the legal size [64]. The meaning of the sentence was that before the introduction of prophylaxis of bleeding from large varices, when a doctor made a diagnosis of varices, the general policy was that of waiting until a first bleeding, and then treating. After the introduction of prophylaxis of first bleeding in patients with large varices, we started to treat large varices before bleeding. If the present lines of research show a benefit from earlier treatment, we will move the time of starting treatment of portal hypertension to an earlier stage.

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Baveno III Consensus Statements: Preprimary Prophylaxis

Roberto J. Groszmann, Carlo Merkel (Chairpersons), Thomas Boyer, Paul Calès, Angels Escorsell, Didier Lebrec, Fa-Yauh Lee and Cornel C. Sieber

1 Every patient with cirrhosis without complications of portal hypertension ideally needs HVPG measurements in order to be included in a trial of preprimary prevention.

2 The sequence portal-hypertension–collaterals-varices is an accepted one.

3 Collaterals can be diagnosed before the development of varices.

4 The clinical importance of collaterals as a predictor of more severe portal hypertensive complications should be further investigated.

5 Portal pressure is predictive of varices formation.

6 All patients with cirrhosis should undergo an initial screening for varices.

7 'Low risk varices' are small sized varices without red colour signs.

8 The risk of bleeding within two years of these varices is < 10%.

9 The reproducibility of a diagnosis of low risk varices by endoscopy is variable and influenced by expertise.

10 Spontaneous regression of small varices is a rare event.

11 Regression is related to improvement in liver status, particularly after alcohol abstinence in alcoholic cirrhosis.

12 The risk of bleeding between two consecutive endoscopies performed at yearly intervals in patients with cirrhosis undergoing surveillance for low risk varices is < 5%.

13 More data are needed before a conclusion can be drawn on the usefulness of starting prophylaxis of variceal bleeding in patients with low risk varices.

LECTURE

Antifibrotic Therapy: Future Cure for Portal Hypertension?

Detlef Schuppan, Jae Jin Cho, Masahiko Koda and Eckhart G. Hahn

PATHOGENESIS OF LIVER FIBROSIS

Fibrosis results from the excessive accumulation of extracellular matrix (ECM). ECM comprises the connective tissue molecules found in all multicellular organisms. These are grouped into major molecular classes, the collagens, the noncollagenous glycoproteins, the glycosaminoglycans, the proteoglycans and elastin. In most organs, collagens, especially the fibril forming collagens type I and III, but also basement membrane collagen type IV, are the most abundant ECM components [1]. In liver cirrhosis the relative ECM content may increase up to 10-fold. This mere increase explains most of the complications of cirrhosis, such as an impaired exchange of metabolites between the sinusoidal blood and the hepatocytes via sinusoidal sclerosis (capillarization) and the formation of porto-venous shunts that prevent sinusoidal perfusion. The latter is also an important basis for the increase in portal pressure that leads to oesophageal or gastric varices and the development of ascites. Lastly, the continuous stimulus for hepatocyte proliferation in an abnormal ECM environment (regenerative nodules) predisposes for the development of hepatocellular carcinoma (Fig. 16).

As shown in Fig. 17, a variety of adverse stimuli (e.g. hepatotoxins, hepatotropic viruses, hypoxia, immune reactions to the liver, metabolic diseases, biliary stasis or simply mechanical stress) can trigger liver *fibrogenesis*, i.e. the excess synthesis and deposition of ECM. In acute and self-limited liver diseases, such as viral hepatitis A, fibrogenesis is balanced by *fibrolysis*, i.e. the removal of excess ECM by proteolytic enzymes. The most important of the fibrolytic enzymes are the matrix metalloproteinases (MMPs). With repetitive injury, as occurs in many chronic liver diseases, fibrogenesis prevails, finally resulting in morphologically apparent fibrosis or cirrhosis. Thus, fibrogenesis is characterized by an upregulation of collagen synthesis, a downregulation of MMP secretion and activity, and by an enhanced expression of the physiological inhibitors of the MMPs, the tissue inhibitors of MMPs (TIMPs), of which the universal MMP-inhibitor TIMP-1 is the most important [1,2]. Collagens,

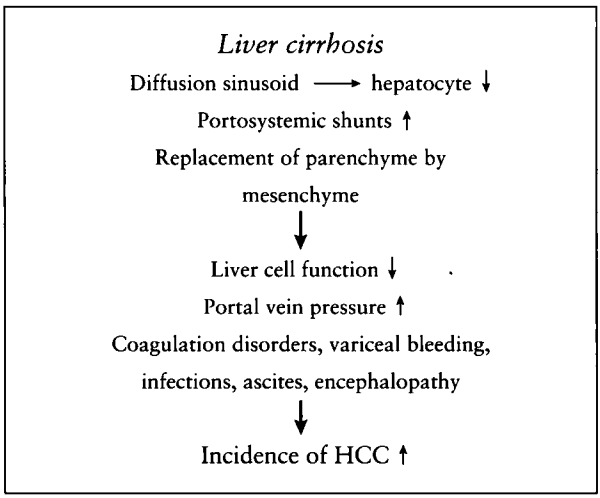

Fig. 16 Liver cirrhosis.

TIMPS but also MMPs are mainly produced by activated hepatic stellate cells (HSC, synonymous with Ito cells) and by activated portal fibroblasts (PF) which resemble the myofibroblasts found in wound healing [1–4].

Activated Kupffer cells or proliferating bile duct epithelia are major sources of potentially fibrogenic cytokines and growth factors that stimulate HSC and PF to become activated myofibroblastic cells [1–4]. Such fibrogenic cells are equally found in other organs prone to fibrosis such as the pancreas, kidney and lung, intestine, skin and arteries [1,5] (Table 27). The appearance of myofibroblasts is self-limiting if the offending agent is present for a short period of time. However, when liver injury continues these cells expand, with resultant fibrosis and cirrhosis. It follows that the activated HSC and PF are the prominent target for antifibrotic therapies in chronic liver diseases.

POTENTIAL ANTIFIBROTIC AGENTS

Knowing the cellular effectors of fibrogenesis (HSC and PF), the stage has been set for the development of specific antifibrotic agents. Such agents are currently identified and tested in several laboratories worldwide. Once effective *in vitro* in cell culture where these cells undergo spontaneous activation, all substances have to be tested in a suitable animal model, preferably hepatic fibrosis and cirrhosis in the rat. Models that evolve chronically and reproducibly, such as biliary cirrhosis due to bile duct occlusion or serum-induced fibrosis, are preferable over those characterized by major hepatocyte necrosis, such as those induced by carbon tetrachloride, dimethylnitrosamine or

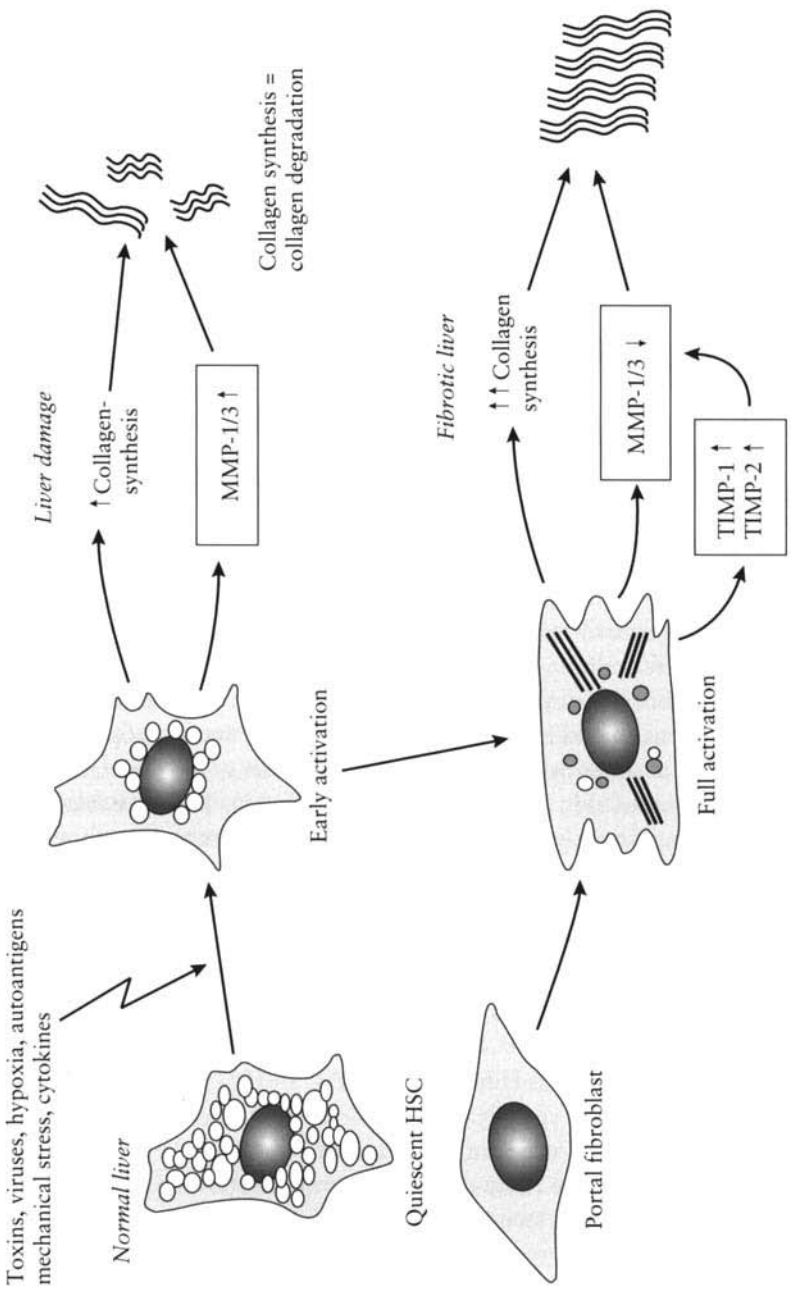

Fig. 17 Initiation and maintenance of fibrogenesis.

Table 27 Related fibrogenic cell types.

Liver	Pancreas	Lung	Kidney
Portal fibroblast Stellate cell	Interstitial fibroblast Stellate cell	Interstitial fibroblast Alveolar cell	Interstitial fibroblast Mesangial cell

galactosamine, because the former more closely resemble human chronic liver disease and allow to identify a 'true' antifibrotic instead of an anti-inflammatory, anti-necrotic or radical scavenging effect. However, once cirrhosis is induced and the toxin withheld, the carbon tetrachloride model which produces a prominent pericentral and perisinusoidal fibrosis is suitable for testing agents that may speed up removal of excess ECM.

Table 28 lists substances which have been tested in suitable rat models [5]. Some of these drugs are currently undergoing phase 2 or 3 clinical testing with pre- and post-treatment biopsy for exact morphometrical determination of the area of connective tissue and with a spectrum of surrogate markers of liver fibrogenesis (see below). Promising drugs are silymarin [6], interferon alpha [7,8], and derivatives of pentoxifyllin [9].

Transforming growth factor beta (TGF-β) is considered a potent fibrogenic cytokine and its inhibition therefore appears attractive. despite the availability of peptidic antagonists to TGF-β [10,11], only a targeted approach (see below) is feasible, since TGF-β-receptors are expressed on most cell types, and systemic inhibition of TGF-β is expected to trigger autoimmune disease and cellular dedifferentiation. Connective tissue growth factor (CTGF) is a fibrogenic cytokine which is released by TGF-β, primarily in mesenchymal but also in proliferating biliary epithelial cells in an auto- and paracrine manner [12,13]. Therefore, blocking CTGF activity may allow for a more specific antifibrotic strategy.

Table 28 Antifibrotic drugs.

	Antifibrotic effect		
Drug	Rat model	Man	Mechanism
Silymarin	Yes	Studies	Free radicals/collagen↓
Interferon α, β, γ	(Yes)	Studies	Proliferation↓, MMPs↑
Pentoxifyllin	Yes	?	Proliferation/collagen↓
anti-TGF-β/CTGF	(Yes)	?	Collagen↓, MMPs↑
hepatocyte growth factor	(No)	?	Hepatocyte/bile duct proliferation↑, HCC↑?
ET_AR-antagonists	Yes	Studies	HSC activation↓

The reported antifibrotic activity of hepatocyte growth factor (HGF) [14] has to be interpreted with care, since this cytokine rather causes hypertrophy and hyperplasia of hepatocytes and bile duct epithelia, thus reducing the *relative* and not the *absolute* collagen content in the liver. HGF therapy bears the additional danger of promoting hepatic malignancy.

A promising strategy is the induction of stress relaxation of fibrogenic cells, a matrix (integrin) receptor-mediated process that leads to a decrease in collagen synthesis and an increase in collagenase activity. This strategy also makes reversibility of established fibrosis and cirrhosis a realistic option. Stress relaxation occurs once mesenchymal cells are placed from a 'stressed', two-dimensional environment (mimicking a situation of wounding) into a 'relaxed', three-dimensional environment [5,15]. Stress relaxation mitigates or even abrogates signals transferred via certain mitogenic growth factors and can transform the same cell types that cause fibrogenesis, i.e. HSC and PF in the liver, into fibrolytic cells that preferably release MMPs instead of collagens. As an example the receptor for platelet-derived growth factor (PDGF) transmits stress signals that trigger proliferation and ECM synthesis in activated HSC and PF. In addition, soluble proteolytic fragments of collagen VI which are released from the liver matrix during remodelling serve as potent growth and anti-apoptotic factors for fibrogenic cells, an effect that is mediated via a non-integrin collagen VI receptor [16–18] (Fig. 18).

These stress-induced receptors can be inhibited by peptides or peptide analogues. More importantly, the coupling of specific stress-receptor recognizing cyclic peptides or peptide mimetics to a drug carrier allows for highly specific targeting of the activated fibrogenic cells in the liver (Fig. 19). This has been shown both *in vitro* and *in vivo* with cyclic peptides recognizing the receptors for platelet-derived growth factor (PDGFR), collagen VI (CVIR) and with mannose-6-phosphate which targets the mannose-6-phosphate receptor [19–21]. With the cyclic CVIR recognizing peptide, *in vivo* uptake of an albumin carrier in activated HSC of fibrotic rat livers reaches an unpreceded 50% [20].

THE ROLE OF VASOCONSTRICTORS AND VASORELAXANTS IN HEPATIC FIBROGENESIS

The endothelin (ET)-system does not only play a role in portal hypertension [22–25], but also modulates the fibrogenic potential of activated HSC and PF. Thus the ET A receptor (ET_AR) [26,27], but not the often opposing ET B (ET_BR) receptor [23,28], mediates contraction and proliferation of smooth muscle cells and myofibroblasts, and is upregulated on HSC and PF in their intermediate state of activation [26,27] (Fig. 20, kindly provided by M. Pinzani, Florence, Italy). Therefore, inhibition of the ET_AR would be an attractive

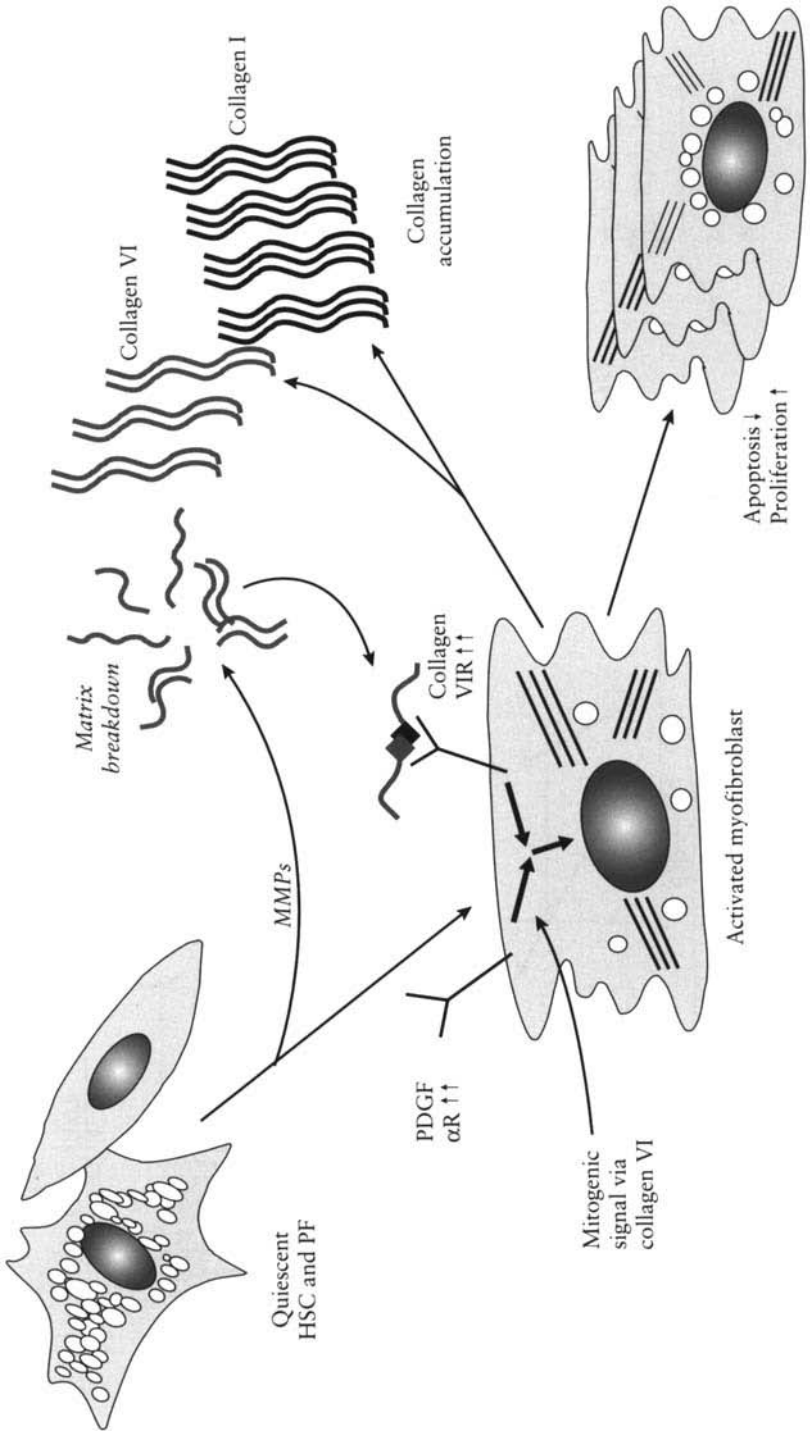

Fig. 18 Collagen VI as auto/paracrine fibrogenic factor.

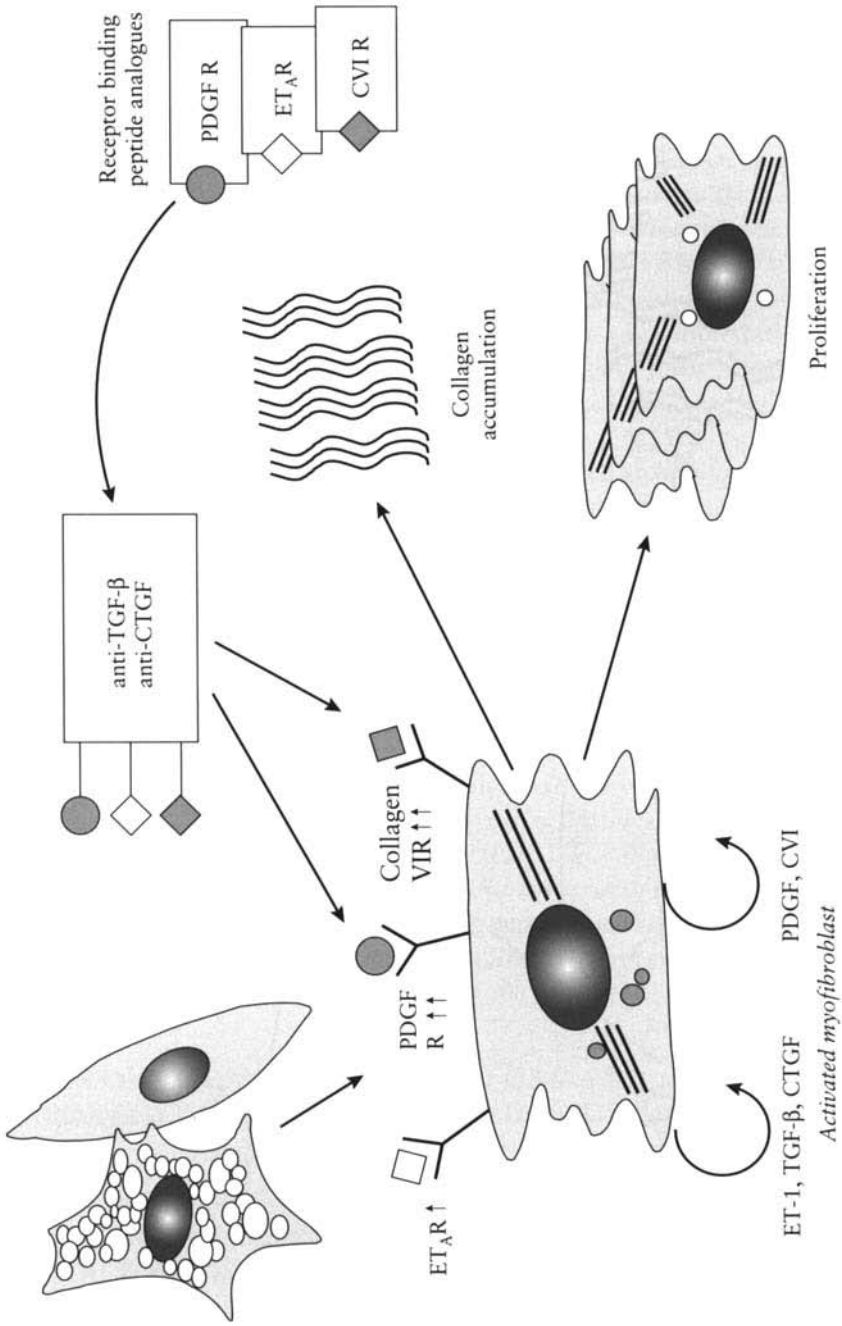

Fig. 19 Receptor-targeted antifibrotic therapy.

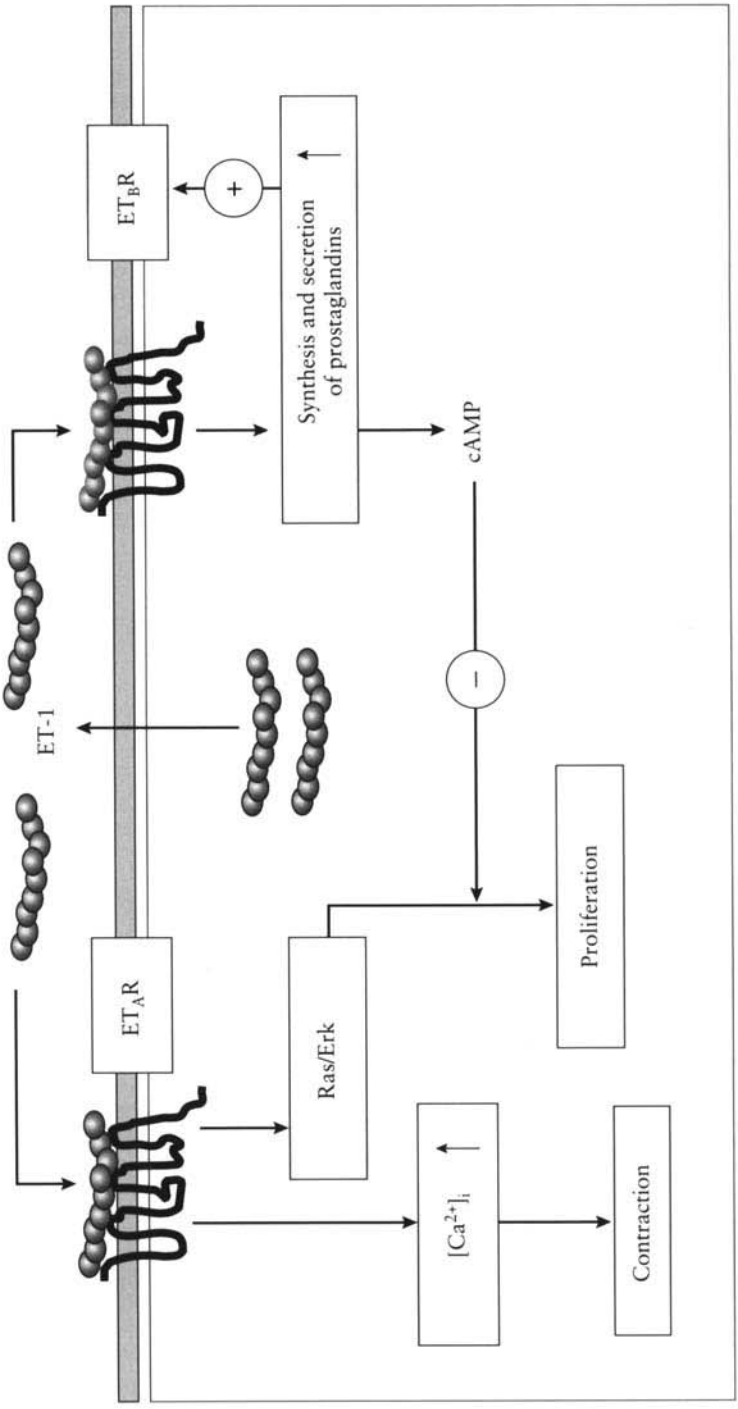

Fig. 20 Signal transduction by endothelin receptors.

strategy to mitigate HSC and PF activation and thus fibrogenesis (Fig. 21). This has in fact been demonstrated in rat biliary fibrosis where the oral ET_AR antagonists LU 135252 can block both total and relative (per gram of tissue) hepatic collagen accumulation by more than 50%, the best effect observed so far in this 'refractory' model of fibrosis [29]. At the highest dose, however, LU 135252 exhibited renal toxicity, possibly due to a low residual (1:130) ET_BR antagonistic effect [29]. In line with these findings the mixed $ET_{A/B}R$ antagonist bosentan does not influence hepatic fibrogenesis [30].

Recent light and electron microscope studies on rat livers after perfusion with ET-1 have shed more light on the contractile intrahepatic structures. These could be localized to the preterminal portal venules, which contain a subpopulation of PF, whereas perisinusoidal HSC seemingly play only a minor role *in vivo* [25] (see also Session 4 by Pinzani). Accordingly, we could find a focal upregulation of the expression of ET-converting enzyme, which generates bioactive ET from the precursor big-ET, in just these preterminal portal venules [30].

Nitric oxide (NO) is a potent vasorelaxant that has both beneficial and detrimental effects in cirrhosis and portal hypertension [23,24,32–36]. Its major cellular source is the endothelium, but myofibroblasts (activated HSC and PF) and Kupffer cells also contribute to its production. Endothelial NO is upregulated by numerous factors such as interferon-γ (IF-γ), interleukin-1 (IL-1), lipopolysaccharide (LPS), ET-1 (via the ET_BR), mechanical stress and hypoxia [23,24,35–36] (Fig. 22). NO lowers portal pressure, but exacerbates splanchnic vasorelaxation and central volume expansion, either directly or via downregulation of the contraction-inducing receptors for angiotensin (ATIIR), arginine-vasopressin (VPR) and endothelin (ET_AR) [32,36]. Systemic modulation of the NO-system did not produce clear anti- or profibrogenic effects in rat models of hepatic fibrosis. This can be explained by a potential antifibrotic action of NO on myofibroblasts (activated HSC or PF), which may be offset by a potential profibrogenic effect of its oxidative metabolite, peroxinitrite. The antifibrotic potential of other vasorelaxants, including prostacyclin, prostaglandin E and adrenomedullin, in humans remains to be explored. This includes carbon monoxide (CO) which is generated from oxidation of bilirubin in hepatocytes by the enzyme haemoxigenase [37] (Fig. 22).

SERUM MARKERS OF LIVER FIBROSIS

Most of the serum fibrosis markers appear to reflect fibrogenesis rather than fibrolysis [3,5,38] (Fig. 23). Their clinical use opens the possibility to assess the evolution of fibrosis and the effect of potential antifibrotic treatment in the individual patient early in the course of the disease and on a frequent basis. However, these markers still await validation in large prospective follow-up

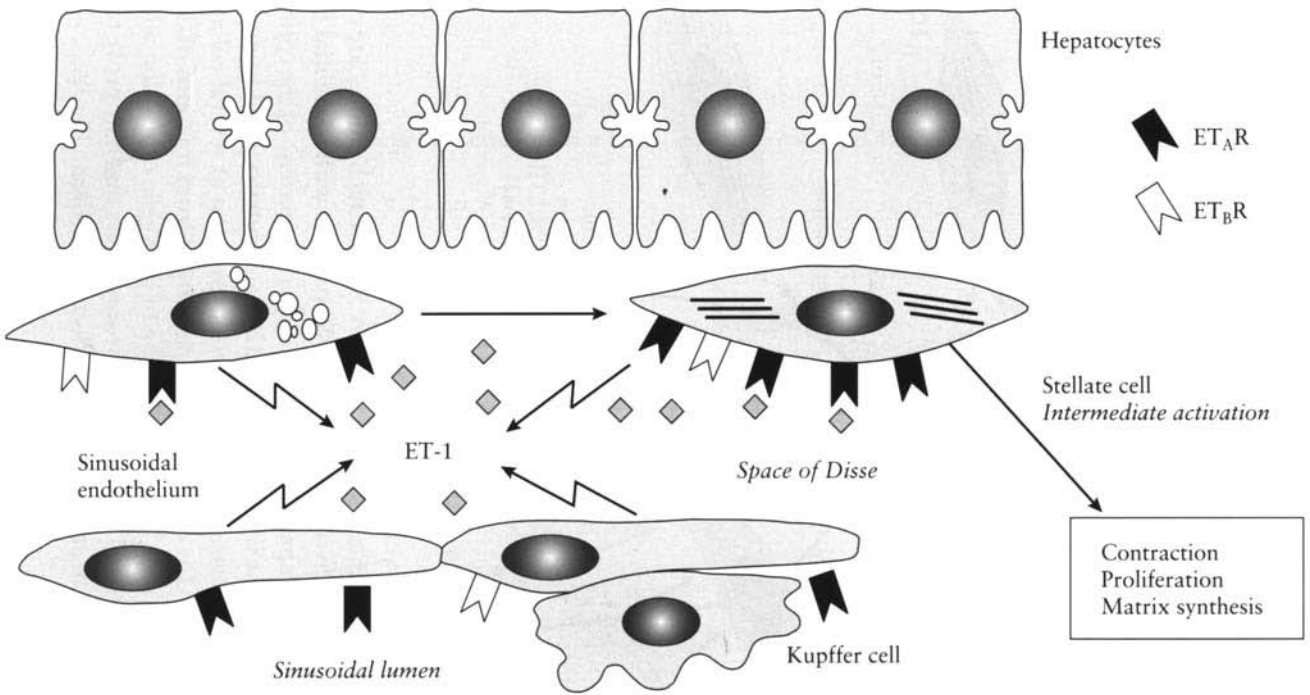

Fig. 21 ET-1/ET_AR system and stellate cell/myofibroblast activation.

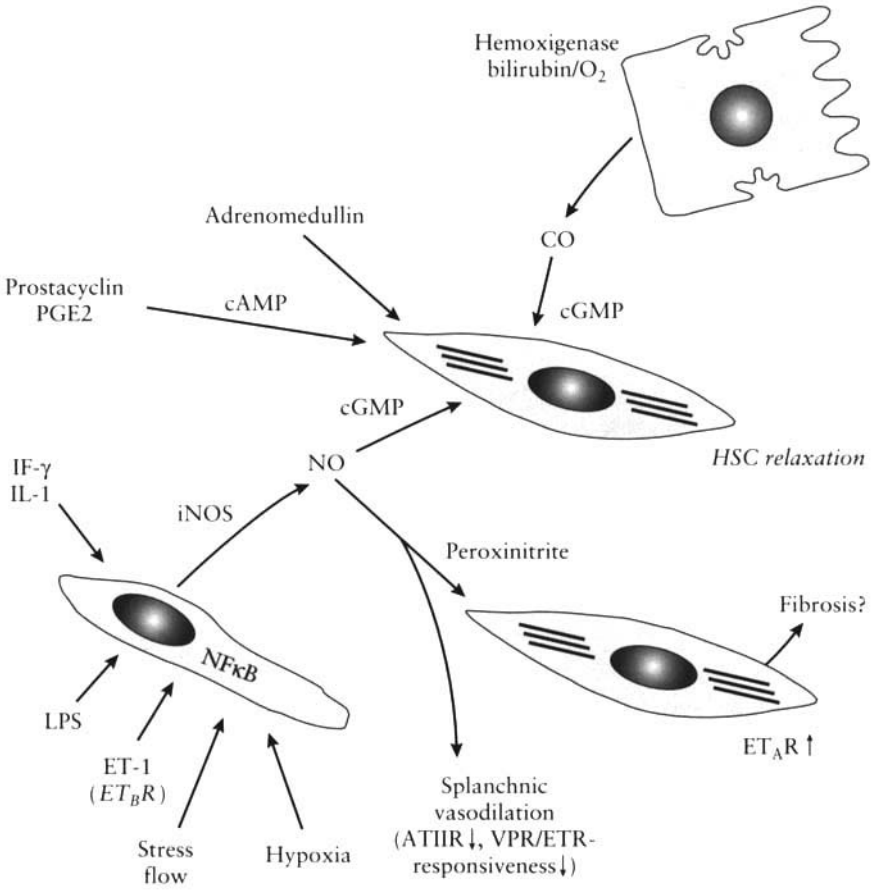

Fig. 22 Induction of stellate cell relaxation.

studies of patients with liver diseases. Several such studies are currently underway. They involve more than 1000 patients with sequential liver biopsies 12–24 months apart. From these biopsies the increase of the connective tissue area and volume will be determined by densitometry. In addition, quantitative RT-PCR, to measure hepatic mRNA expression of several collagens, MMPs and of TIMP-1 is currently being performed from fractions of diagnostic biopsies, allowing a direct comparison of liver gene expression with the serum fibrosis markers. Table 29 shows those markers that may prove to be useful in future studies of antifibrotic drug effects in the liver.

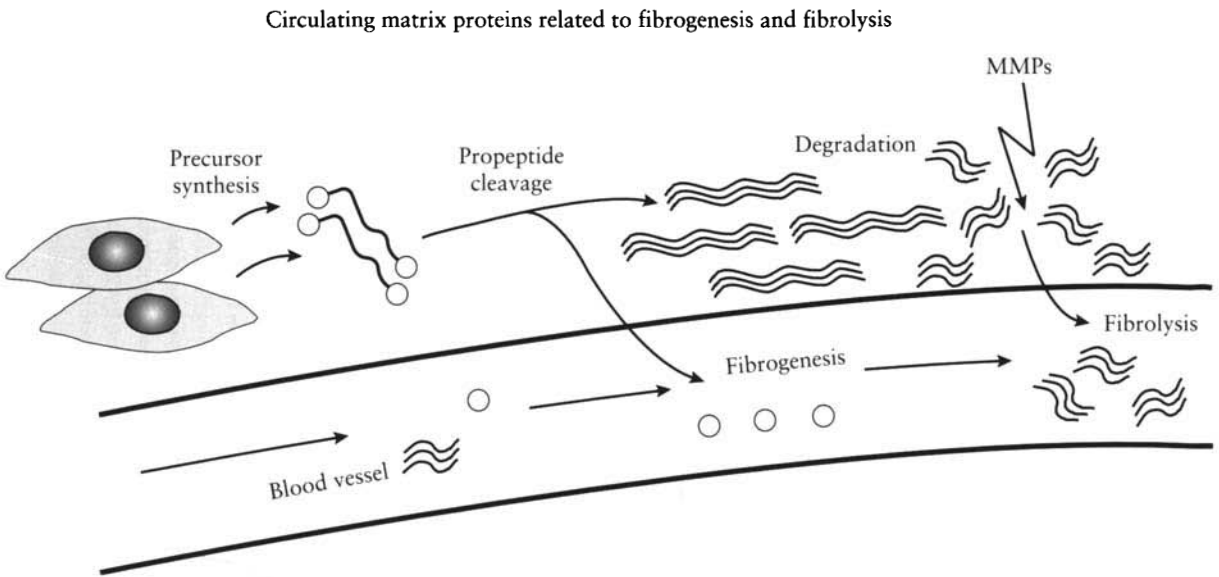

Fig. 23 Circulating matrix proteins related to fibrogenesis and fibrolysis.

Table 29 Serum assays for liver fibrosis.

	Fibrolysis	Fibrogenesis	Liver specificity
PIIINP	+	(+)	+
Collagen IV	+	–	+
Collagen VI	+	(+)	+
Collagen XIV	+ (portal)	–	+
Laminin	+	(+)	(+)
Tenascin	+ (lobular)	–	(+)
Hyaluronan	(+)	(+)	(+)
TIMP-1	+	–	+
MMP-1	–	+	(+)
MMP-2	+	(+)	+
MMP-9	(+)	(+)	(+)

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SESSION 5

Primary Prophylaxis

Juan Carlos Garcia-Pagàn and Norman D. Grace

PREVENTION OF FIRST VARICEAL BLEEDING

In patients with cirrhosis and oesophageal varices the incidence of variceal bleeding ranges from 19 to 40% at two years of follow-up. Oesophageal variceal size, the presence of red colour signs in the wall of the varices and the degree of liver failure are the main variables correlating with an increased risk of variceal bleeding.

Nonselective beta-blockers such as propranolol or nadolol have been shown to reduce significantly the incidence of variceal bleeding. This beneficial effect was found in patients either with or without ascites, and with good or impaired liver function. In all these categories, the risk of bleeding is reduced by 40–50% by beta-blockers. In addition, nonselective beta-blocker therapy is associated with an almost significant reduction in mortality, and with a significant reduction in bleeding-related deaths. Beta-blockers are the only accepted treatment for the prevention of variceal bleeding in patients with cirrhosis and large oesophageal varices. However, beta-blockers do not protect every patient from the risk of bleeding. The residual risk of bleeding in patients with large varices being treated with propranolol or nadolol is about 15–20% at two years. On the other hand, up to 25–30% of eligible patients may either have contraindications to beta-blockers or develop side effects during their administration that precludes their continued use. Very few patients with small varices were included in these RCTs, with four of seven trials only including patients with large varices [1]. Therefore, there is insufficient data to make a recommendation for prophylactic treatment of small varices.

Endoscopic screening strategies to detect oesophageal varices in patients with cirrhosis have been clearly defined. Whether it is cost effective to screen all patients with cirrhosis to prevent variceal haemorrhage in less than one third of patients has not been demonstrated. Therefore, criteria for selecting a higher risk population may be useful. Thrombocytopenia has been shown to be an early sign for the development of portal hypertension and may be useful in selecting patients for screening [2]. If a patient does not have varices on the

initial screening exam, the frequency of repeat endoscopy should take into consideration the aetiology and severity of liver disease. For example, the rate of development of varices is higher in patients with alcoholic liver disease than patients with chronic HCV hepatitis and cirrhosis and is higher in patients with decompensated liver disease [3,4,5].

Haemodynamic studies have shown that the portal hypertensive effect of propranolol or nadolol is significantly enhanced by adding isosorbide-5-mononitrate (ISMN) to the beta-blocker treatment [6]. After adjusting the dose of beta-blockers, ISMN is initiated, starting with 20 mg at bedtime and increasing progressively until reaching the maintenance dose (20–40 mg twice per day). At the beginning of treatment cephalea and orthostatic hypotension could be a problem, but this usually subsides after 3–4 days. Up to now three RCTs have been reported addressing the role of combined treatment in the prevention of first variceal bleeding [7,8,9]. One study was open and the other two were double blind, placebo controlled. Overall 552 patients have been included in the three studies. Although two of these studies showed a marginal benefit for the combination therapy, this was not confirmed in a large multicentre study. The combined analysis of the three studies showed a nonsignificant difference in the bleeding rate and in mortality. (Bleeding: 15% in the beta-blocker treated patients and 10% in the combination therapy patients; Mortality rate: 10% in both groups) with more side effects in the combination therapy group [10]. Although none of these studies assessed efficacy of treatment by a haemodynamic response (i.e. $\geq 20\%$ decrease in HVPG) the available evidence does not support the use of this combination in the prevention of the first variceal bleed.

Therefore, since propranolol is highly efficacious in preventing variceal bleeding when considering the overall population of cirrhotic patients with varices, it is difficult to improve on the present results. Because of the high efficacy of beta-blockers, more aggressive techniques, such as endoscopic band ligation should probably be restricted to patients with a very high risk of bleeding if these could be identified. Indeed, a recent study in India suggested that endoscopic band ligation of oesophageal varices is more effective than propranolol in preventing variceal bleeding in such high risk patients [11]. However, in this study, the bleeding rate in patients treated with propranolol was equal to that for a placebo in a previous study by the same group [12], and no effort was made to assess or improve compliance to drug therapy. Two additional studies comparing variceal ligation to non-selective beta-blockers have supported the use of EVL. However, the sample size in all these studies was small and the length of follow-up short. These observations need to be confirmed in a large scale, carefully conducted multicentre RCT before endoscopic band ligation can be recommended for the prevention of first variceal

bleeding. The sample size for such a study has been estimated at 600–1200 patients.

Vasodilators have drawn interest in recent years as a possible alternative to beta-blockers in the pharmacological treatment of portal hypertension. These drugs may reduce portal pressure by decreasing the vascular resistance to porto-collateral blood flow, and also, by promoting reflex splanchnic vasoconstriction as a response to reduced mean arterial and cardiac filling pressures [13,14]. A theoretical advantage of vasodilators over beta-blockers is that the former may reduce portal pressure without impairing liver perfusion. Long-acting nitrovasodilators, such as isosorbide dinitrate [15] or isosorbide-5-mononitrate [14,16] have been shown to markedly reduce HVPG in acute administration but the effect is reduced after chronic administration, probably due to the development of partial tolerance [16]. Isosorbide-5-mononitrate has also been shown to reduce oesophageal variceal pressure [17]. Isosorbide-5-mononitrate, unlike isosorbide dinitrate, has minimal first-pass metabolism, which makes isosorbide mononitrate the long-acting nitrate of choice, especially in patients with liver failure and portal systemic shunting. The major concern with the use of vasodilators in patients with advanced cirrhosis is that they can reduce arterial blood pressure and thus promote the activation of endogenous vasoactive systems that may lead to water and sodium retention [18]. However, recent studies have shown that long term treatment with isosorbide-5-mononitrate is safe in compensated cirrhotics without affecting renal function or sodium handling. Only in a few patients with ascites was hypotension and slight sodium retention observed, but was not accompanied by a need to increase the dose of diuretics [19].

A recent RCT including 118 patients with varices of any size initially suggested that ISMN (20 mg three times per day; $n = 57$) was as effective as propranolol in the prevention of first variceal bleeding. However, a seven-year follow-up of these patients demonstrated an increased mortality in the ISMN group that was significant in those patients over 50 years of age [20]. These results suggested that ISMN may represent an alternative in patients with contraindications or intolerance to beta-blockers. In another small RCT including 30 patients with ascites, bleeding was significantly more frequent in patients receiving ISMN (40 mg twice per day) than nadolol. No differences in mortality were found [21]. In addition, a recent multicentre RCT performed in a large series of patient with contraindications or intolerance to beta-blockers failed to show any benefit for the use of ISMN in the prevention of the first variceal bleeding [22]. Therefore, available evidence does not support the use of ISMN as monotherapy for primary prophylaxis even in patients with contraindications or intolerance to beta-blockers.

Future developments include the assessment of new drugs or procedures, and the use of better means of assessing the individual risk of variceal bleeding and the response to treatment.

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Baveno III Consensus Statements: Primary Prophylaxis

Norman D. Grace, Juan Carlos Garcia-Pagàn (Chairpersons), Mario Angelico, Roberto J. Groszmann, Carlo Merkel, Richard Moreau, Shiv K. Sarin and Tilman Sauerbruch

1 Monitoring of beta-blockade:
(a) Increasing the dose of beta-blockers to achieve a 25% reduction in resting heart rate or down to 55 b.p.m. or development of symptoms are the most commonly used approaches for adjusting the dose of beta-blockers in cirrhotic patients
(b) Some, but not all, patients treated with beta-blockers achieving these targets will be protected from variceal bleeding
(c) However, there is no relationship between reduction in portal pressure or protection from variceal bleeding and the degree of beta-blockade, as assessed by the reduction in resting heart rate
(d) A reduction in HVPG below 12 mmHg or more than 20% from baseline is the only tested parameter to detect those patients treated with beta-blockers who are protected from variceal bleeding
(e) However, since about 60% of patients treated with beta-blockers who do not achieve these targets will not bleed (for two years), in primary prophylaxis it is not mandatory to check the HVPG response.

2 Treatment of patients with contraindications or intolerance to beta-blockers or noncompliant:
(a) There is no consensus about how we should treat patients with large esophageal varices (more than 5 mm size) who have contraindications or intolerance to beta-blockers
(b) There are no published studies specifically addressing this issue. However, preliminary data suggests that Is-MN may not be a good alternative
(c) Preliminary data with prophylactic endoscopic band ligation are encouraging in high risk patients but more studies are needed in patients with contraindications
(d) There is no consensus on how to treat noncompliant patients.

3 Use of combined treatments:
(a) Available evidence is insufficient to support the use of combination therapy in the prevention of the first variceal bleed
(b) The combination of endoscopic treatment and pharmacologic therapy cannot be recommended at the moment because there is no data to support its use.

4 Indications for treatment/follow-up endoscopy:

(a) Based on available data, there is no indication to treat patients with small varices

(b) All patients with large varices should be treated

(c) Additional endoscopic signs do not influence the indication for therapy

(d) There is no need for follow-up endoscopy in patients on pharmacologic therapy.

5 Future studies:

(a) In the absence of specific data, RCTs should be performed in patients with gastric varices.

SESSION 6

Treatment of the Acute Bleeding Episode

Loren A. Laine, Andrew K. Burroughs, Christine Silvain, Jean Pierre Vinel and Jaime Bosch

INTRODUCTION

Acute variceal bleeding represents the main complication of portal hypertension. Despite the advances in therapy that occurred during the past decade, acute variceal bleeding still carries a high mortality, and represents a leading cause of death in patients with cirrhosis. The aim of this chapter is to review the current approach to acute variceal bleeding, including its diagnosis, general management, prognosis and specific therapies.

At the Baveno III Consensus Conference, Session 6 was devoted to acute variceal haemorrhage. This session was structured as a series of introductory lectures reviewing the relevant aspects to be considered, followed by the general discussion of preliminary consensus statements developed within the panel and based on current knowledge and on the answers to a specific questionnaire (appended at the end of this chapter), which was circulated to all panellists participating at the Baveno III conference. This chapter summarizes the introductory lectures, as prepared by the panellist in charge.

General management of the cirrhotic patient with acute variceal bleeding

Andrew K. Burroughs

PRESENTATION AND DIAGNOSIS

Variceal bleeding is a life-threatening complication with substantial resource-use implications [1]. Although overall survival may be improving, mortality is still closely related to failure to control haemorrhage or early rebleeding, which is a distinct characteristic of portal hypertensive bleeding and occurs in as many as 50% of patients [3].

Effective resuscitation, accurate diagnosis and early treatment can reduce mortality. The aims are not only to stop bleeding as soon as possible but also to prevent early rebleeding, which is associated with increased mortality [5]. Thus treatment regimes should be evaluated not only in terms of immediate cessation of haemorrhage, but also in terms of providing a bleed-free interval of at least 5 days. This provides an opportunity for secondary preventive therapy to be instituted.

Patients usually present with haematemesis or melaena. Specific features to be noted in the history are those of prolonged alcohol excess, ingestion of NSAIDs or aspirin [6], previous variceal bleeding, previously diagnosed liver disease, past abdominal sepsis or history of umbilical vein catherization (re: portal vein thrombosis). Examination must include a search for signs of chronic liver disease. Bleeding due to portal hypertension may occur in the absence of specific clinical signs of chronic liver disease. These patients may have portal vein thrombosis or other causes of noncirrhotic portal hypertension.

The initial examination and investigations need to include an assessment of the severity of bleeding, the presence of renal dysfunction, disease in other systems, the presence of infection and the severity of liver disease. The latter is still most reliably obtained by using the Child–Pugh score. The presence of portal vein thrombosis and/or hepatoma needs to be established early on, by ultrasound imaging.

Upper gastrointestinal endoscopy is essential to establish an accurate diagnosis as 26–56% of patients will have a nonvariceal source [7], particularly from peptic ulcers and portal hypertensive gastropathy. Endoscopy should be performed as soon as resuscitation is adequate, and preferably within 12 hours of admission. Endoscopic diagnosis during upper GI bleeding can be difficult when the view is obscured by blood. A diagnosis of bleeding varices is accepted either when a venous (nonpulsatile) spurt is seen, or there is fresh bleeding from the O-G junction in the presence of varices, or fresh blood in the fundus when gastric varices are present. In the absence of active bleeding

(approximately 50% of cases) either a 'white nipple sign' or the presence of varices in the absence of other lesions [8,9] suggests varices as the source of haemorrhage. Gastric varices are particularly difficult to diagnose.

If the patient is exanguinating and varices are suspected, a Sengstaken–Blakemore tube (SBT) should be passed [10]. If control of bleeding is obtained, varices are likely to be the source of haemorrhage. If not, then oesophageal varices are less likely to be the cause of blood loss, or fundal bleeding should be suspected, and emergency angiography performed.

THERAPY AIMS IN ACUTE VARICEAL BLEEDING

These are: (1) correct hypovolaemia; (2) stop bleeding as soon as possible; (3) prevent early rebleeding; (4) prevent complications associated with bleeding; (5) prevent deterioration in liver function.

It is important to identify those at high risk of dying during the initial assessment. Individuals in this category should have early definitive therapy, the precise treatment regimen depending on availability. Predictive factors for early death are: severity of bleeding [11–15]; severity of liver disease [11–13]; presence of infection [14]; presence of renal dysfunction [11]; active bleeding [5,16]; concomitant diseases and portal pressure [17,18].

RESUSCITATION

Resuscitation follows the general rules of: Airway, Breathing, and Circulation.

Lung aspiration of gastric contents and blood is a particular risk, especially in encephalopathic patients; and it is further exacerbated by endoscopic procedures. Endotracheal intubation is mandatory if there is any concern about the safety of the airway.

An internal jugular line is safer than a subclavian approach. Peripheral and central venous lines must be inserted. The presence of coagulopathy and thrombocytopenia is not a contraindication to central venous access.

Table 30 Acute variceal bleeding and subsequent mortality.

Failure to control bleeding
• inability to control ≤ 24 hours
• early rebleeding
High mortality
Treat the patient, not just the bleeding!

We recommend initial volume replacement should be with human albumin fraction or gelatine based colloid as this has no effect on clotting or bleeding times compared to dextran [19].

Following this, specific treatment can be started with a vasopressor agent. In this respect, there is evidence from a recent trial that terlipressin should be instituted early (for example, in the emergency room) [20].

CARDIORESPIRATORY MONITORING

Pulse oximetry and oxygen are essential during endoscopy and adequate suction and extreme care of the airway must be maintained. The haemodynamic consequences of haemorrhage in cirrhotic patients with cirrhosis may differ from normal individuals [1–3,22]. In addition 'silent' cardiomyopathy in alcoholics and pulmonary hypertension may impair the cardiovascular response to haemorrhage. The usual indications for pulmonary capillary wedge pressure measurement apply in bleeding varices. The priority of management is resuscitation first, invasive monitoring last.

Positive pressure ventilation (PPV) and positive end expiratory pressure (PEEP) can cause a reduction in mean arterial pressure, cardiac output, portal venous and hepatic arterial blood flow. These can be accompanied by deterioration in hepatic function [26].

TRANSFUSION

Optimal volume replacement remains controversial. Following a variceal bleed in animal models, return of arterial pressure to normal with immediate transfusion results in overshoot in portal pressure, with associated risk of further bleeding [27]. Over-transfusion should certainly be avoided, and it is usual to aim for an Hb between 9–10 g/dL, but fluid replacement may need to be greater. Large volume transfusion may lead to impaired haemostasis and thrombocytopenia [28], so that fresh frozen plasma and platelets need to be replaced. Optimal regimens for this are not known. Platelet transfusions are necessary to improve primary haemostasis and should be used occasionally. Many cirrhotics have a background tendency of fibrinolysis. With large volume transfusion there is still a risk of citrate toxicity, despite the low concentrations in current blood products. Changes in ionized calcium levels and associated effects on the heart, (prolonged QT interval) manifest this [28]. The associated toxicity may be enhanced by hypothermia, which potentiates the cardiac side effects of hypocalcaemia. Massive transfusion may cause pulmonary microembolism, and the use of filters is recommended for transfusions of 5 L or more in normal humans [29].

Further measures in patients who continue to bleed may include the use of desmopressin (DDAVP) [30]. In stable cirrhotics it produces a two to fourfold increase in factors VIII and VWF and may shorten or normalize the bleeding time [31]. However, DDAVP should not be used in association with terlipressin [32]. The use of antifibrinolytics has been established in liver transplantation [33]. Their clinical utility when increased fibrinolysis has been documented in variceal bleeders should be established in clinical trials. Recombinant factor VII may be useful in variceal bleeding as it has been shown to normalize prothrombin time and bleeding times in cirrhotics [34].

PREVENTION OF COMPLICATIONS AND DETERIORATION IN LIVER FUNCTION

Infection control and treatment

Sepsis remains a major complication in cirrhotic patients [14], particularly during bleeding episodes. Bacterial infections have been documented in 35–66% of patients with cirrhosis who have variceal bleeding, and may worsen the high concentration of endotoxin (lipopolysaccharide component of the outer wall of gram-negative bacteria) that have been detected in patients with cirrhosis [35]. Bernard *et al.* [36] identified in a multivariate analysis bacterial infections as predictive of early rebleeding ($p < 0.02$). More importantly, they demonstrated on meta-analysis that antibiotic prophylaxis significantly increased survival (9.1% mean improvement rate, 95% confidence interval CI:2.9–15.3%, $p = 0.004$) and increased the percentage of patients free from infection (32% mean improvement rate, 95% CI:22–42%, $p < 0.001$) [36]. Thus, all cirrhotics with upper gastrointestinal bleeding should now receive prophylactic antibiotics using oral quinolones or intravenous cephalosporins [37].

Ascites and renal function

Renal failure may be precipitated by a variceal bleed, usually due to a combination of acute tubular necrosis and hepatorenal syndrome (HRS). HRS is associated with over 95% mortality. Thus any iatrogenic precipitants must be avoided. To this aim, the intravascular volume should be maintained and nephrotoxic drugs should be avoided, especially aminoglycosides and nonsteroidal drugs.

Increasing ascites may occur shortly after bleeding, but should not be the main focus of fluid and electrolyte management until bleeding has stopped

and the intravascular volume is stable. Despite these measures, patients with cirrhosis may develop increasing renal impairment, particularly following variceal haemorrhage. This sequence of events has been felt to be irreversible. However, there is now increasing evidence for the use of vasopressin analogues (terlipressin) in this condition. The beneficial effect of terlipressin with respect to bleeding and survival in trials to date may be in part through the prevention of this complication [41–43].

Porto-systemic encephalopathy

Precipitant factors should be evaluated and corrected. As soon as the patient is taking oral fluid, lactulose 5–10 mL QDS can be started.

Alcohol withdrawal

It is important to be forewarned about the possibility of withdrawal from the history. Signs of encephalopathy may overlap it. Intravenous clormethiazole is easy to titrate and has a short half-life, and is an useful drug to control acute withdrawal.

Nutrition and vitamin replacement

There are very few cirrhotics who are not malnourished [44], particularly with severe liver disease. This is worsened after bleeding, which calls for early enteral feeding, using a nasogastric tube if required.

All patients with a significant alcoholic history should be assumed to be folate and thiamine deficient, and be given at least three doses of the latter without awaiting red cell transketolase activity levels.

TRANSFER OF THE PATIENT WITH BLEEDING VARICES AND USE OF BALLOON TAMPONADE

Interhospital transport should not be attempted unless the bleeding has been controlled, either with vasopressor agents/endoscopic therapy or tamponade. The Sengstaken–Blakemore tube will arrest bleeding in 90% of cases. Prior endotracheal intubation is necessary when there is any concern about the patients airway. This is particularly important when the SBT is being put down prior to transfer. Lack of expertise increases the complication rate. SBT should only be used as a 'bridge' until definite therapy is provided.

The precautions and principal aspects that need to be taken into consideration in any patient with acute variceal bleeding are summarized in Fig. 24.

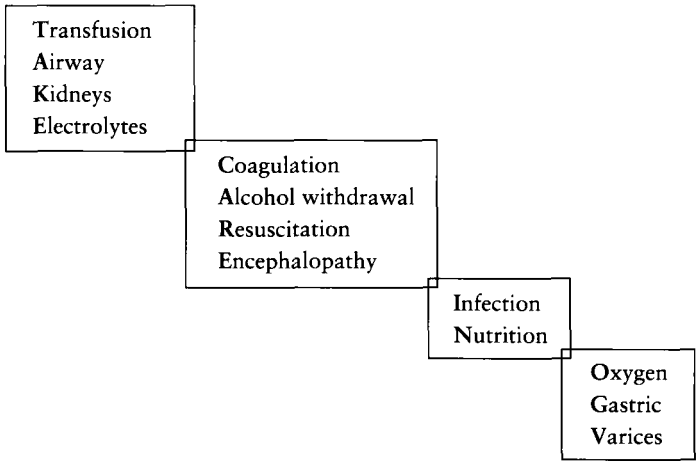

Fig. 24 The precautions and principal aspects that need to be taken into consideration in any patient with acute variceal bleeding.

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Acute variceal bleeding and vasoactive drugs

Christine Silvain

The treatment of acute variceal bleeding is aimed at controlling the index bleeding, at the prevention of early rebleeding and at reducing mortality. The optimal agent for pharmacotherapy in such emergency should be effective, easy to administer and have both a rapid action and limited side effects. The drugs available are vasopressin and its analogue terlipressin, and somatostatin and its analogues octreotide and vapreotide. Studies using lanreotide are ongoing. This report is based on the last meta-analysis by D'Amico *et al.* [1] adding the few studies published since then.

VASOPRESSIN

Vasopressin is a very powerful vasoconstrictor of the splanchnic circulation which at pharmacological doses reduces splanchnic blood flow and decreases portal blood flow and portal pressure [2]. As the haemodynamic effects of vasopressin are not restricted to the splanchnic circulation, systemic vasoconstriction can occur leading to severe cardiovascular adverse events.

Since the meta-analysis by D'Amico *et al.* [3], no further studies have been published. Four RCTs including 157 patients compared vasopressin with non-active treatment [4–7]. Failure to control bleeding was reduced from 82% in control patients to 50% in treated patients (ARD = -32%; CI, from -59% to -6%; NNT = 3) with no differences in mortality. There were no advantages when vasopressin was infused into the superior mesenteric artery as compared with intravenous vasopressin in three trials [8–10].

The side effects from vasopressin are markedly reduced by the combined administration of glyceril-trinitrate (NTG). This drug combination was proved to be superior to vasopressin alone in controlling the bleeding and in reducing the adverse effects of vasopressin in three RCTs including 176 patients [11–13].

TERLIPRESSIN

Terlipressin (Glypressin) is a long-acting triglycyl lysine derivative of vasopressin. This derivative has intrinsic vasoactive activity and is also slowly transformed to vasopressin by enzymatic cleavage. Because of the low blood levels consequent to the slow release of the active agent, side effects are less frequent and terlipressin can be used without NTG. Haemodynamic studies

have shown that terlipressin causes a marked and sustained reduction of portal pressure and collateral blood flow, which results in a rapid and sustained reduction of oesophageal variceal pressure [14,15].

Terlipressin was compared with placebo or nonactive treatment in five RCTs [16–20], to vasopressin in five [21–25], to somatostatin in three [19,26–28], to octreotide in two [29–30], to sclerotherapy in one [31] and to oesophageal tamponade in three [32–34] (see Table 31).

Terlipressin compared with placebo or nonactive treatment

A total of 256 patients were included in five RCTs [16–20]. In one study balloon tamponade was associated with treatment in 80% [16] and in one study terlipressin was associated with NTG and started at the patient's home [20]. The overall rate of failure to control bleeding was 50% in control patients and 26% in treated patients (Absolute Risk Difference = –24%; 95% Confidence Interval –36 to –13; Number NT = 4) with a significant reduction of transfusion requirements. Mortality was significantly reduced with terlipressin (ARD = –18%; CI, from –28% to –7%; NNT = 6).

Terlipressin compared with balloon tamponade

Three RCTs [32–34] comprising 141 patients compared terlipressin with oesophageal tamponade with no significant differences concerning failure to control bleeding (ARD = 8%; CI from –8% to 24%), early rebleeding (4–7 days) and mortality (in hospital or at 1 month).

Terlipressin compared with vasopressin

Five unblinded trials [21–5] compared terlipressin with vasopressin, which was associated with transdermal or sublingual nitro-glycerine in two studies [23,25]. No statistically significant differences were found in the rate of failure to control bleeding, rebleeding or mortality. Side effects were less frequent and less severe with terlipressin than with vasopressin plus transdermal nitroglycerine [25].

Terlipressin compared with endoscopic variceal sclerotherapy (EVS)

There is one study comparing terlipressin with EVS in an acute setting and one study reported in abstract form and including 219 patients [31]. Treatment failure (failure to control bleeding or early rebleeding within 5 days) was 32% with EVS and 37% with terlipressin [$P = 0.39$]. Side effects and 6 weeks mortality were not different.

Table 31 Summary of RCTs on the use of terlipressin (modified from D'Amico *et al.* 1999).

Trial vs.	Number of patients	Failure to control bleeding			Rebleeding rate			Mortality rate		
	C/T	C/T (%)	Abs dif	95% CI (%)	C/T (%)	Abs dif	95% CI (%)	C/T (%)	Abs dif	95% CI
Placebo	127/129	50/126	–24	–36 : –13	30/24	–6	–21 : 9	38/20	–18	–28 : –7
VP	124/123	43/33	–10	–32 : 11	26/39	13	–2 : 28	26/34	8	–3 : 19
BT	71/70	13/21	8	–8 : 24	22/19	–3	–21 : 16	16/15	–1	–14 : –13
EVS	114/105	17/21	4	–6 : 15	13/15	2	–7 : 11	16/23	7	–3 : 17

VP, vasopressin; BT, ballon tamponade; EVS, endoscopic variceal injection sclerotherapy

Terlipressin plus endoscopic treatment

In a study [35], patients matched for Child–Pugh and variceal grade received either ESV alone ($n = 27$) or ESV and terlipressin (2 mg/6 h; $n = 28$) for 2 days. Control of active bleeding over 5 days was significantly improved in patients receiving combination therapy ($p < 0.001$) while the mean blood transfusion was reduced from 4 units to 2 units in the group receiving ESV plus terlipressin. Mortality was similar in both treatment groups.

SOMATOSTATIN

Somatostatin is a natural peptide inducing splanchnic vasoconstriction, decreased splanchnic blood flow and decreased portal and collateral blood flow and portal pressure [36]. Somatostatin lacks most of the adverse effects of vasopressin on systemic circulation [37].

Somatostatin compared with placebo or nonactive treatment

Three double-blind placebo controlled trials of somatostatin comprised 290 patients [38–40]. None of these three studies found beneficial effects on survival. Four unblinded RCTs compared somatostatin with nonactive treatment and showed a trend towards a benefit from somatostatin [1,19]. In one study [41], somatostatin administered before emergency ESV made the endoscopy procedure significantly easier. Overall, these studies showed a significant reduction of failure to control bleeding with somatostatin (ARD = –17%; CI from –29% to –6%; NNT = 6) when the outlier Valenzuela study [38] is not included. There was not significant reduction in mortality. In a recent study [42], failure to control bleeding were assessed in 30 patients treated with somatostatin plus NTG compared to 30 patients treated with somatostatin plus placebo, with no differences (see Table 32).

Somatostatin compared with vasopressin

There are seven RCTs comprising 301 patients [1,43–48]. Failure to control bleeding was not different between the two treatments. The lack of benefit from somatostatin in the definitive control of bleeding is explained by a higher rebleeding rate after initial control (ARD = 18%; CI from 8% to 27%). Side effects are significantly less with somatostatin (ARD = –47%, CI from –69% to –25%). Overall, these studies indicate that somatostatin is equivalent to vasopressin with significantly less frequent and less severe side effects.

Table 32 Summary of RCTs on the use of somatostatin (modified from D'Amico *et al.* 1999).

	Number of patients	Failure to control bleeding			Rebleeding rate			Mortality rate		
Trial vs.	C/T	C/T (%)	Abs dif	95% CI (%)	C/T (%)	Abs dif	95% CI (%)	C/T (%)	Abs dif	95% CI
Placebo or non act	312/326	50/38	–12	–27 : 2	nd	nd	nd	25/28	3	–3 : 9
VP	148/153	53/44	–9	–25 : 8	17/32	15	8 : 27	39/38	–1	–12 : 9
TERL	150/152	21/21	0	–15 : 13	31/27	–4	–16 : 8	20/20	0	–9 : 9
BT	50/50	40/36	–4	–22 : 15	32/20	–12	–48 : 23	30/24	–6	–23 : 11
EVS	181/196	15/22	7	–4 : 18	17/21	4	–5 : 13	30/24	–6	–23 : 11

Non act, non-active treatment; TERL, terlipressin

Somatostatin compared with terlipressin

Somatostatin was compared with terlipressin in three studies comprising 302 patients [26–28]. No differences were found for failure to control bleeding, rebleeding, mortality and side effects.

Somatostatin compared with emergency EVS

Four RCTs comprising 367 patients compared somatostatin with sclerotherapy [52–55]. No significant differences were found in failure to control bleeding, rebleeding and mortality. Complications were significantly less frequent and less severe with somatostatin.

Somatostatin compared with balloon tamponade

Two RCTs failed to show differences between somatostatin and balloon tamponade for failure to control bleeding, rebleeding and mortality [56–57]. In a recent study published only in abstract form, 38 patients received somatostatin or balloon tamponade before variceal ligation. No differences for successful haemostasis before EVL, active bleeding at EVL, rebleeding and mortality were noted [58].

Somatostatin with endoscopic treatment

Villanueva *et al.* [59] studies 50 patients treated with somatostatin (250 mg/h for 5 days) and 50 patients treated with somatostatin and sclerotherapy. Therapeutic failure occurred more frequently in the SMT group than in the SMT plus EVS group. The actuarial probability of failure during the first 5 days was significantly higher in the SMT group than in the SMT plus EVS group. The same happened with regards to early rebleeding. Transfusion requirements during the treatment period were also significantly higher in the group treated only with SMT as compared with combined therapy group, but side effects were significantly more frequent and severe in the group treated with SMT and EVS. The probability of survival at 6 weeks was similar in both groups.

SOMATOSTATIN ANALOGUES: OCTREOTIDE, VAPREOTIDE

Octreotide is a cyclic octapeptide analogue of somatostatin with a longer biological half-life. Contradictory results on its effects on portal pressure and azygos blood flow have been shown, a preferential effect on the portocollateral circulation has been suggested.

Octreotide compared with placebo

In one double-blind study, still in abstract form [61], sclerotherapy was used in octreotide or placebo failures. In another double-blind study, octreotide was given after sclerotherapy [62] as well as in another open study [63]. In the fourth study [64], octreotide was given after band ligation. In the four RCTs, failure to control bleeding was significantly reduced from 44% with placebo to 29% with octreotide (ARD = −15%, CI from −26% to −3%; NNT = 7). The same results were found in a study published only in abstract form [65]. When sclerotherapy or ligation were performed before or at the same time as octreotide, a significant benefit was found in two studies [62,64] and near significance in the third [63]. The same results were found with another somatostatin analogue [66] with a significant increase of survival with haemostasis of 66% with vapreotide compared with placebo (50%). These results suggest that somatostatin analogues improve the outcome of endoscopic therapy.

In a double-blind placebo-controlled RCT [67], octreotide was administered subcutaneously (100 mg three times a day) over a 15 day period to decrease early rebleeding in patients treated with beta-blockers or sclerotherapy for long-term prevention of rebleeding. Among 198 patients treated, the 15-day rebleeding rate was reduced from 26% to 16% ($p = 0.005$) with octreotide (see Table 33).

Octreotide compared with vasopressin or terlipressin

Octreotide was better than vasopressin for control of bleeding in two RCTs [48,49] and equivalent to terlipressin in two [68,69]. Side effects were less frequent and severe with octreotide.

Octreotide compared with sclerotherapy

Octreotide has been compared with emergency sclerotherapy in five RCTs, three only available in abstract [70–74]. No differences were found for failure to control bleeding, rebleeding, or mortality, but the meta-analysis is difficult to interpret because of a significant heterogeneity. Another study [75] compared octreotide with sclerotherapy in 100 patients with schistosomal portal hypertension. Failure to control bleeding was significantly higher with octreotide (42%) than with sclerotherapy (6%).

Octreotide compared with balloon tamponade

Only one RCT compared octreotide with balloon tamponade [76] showing a

Table 33 Summary of RCTs on the use of octreotide (modified from D'Amico *et al.* 1999).

	Number of patients	Failure to control bleeding			Rebleeding rate			Mortality rate		
Trial vs.	C/T	C/T (%)	Abs dif	95% CI (%)	C/T (%)	Abs dif	95% CI (%)	C/T (%)	Abs dif	95% CI
Placebo	327/312	44/29	–15	–26 : –3	22/20	–2	–4 : 11	19/17	–2	–10 : 7
VP	145/44	60/39	–21	–42 : –1	nd	nd	nd	47/36	–11	–31 : 9
TERL	71/76	51/35	–16	–32 : 0	11/19	8	–10 : 25	21/17	–4	–16 : 8
BT	20/20	30/50	20	–10 : 50	25/40	15	–14 : 44	25/0	–25	–44 : –6
EVS	172/169	23/22	–1	–10 : 8	18/16	–2	–12 : 16	23/21	–2	–12 : 16

nonsignificant trend in favour of tamponade for control of bleeding, but side effects were more frequent with tamponade.

Overall, these studies show that pharmacological treatment is effective in controlling variceal bleeding. Furthermore, terlipressin and somatostatin appeared to be equivalent to EVS with a lower incidence and severity of side effects. Terlipressin reduces mortality when compared to placebo. Octreotide and vapreotide improve the efficacy of EVS. It seems that all these drugs should be started immediately when variceal bleeding is suspected before endoscopy. This may be an important point in order to minimize side effects of endoscopic treatments and improve survival.

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Endoscopic treatment of acute or active variceal bleeding

Loren A. Laine

SCLEROTHERAPY

Endoscopic sclerotherapy controls active bleeding from varices in 62–100% of patients and appears to be more effective than sham therapy or medical therapy with vasopressin or balloon tamponade. A meta-analysis of five studies ($n = 251$) [1–5] comparing sclerotherapy with sham, balloon tamponade, and/or vasopressin in patients with documented active bleeding revealed significant benefits of sclerotherapy in terms of cessation of acute bleeding (OR = 8.5, 95% CI 3.6–20.0%), rebleeding during hospitalization or within 2 weeks (OR = 0.36, 0.21–0.62), and mortality (OR = 0.57, 0.33–0.98) (Laine L, personal communication). A meta-analysis of seven studies ($n = 623$) comparing sclerotherapy to standard medical therapy in the short term (7–40 days) treatment of patients presenting with oesophageal variceal haemorrhage revealed significant benefit in terms of achieving haemostasis (OR = 2.1, 1.5–2.9) and mortality (OR = 0.45, 0.27–0.77) (Laine L, personal communications). Thus, sclerotherapy does appear to be beneficial in the acute treatment of patients with oesophageal variceal bleeding.

More recent studies which compare sclerotherapy with somatostatin or octreotide in acute variceal bleeding do no demonstrate significant differences in favour of sclerotherapy in the initial control of oesophageal variceal bleeding [6–10]. Two studies provide information on the actively bleeding patients: they report a permanent haemostasis for sclerotherapy vs. octreotide/somatostatin in 10/18 (56%) vs. 15/25 (60%) [7] and 13/17 (76%) vs. 13/18 (72%) [8]. A recent comparison of somatostatin alone vs. somatostatin plus sclerotherapy in acute variceal bleeding [11] revealed a significant benefit of combined therapy in a permanent control (29/50 (58%) vs. 43/50 (86%)) and transfusions (3 units vs. 2 units); however the difference in the subgroup of patients with actively bleeding varices did not reach statistical significance: 6/12 (50%) vs. 11/15 (73%) ($p = 0.2$). Other studies have suggested that the addition of octreotide [12,13,14] or somatostatin [15] improves the efficacy of endoscopic therapy.

LIGATION VS. SCLEROTHERAPY

A single published randomized trial directly compares ligation vs. sclerotherapy specifically in the population of patients presenting with actively bleeding oesophageal varices [16]. Seventy-one patients with cirrhosis (65% with hep-

atitis, 28% due to alcohol; 7% Child A, 34% Child B, 59% Child C) were enrolled. Continued active bleeding (during the first 72 hours) was significantly more frequent in the sclerotherapy group (24% vs. 3%; RRR = 88%, ARR = 21% (95% CI 6–36%), NNT = 5). The ARR for rebleeding (17%, 95% CI –4–37%) and mortality (16%, 95% CI –4–36%) showed a nonsignificant difference in favour of ligation.

Other trials [17–21] which compare ligation to sclerotherapy in patients with bleeding oesophageal varices have included rates of haemostasis in the subset of patients with active bleeding, although these trials were not primarily designed to assess this group. Rates of control of the subset of patients with actively bleeding oesophageal varices in these randomized trials were generally comparable for ligation and sclerotherapy in the range of 80–100%; the exception was a study by Gralnek *et al.* [21] which reported haemostasis in seven (58%) of 12 patients treated with ligation vs. 9/9 treated with sclerotherapy.

Ligation can sometimes be difficult to accomplish in patients with large amounts of blood in the oesophagus. The outer cylinder placed on the tip of the endoscope for ligation therapy may decrease the field of view, and blood may fill the cylinder, further obscuring the endoscopist's view. Therefore, the initial treatment of patients with actively bleeding varices may sometimes be more easily accomplished with sclerotherapy than with ligation. Ligation therapy can then be instituted at subsequent treatment sessions. In a randomized study comparing ligation to sclerotherapy after initial control of haemorrhage with sclerotherapy, ligation was found to have significantly less rebleeding, fewer complications, and achieve eradication with fewer sessions [22].

TISSUE ADHESIVES

Few data are available from randomized trials regarding the use of tissue adhesives such as cyanoacrylate in actively bleeding varices. Feretis *et al.* [23] compared polidocanol plus cyanoacrylate vs. polidocanol sclerotherapy alone and found no significant difference in control of active bleeding (19/20 (95%) vs. 14/18 (78%)), but among those with active bleeding did find significantly less recurrent bleeding over 1 month (2/10 (10%) vs. 8/18 (44%)) and lower hospital mortality (3/20 (15%) vs. 9/18 (50%)) in the combined treatment group. There were no significant differences in these parameters in patients without active bleeding at entry. Sung *et al.* [24] found no significant benefit of cyanoacrylate as compared to tetradecyl sclerotherapy in 100 patients with hepatocellular carcinoma and acute variceal bleeding; although 42% of patients had active bleeding, separate data on this subgroup were not provided. Omar *et al.* also found similar efficacy with cyanoacrylate as compared to

polidocanol or ethanolamine sclerotherapy in 60 patients with acute oesophageal variceal bleeding [25].

Abstract reports of randomized trials of tissue adhesive vs. ligation for acute variceal bleeding do not provide specific information on patients with active bleeding [26–28]. Sung *et al.* [26] found cyanoacrylate to be similar to ligation in achieving an initial haemostasis of oesophageal varices (100% in each group) but inferior to ligation over a 7–8 month follow-up with significantly more rebleeding (10/15 (67%) vs. 5/18 (28%)) and complications (9/15 (60%) vs. 3/18 (17%)). Duvall *et al.* [27] reported that failure to control bleeding at 72 hours in patients with oesophageal and gastro-oesophageal junction varices occurred in 2/18 (11%) with cyanoacrylate and 3/19 (16%) with ligation; failure to control gastric variceal bleeding at 72 hours occurred in 0/8 vs. 4/9 ($p = 0.08$). Finally, Hou *et al.* [28] found similar efficacy of tissue adhesive and ligation (control of bleeding in 95% of each group) in 42 patients with acute gastric variceal bleeding.

CONCLUSIONS

Ligation should be the initial endoscopic therapy employed in patients with acute or active oesophageal variceal bleeding. If technical difficulty (e.g. poor visualization) is encountered, sclerotherapy can then be attempted; ligation should be used at subsequent treatment sessions. Co-therapy with somatostatin or octreotide for 2–5 days appears to be beneficial compared to endoscopic therapy alone. Little information from randomized controlled trials is available on the treatment of acute or actively gastric variceal bleeding. Cyanoacrylate therapy may be the treatment on choice in this group, based largely on case series and individual experiences.

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TIPS and surgery in the management of acute variceal bleeding

Jean Pierre Vinel

No treatment has so far proved to be more effective for variceal bleeding in patients with cirrhosis than portacaval decompression. However, randomized studies performed in the 1970s failed to find any improvement in survival, probably because the efficacy of surgery was counterbalanced by operative mortality, chronic encephalopathy along with progressive deterioration of liver function.

J. Rösch advocated the use of the transjugular route to perform intrahepatic nonsurgical portacaval anastomoses as far back as 1969 [1]. However this technique remained experimental until the development of interventional vascular radiology prompted the manufacturing of expandable prostheses.

TIPS

TIPS was initially used in Child–Pugh's C cirrhotic patients with uncontrolled variceal bleeds and was found to be a life saving procedure [2]. Thereafter, two large uncontrolled series supported the use of TIPS in the management of portal hypertension [3,4]. Available randomized trials comparing TIPS and endoscopic treatments whether or not associated with propranolol showed as a whole that TIPS prevented rebleeding more effectively but failed to improve survival, the two main drawbacks of the technique being an increased risk of encephalopathy and a high obstruction rate [5–12]. A meta-analysis confirmed these results [13].

With regard to acute bleeding, no randomized trial has been published so far. A few patients in most uncontrolled series were treated in emergency conditions. But results were generally not specified for this subgroup of patients.

Seven series were specifically devoted to TIPS in acutely bleeding patients, either from oesophageal or from gastric varices. Their main results are summarized in Table 34.

As a whole, TIPS seems to be an effective salvage procedure in refractory bleeding episodes from oesophageal as well as gastric varices. Furthermore, it can been used in varices that are not amenable to endoscopic treatment (e.g. intestinal, stomal, rectal...).

SURGERY

Different surgical techniques were described to decrease the detrimental effects

Table 34 Results of TIPS in acute variceal bleeding in seven series.

First author (citation)	Number of patients	Haemostasis	Early rebleeding	Early mortality
McCormick PA (*Br J Surg* 1994; **81**:1324–7)	20	20 (100%)	6 (30%)	12 (60%)
Jalan R (*Am J Gastroenterol* 1995; **90**:1932–7)	19	17 (89%)	3 (16%)	6 (36%)
Sanyal AJ (*Gastroenterol* 1996; **111**:138–46)	30	29 (97%)	2 (7%)	12 (40%)
Gerbes AL (*Dig Dis Sci* 1998; **43**:2463–9)	11	10 (91%)	3 (27%)	3 (27%)
Chau TN (*Gastroenterol* 1998; **114**:981–7)	112	110 (98%)	15 (13%)	43 (38%)
Bañares R (*Am J Gastroenterol* 1998; **93**: 75–9)	56	53 (95%)	8 (14%)	15 (22%)
Barange K (*Hepatol* 1999; **30**:1139–43)	32	30 (94%)	9 (14%)	4 (14%)

of shunting on liver function, including selective shunts, calibrated H-grafts and devascularization procedures.

TIPS was compared to H-graft portacaval shunt in one study and found to be more expensive and less effective than surgery [14,15]. A decision-analysis study concluded distal splenorenal shunts is much more cost-effective than TIPS in Child A patients [16].

However, in emergency conditions, shunting procedures should be considered only for patients with uncontrolled bleeding, a situation very seldom encountered in patients with Child's A cirrhosis.

CONCLUSION

Because of the very high efficacy of drugs and endoscopic treatments, shunting procedures have no place as first line therapy. Whenever these procedures fail to control a variceal haemorrhage, TIPS should be considered the treatment of choice, although a few patients with preserved liver function might benefit form surgery.

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Appendix: questionnaire on the treatment of the acute bleeding episode

Loren A. Laine and Jaime Bosch

DIAGNOSIS

From previous Baveno Meetings it was clear that endoscopy is the gold standard for diagnosis. However, a few questions may deserve attention:

1 Timing of endoscopy:
Would you favour 'early' (immediate) endoscopy if clinically significant (severe) bleeding and 'elective' (within 16 hours from admission) if mild (no haemodynamic changes, Hgb drop, transfusions), or would you rather:
- do all early
- do all electively?

2 Would you adopt a different approach in suspected cirrhotics or would you treat in the same way as any patient with UGI bleeding:
- all patients with known cirrhosis or reason to suspect (e.g. alcoholism, chronic viral hepatitis, physical findings or labs suggestive of cirrhosis) should have early endoscopy to rule varices in or out, since if variceal bleeding is associated with a worse prognosis (rebleeding, transfusions, other interventions, length of hospital stay, mortality) than other causes of UGI bleeding
- as in any patient with UGI bleeding.

3 Requirements for endoscopic diagnosis of acute variceal bleeding:
- any patient with clinical evidence of UGI bleeding and only varices identified (even if no blood seen)
- any patient with clinical evidence of UGI bleeding and varices with stigmata seen (clot, white nipple)
- blood seen emanating from varix.

4 Definition of active bleeding:
- blood seen emanating from varix (this is my definition)
- red blood seen in oesophagus but not clearly seen emanating from varix.

5 Defining gastric vs. oesophageal variceal bleeding:
If both gastric and oesophageal how do you decide which was the source—especially in terms of making treatment decisions?
- if active bleeding seen emanating from varix or clots, white nipple sign on varix
- differential size (e.g. large oesophageal and small gastric). (If not one or two, just assume source was oesophageal and treat these; if recurrent

bleeding after eradication, then assume gastric even if you don't see active bleeding or stigmata at EGD).

GENERAL MANAGEMENT

6 Blood volume restitution policy:
- aimed at restore all blood loss by transfusing whole blood until the haematocrit is of about 35% and the systolic blood pressure is > 100 mmHg, since hypotension and low haematocrit and oxygen delivery to tissues may further deteriorate liver function
- cautious attitude, transfusing plasma expanders to maintain an acceptable haemodynamic condition (i.e., a systolic blood pressure > 85–90 mmHg, a heart rate < 100–110 b.p.m., ...) and blood/PRC to maintain the haematocrit between 25–30%, because more vigorous transfusion may worsen the bleeding.

7 Use of blood or blood products
- whole blood is better
- PRC is better
- fresh frozen plasma if prothrombin index less than 40%
- platelet concentrates if platelet count less than 50 000 per cubic mm.

8 Use of antibiotics to prevent bacterial infections/SBP:
- nonabsorbable antibiotics (i.e. norfloxacin) preferred
- systemic (IV, IM) antibiotics (amoxycilin/clavulamic acid or other) preferred since have quicker action and may be better to prevent bacteremia
- this question is relevant and requires RCTs.

9 Prevention of encephalopathy:
- this is done effectively by nasogastric aspiration of blood in the GI tract
- this requires administration of lactulose per os or via nasogastric tube.

10 Assessment of prognosis:
- Child–Pugh classification is sufficient to assess individual risk
- Child–Pugh should be modified to introduce other important descriptors and/or other important prognostic indicators should also be taken into account, including:
  - presence of concomitant chronic disease (diabetes, COPD, renal failure...)
  - active bleeding at endoscopy or fresh blood haematemesis after admission
- you think that it is time to try to use HVPG monitoring.

11 Use of balloon tamponade:
- never use tamponade since it is too dangerous and uncomfortable

- only in massive bleeding, as a temporal measure to 'bridge' until adequate treatment
- I would use it more often if a safer and more effective balloon technique were available.

PHARMACOLOGICAL TREATMENT

12 Do you treat all patients with potential variceal bleeding with medical therapy immediately after presentation, prior to endoscopy, or only after confirming the diagnosis of variceal haemorrhage?

13 Which drug(s) do you use (underline *which*, and indicate *doses* and *length* of therapy):

- somatostatin:
- octreotide:
- terlipressin:
- vasopressin + nitroglycerin:
- other (indicate):

14 If patient has known varices and pharmacological therapy controls the bleeding based on clinical grounds, would you:

- always perform an early endoscopy
- delay endoscopy and do it on a non-urgent setting ('next day', 'working hours')
- perform endoscopy only if bleeding recurs or after a few days, when starting elective therapy.

15 If under pharmacological therapy you perform endoscopy and the varices are not bleeding at the time of endoscopy, would you:

- perform endoscopic therapy anyway and stop drug therapy
- perform endoscopic therapy anyway and maintain drug therapy
- maintain drug therapy alone.

16 If a bleeding has been clinically controlled by pharmacological therapy, for how long will you maintain drug administration?

- 24 hours
- 48 hours
- 5 days
- other:

17 If bleeding that has been clinically controlled by pharmacological therapy recurs after discontinuing drug administration, would you:

- resume drug therapy again
- proceed to endoscopic therapy
- associate both
- proceed to TIPS/surgery.

ENDOSCOPIC THERAPY AND COMBINED ENDOSCOPIC AND MEDICAL THERAPY

18 What is your first line endoscopic therapy of oesophageal varices?

- sclerotherapy
- ligation
- glue
- other:

19 Do you prefer to start treatment using endoscopic therapy from the beginning or you start drug therapy before?

20 If the patient was not receiving drug therapy at the time of endoscopy, do you associate drugs after endoscopy?

- always
- only if there was active bleeding at endoscopy
- only if you were not totally happy with your endoscopic treatment
- depends on which endoscopic treatment you used (EBL, EIS...)
- depends on the Child–Pugh score of the patient.

21 Management of treatment failure:

- TIPS
- shunt surgery
- other liver transplant.

22 Does baseline degree of liver disease influence decision of TIPS vs. surgery?

- no
- yes: if so, what are the limits for surgery and for TIPS?

RECOMMENDED TREATMENT

23 What is your recommended algorithm for the treatment of acute variceal bleeding?

24 Summarize the main differences in your algorithm when you manage patients bleeding from gastric varices (primarily and after failure of the initial treatment):

PROSPECTIVE

25 Indicate the main advances in the field during the past decade:

26 Indicate the three main areas that require further study:

27 Indicate your priorities for new randomized clinical trials:

Baveno III Consensus Statements: Treatment of the Acute Bleeding Episode

Jaime Bosch, Loren A. Laine (Chairpersons), Andrew K. Burroughs, Norman Marcon, Frederik Nevens, Christine Silvain and Jean Pierre Vinel

1 Timing of endoscopy:
(a) Endoscopy should be performed as soon as possible after admission (within 12 hours), especially in patients with clinically significant bleeding or in patients with features suggesting cirrhosis
(b) In mild bleeds, causing neither haemodynamic changes nor requiring blood volume restitution, endoscopy can be done electively.

2 Blood volume restitution:
(a) Blood volume restitution should be done cautiously and conservatively, using PRC to maintain the haematocrit between 25–30%, and plasma expanders to maintain haemodynamic stability
(b) Further data are required on the need for treating coagulopathy and thrombocytopenia.

3 Use of antibiotics to prevent bacterial infections/spontaneous bacterial peritonitis:
(a) The presence of infection should be considered in all patients. Antibiotic prophylaxis is an integral part of therapy and should be instituted from admission, RCTs of oral non-absorbable vs. systemic antibiotics are needed.

4 Prevention of hepatic encephalopathy:
(a) Lactulose should be given by mouth, naso-gastric tube, or enema to prevent hepatic encephalopathy.

5 Assessment of prognosis:
(a) The Child–Pugh classification is not sufficient to assess individual risk and prognosis, and the additional utility of other prognostic indicators should be assessed
(b) The effect of other chronic diseases, renal failure, bacterial infections, HCC and active bleeding at endoscopy should be evaluated
(c) Portal pressure monitoring should be further investigated.

6 Use of balloon tamponade:
(a) Balloon tamponade should only be used in massive bleeding as a temporary 'bridge' until definitive treatment can be instituted.

7 Pharmacological treatment:
(a) In suspected variceal bleeding, vasoactive drugs should be started as soon as possible, before diagnostic endoscopy
(b) Even if there is no active bleeding at endoscopy, it is recommended to perform endoscopic therapy, especially in high risk patients

(c) Drug therapy may be maintained for up to 5 days to prevent early rebleeding. RCTs should be done to determine the optimal duration.

8 Endoscopic treatments:

(a) In acute bleeding either ligation or endoscopic sclerotherapy can be used. For subsequent treatment, endoscopic banding ligation is replacing injection sclerotherapy as first-line endoscopic treatment for bleeding oesophageal varices

(b) Endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started before endoscopy.

SESSION 7

Prevention of Recurrent Variceal Haemorrhage (Secondary Prophylaxis)

Didier Lebrec and Gregory V. Stiegmann

INTRODUCTION

Pharmacological, endoscopic and radiological treatments are effective in preventing recurrent gastrointestinal bleeding and improving the survival rate in patients who have had an episode of variceal haemorrhage [1,2].

This review will summarize trials of these treatments and give current perspective to their role for prevention of recurrent variceal haemorrhage.

BETA-BLOCKERS VS. 'NONACTIVE' TREATMENTS

Beta-blockers administration significantly reduces the risk of rebleeding and improves survival rate compared to a placebo in patients with cirrhosis [3]. Certain factors were shown to be associated with the risk of rebleeding in patients treated with beta-blockers: lack of compliance, lack of persistent decrease in heart rate, occurrence of hepatocellular carcinoma, lack of alcohol abstinence and a previous episode of bleeding [4]. Neither the dose of beta-blockers nor the cause or severity of cirrhosis was associated with rebleeding. The incidence of mild and transient hepatic encephalopathy was 0.025%, which was similar to patients receiving a placebo.

ENDOSCOPIC SCLEROTHERAPY VS. 'NONACTIVE' TREATMENTS

Endoscopic sclerotherapy was one of the first active treatments for prevention of recurrent variceal bleeding. Initially, this treatment was done with a rigid endoscope using general anaesthesia. Flexible endoscopic methods evolved during the late 1970s and injection sclerotherapy was widely adopted for secondary prophylaxis in the 1980s. Sclerotherapy for prevention of recurrent haemorrhage is performed on a repeated basis until varices in the distal oesophagus are obliterated.

Sclerotherapy has been compared with or in combination with a variety of alternate medical, pharmacological, surgical and radiological treatments as well as with the newer endoscopic treatment, band ligation.

Endoscopic sclerotherapy was compared with 'nonactive' treatment in nine trials. In most of these studies, recurrent haemorrhage in the no-sclerotherapy cohort was treated with balloon tamponade or vasopressin as opposed to acute injection sclerotherapy. Meta-analyses of these trials demonstrated that patients treated with sclerotherapy to accomplish eradication of distal oesophageal varices had less recurrent haemorrhage and better survival than those who received no treatment [1,5,6].

BETA-BLOCKERS VS. ENDOSCOPIC SCLEROTHERAPY

Trials comparing endoscopic sclerotherapy with beta-blockade have been assessed in three meta-analyses [1,6,7]. One of the three meta-analyses concluded that there was no difference in the incidence of either recurrent haemorrhage or mortality [6]. A second meta-analysis showed sclerotherapy patients had a lower incidence of recurrent bleeding but no difference in mortality [1]. The third meta-analysis found that sclerotherapy-treated patients had a lower incidence of recurrent bleeding from varices; however, the incidence of recurrent bleeding from all upper gastrointestinal sources was the same and there was no survival difference [7]. The latter study also found the incidence of adverse events to be greater in sclerotherapy-treated patients. Results from these meta-analyses, combined with our current general understanding of the risks and benefits of endoscopic sclerotherapy, indicate that sclerotherapy may be superior to beta-blockade for prevention of recurrent haemorrhage from oesophageal varices but that sclerotherapy is associated with greater morbidity. Neither treatment confers a survival advantage over the other.

BETA-BLOCKERS VS. BETA-BLOCKERS PLUS NITRATES

Preliminary results of a comparison between nadolol and isosorbide-5-mononitrate versus nadolol alone showed no significant difference in rebleeding between the two groups but a higher mortality in patients receiving the combination than in those receiving nadolol alone [8].

ENDOSCOPIC SCLEROTHERAPY COMBINED WITH BETA-BLOCKERS VS. SCLEROTHERAPY OR BETA-BLOCKADE

Ten trials compared patients treated using endoscopic sclerotherapy combined with beta-blockers versus endoscopic sclerotherapy alone. These were

assessed in two meta-analyses [1,9]. There was no difference in the incidence of recurrent bleeding between the two treatments if results from one of the trials (which had an inordinately high incidence of recurrent haemorrhage in sclerotherapy treated patients) were excluded. There was no difference in survival between the two treatments.

A single trial compared endoscopic sclerotherapy and beta-blockade with beta-blockade alone for prevention of recurrent bleeding [10]. This study found significantly less recurrent *variceal* bleeding in patients treated with both sclerotherapy and propranolol but no statistically significant difference in the overall incidence of upper gastrointestinal bleeding from all causes. There was no difference in mortality between the two treatments.

These studies suggest that the combination of beta-blocker therapy and endoscopic sclerotherapy provides little added value as compared with either treatment used alone.

ENDOSCOPIC SCLEROTHERAPY VS. COMBINATION OF BETA-BLOCKERS PLUS NITRATES

The combination of beta-blockers plus nitrates has been compared with sclerotherapy in one trial [11], and with sclerotherapy or shunt surgery in another [12]. The former showed that the combination significantly decreased the risk of rebleeding, while in the latter the combined medical regimen was not significantly different from endoscopic sclerotherapy in Child–Pugh C patients or shunt surgery in Child–Pugh A or B patients.

ENDOSCOPIC SCLEROTHERAPY VS. SHUNT SURGERY

Seven trials compared portocaval or distal splenorenal shunt with endoscopic sclerotherapy for prevention of recurrent bleeding [3]. Meta-analysis of four of the trials which used the distal splenorenal shunt found that these shunts significantly reduced the incidence of recurrent haemorrhage, slightly increased the risk of encephalopathy but did not provide improved survival [13]. In other trials, shunt surgery was consistently superior in preventing recurrent haemorrhage but was associated with greater risk of hepatic encephalopathy. Survival was improved in the endoscopic cohort in two trials and in the shunt cohort in another. In long-term follow up of the latter trial, sclerotherapy treated patients who lived long distances from the treatment centre had higher mortality as a result of uncontrolled recurrent bleeding [14]. This suggests that shunt operations may have value for patients living distant from the treatment centre.

ENDOSCOPIC LIGATION VS. ENDOSCOPIC SCLEROTHERAPY

Endoscopic band ligation was developed in the 1980s as an alternative to endoscopic sclerotherapy. The initial expectation for this treatment was a diminution of the morbidity associated with endoscopic sclerotherapy. This goal has been confirmed and additional benefits have subsequently emerged. Multiple trials comparing endoscopic ligation with sclerotherapy have been performed and two meta-analyses of these trials have been published. Meta-analyses of seven [15] and ten [16] trials demonstrated a lower incidence of recurrent bleeding, a lower incidence of treatment related complications and fewer treatment sessions needed for eradication of varices with endoscopic ligation. One meta-analysis [15] showed a significant reduction in mortality with the new treatment, the other did not. Several additional trials have been published which are not included in these meta-analyses [17–21]. Findings from these trials are consistent with the conclusions above. It is now generally accepted that endoscopic band ligation is the endoscopic treatment of choice for prevention of recurrent variceal haemorrhage.

ENDOSCOPIC LIGATION COMBINED WITH SCLEROTHERAPY (SYNCHRONOUS) VS. ENDOSCOPIC LIGATION

Seven trials have compared synchronous combined endoscopic ligation and sclerotherapy with endoscopic ligation alone [22–28]. More treatment sessions to eradicate varices were needed with the combined treatment in two of the studies and complications of treatment were greater in the combined treatment cohort in two. There was no difference in the incidence of recurrent bleeding or mortality. Recurrence of varices after initial eradication (generally accepted to occur more often after endoscopic ligation than after sclerotherapy) was less in patients receiving the combined therapy in two of the trials. There appears to be no advantage, and perhaps some disadvantage, to using these two treatments in combination.

ENDOSCOPIC LIGATION VS. DRUG THERAPY

One trial has reported results (abstract) comparing endoscopic ligation with combined Nadolol and isosorbide-5-mononitrate [29]. This trial demonstrated a trend toward fewer rebleeding episodes per patient and fewer complications in the drug treated cohort. There was no difference in mortality. There is a need for additional trials comparing endoscopic band ligation with both

mono and multi-drug regimens as well as with combinations of drug and endoscopic ligation.

ENDOSCOPIC LIGATION VS. BETA-BLOCKERS OR VS. COMBINATION OF BETA-BLOCKERS PLUS LIGATION

No comparison was performed between beta-blockers with or without endoscopic ligation and endoscopic ligation alone but we can expect that the combination of band ligation and beta-blockers is the same or better than the combination of endoscopic sclerotherapy and beta-blockers with fewer side effects. However, confirmation of this hypothesis is necessary before combination of beta-blockers and endoscopic ligation can be officially recommended.

ENDOSCOPIC THERAPY VS. TRANSJUGULAR INTRAHEPATIC PORTAL-SYSTEMIC SHUNT (TIPS)

Eleven trials comparing TIPS with endoscopic therapy (seven sclerotherapy, four endoscopic ligation) have been assessed in three meta-analyses [30–32]. TIPS consistently reduced the incidence of recurrent bleeding but was associated with an increased incidence of encephalopathy and no improvement in survival. It seems unlikely that additional comparisons of TIPS with endoscopic ligation will result in different conclusions with regard to the commonly defined end-points (e.g. recurrent bleeding, encephalopathy, mortality etc) but may reveal differences when such variables as cost or quality of life are examined.

COSTS OF ENDOSCOPIC VS. TIPS OR DRUG TREATMENTS

TIPS was compared with endoscopic ligation or endoscopic sclerotherapy in a hypothetical cost model [33]. This model concluded that TIPS was more cost-effective in the short-term than either endoscopic sclerotherapy or endoscopic ligation. A second study compared actual costs for patients treated with endoscopic sclerotherapy as compared with TIPS and found that aggregate costs for TIPS were greater [34]. If costs were expressed as cumulative cost per month free of rebleeding, there was no difference at the end of an 18 month follow-up.

Two analyses have been published (abstract form) which use Markov models in an attempt to compare the costs of endoscopic ligation, sclerotherapy and drug therapy for secondary prophylaxis. Results of one study measured the hypothetical cost/patient/5 years of intervention and found en-

doscopic ligation ($7,012) most expensive as compared with propranolol ($3,791) which was least expensive [35]. Other drugs and drug combinations were more expensive than propranolol but less than endoscopic treatment. The second study determined that the hypothetical cost/life-year saved with endoscopic ligation was $14,000 as compared to $11,000 for beta-blockade [36]. These are important efforts to begin quantification of the investment required to prevent recurrent variceal haemorrhage. They must, however, be evaluated in the context of the degree of patient compliance that must be sustained, for an indefinite period, outside the supportive setting of a clinical trial, in order for the drug regimens to be successful. A third study examined the degree of compliance required for success of drug therapy as compared with endoscopic ligation [37]. If it were assumed that drug therapy and endoscopic ligation resulted in a nearly equal incidence of recurrent bleeding, compliance with taking the medication had to approach 100% over five years of therapy in order to realize similar prevention of rebleeding in the drug cohort as compared with the endoscopic. Patient compliance had little effect on the rebleeding rate after endoscopic ligation.

SUMMARY

Over the past 20 years, endoscopic therapy has become well established for prevention of recurrent variceal haemorrhage. Endoscopic sclerotherapy has yielded to endoscopic band ligation as the current endoscopic method of choice. Other competing treatments, including pharmacotherapy and TIPS, have emerged during this same period. At this time, the preferred first line treatment for secondary prophylaxis is either band ligation or beta-blockade. Future trials comparing these and other treatments need to focus on traditional outcome variables as well as cost and quality of life measurements.

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Baveno III Consensus Statements: Secondary Prophylaxis

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1 First line treatments: either beta-blockade or hand ligation is the first-line treatment method to prevent recurrent variceal haemorrhage. Patients with advanced liver disease should be evaluated for liver transplantation. Combinations of endoscopic and drug treatments should be further indicated.

2 Treatment of patients with contraindications to beta-blockers:
(a) Band ligation is the preferred treatment to prevent recurrent variceal haemorrhage in patients who have a contraindication to beta-blocker therapy or who have bled while on beta-blockers.

3 Treatment for low-risk patients failing first-line therapy:
(a) Surgical shunt or TIPS is the recommended treatment for good-risk patients who fail first line treatments (beta-blockers/banding) for prevention of recurrent bleeding.

4 Treatment for high-risk patients failing first-line therapy:
(a) TIPS is the recommended treatment for selected *high*-risk patients who fail the preferred first line treatments (beta-blockers/banding) for prevention of recurrent bleeding
(b) These patients should be considered for liver transplantation.

5 Future studies:
(a) Future trials for secondary prophylaxis should include two or more of the following treatment arms: (1) beta-blockers +/– nitrates; (2) band ligation +/– drug therapy; (3) TIPS; (4) DSRS; (5) small diameter shunts; (6) other portal hypotensive drugs +/– beta-blockers (7) combination of treatments
(b) Cost and Life Quality determinations should be measured in future trials.

SESSION 8

Complications in the Medical Treatment of Portal Hypertension

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INTRODUCTION

In the last few years great progress has been made in the medical treatment of portal hypertension. At present, this treatment includes the use of drugs, endoscopy therapy (sclerotherapy and banding ligation) and transjugular intrahepatic portosystemic shunt (TIPS). Pharmacological treatment of patients with bleeding by oesophageal varices is different from the treatment used to prevent rebleeding or in primary prophylaxis. In contrast endoscopic therapy and TIPS are used in both clinical situations. All these therapeutic procedures are relatively efficacious; however, all may be associated with side effects. Therefore, it is essential to achieve a consensus to define the complications observed on using pharmacological treatment, endoscopic therapy and TIPS.

COMPLICATIONS OF TREATMENT FOR ACUTE OESOPHAGEAL BLEEDING

Complications of pharmacological treatment

The main drugs proposed for the pharmacological treatment of gastrointestinal bleeding from ruptured oesophageal varices are: vasopressin, triglycyl lysin vasopressin or terlipressin, somatostatin and octreotide. All these drugs have a vasoconstrictive effect on the splanchnic circulation, and exert their acute therapeutic action mainly through a reduction of blood flow and pressure in the bleeding varices. These side effects observed with these drugs are mainly due to the vasoconstrictive effect.

Vasopressin was the first drug proposed for the therapy of bleeding oesophageal varices. Its action is mediated by the V1 receptors in the vascular smooth muscle [1]. It increases tone in the lower oesophageal sphincter and by inducing smooth muscle contraction, causes arteriolar vasoconstriction particularly in splanchnic arterioles, with a reduction of portal blood flow and of portal pressure. Unfortunately, the vasoconstrictive action is not splanchnic

selective, and this lack of selectivity is frequently responsible for the main side effects, which are related to the cardiovascular and the mesenteric systems. Vasopressin causes an increase in peripheral vascular resistance and in arterial blood pressure, a decrease in cardiac output, due to a direct effect on myocardial contractility, and a decrease in heart rate, through a vagal reflex stimulated by the increase in arterial blood pressure [2]. The decrease in portal pressure is mainly the consequence of a reduction in portal inflow, due to splanchnic vasoconstriction. In published studies, vasopressin was administered for 12 to 48 hours. The drug has a fibrinolytic effect. Side effects were reported in 32% to 64% (45% as an average) of the treated patients. Complications severe enough to require withdrawal of therapy were reported in up to 25% of the patients [3–5]. The mortality reported from complications was about 3–5%. The reported complications were: abdominal pains, angina, skin gangrene, myocardial ischaemia, mesenteric ischaemia and bowel gangrene, peripheral ischaemia, cardiac dysrhythmias, cerebrovascular accidents, bradycardia, hypertension, hyponatremia, fluid retention, tremor, headache, vertigo, cardiac arrest, pallor, nausea, vomiting, confusion, seizures, coma. Side effects requiring withdrawal of therapy were mainly those affecting the cardiovascular system. Potentially lethal side effects occurred in 10% of the patients, but less severe complications requiring the limitation of the dose were observed in 30% of the patients [6]. To decrease side effects with vasopressin, the association with nitroglycerin, a coronary vasodilator, has been proposed. In two out of the three published trials, the combined therapy reduced the incidence of complications. All in all, the number of side effects were halved (from 61% to 25–31%), even though the number of patients who withdrew the therapy because of the side effects remained the same [3]. Nowadays, vasopressin is considered a drug which must not be used alone due to its potential side effects; if vasopressin is used, it must be combined with nitroglycerin [7]. On the other hand, as nitrates have significant systemic effects on their own, the use of combined therapy must be monitored very closely [4].

Terlipressin, or triglycyl lysin vasopressin, is a long-acting synthetic analogue of vasopressin, that, *in vivo*, is slowly activated by cleavage of the N-terminal glycyl residue, to vasopressin [5]. A lower frequency of cardiac side effects was reported with terlipressin. In contrast to vasopressin, this drug does not have a significant influence on fibrinolysis, as it does not increase the plasmatic activator of plasminogen. In alcoholic cirrhosis, terlipressin administration provoked an increase in mean arterial pressure (by 14%) and in systemic vascular resistance (by 48%), a decrease in heart rate (by 10%) and in cardiac index (by 22%), and a marked decrease in hepatic and splenic blood flow (by 31% and 56% respectively) and in hepatic venous pressure gradient (by 31%) [8]. According to published meta-analysis, terlipressin improved survival in cirrhotic patients with GI bleeding from oesophageal varices. As

far as side effects are concerned, a lower incidence of complications in respect of vasopressin has been demonstrated, even when combined with nitroglycerin. When terlipressin was compared with sclerotherapy, a similar number of complications was reported (30% vs. 29%; serious side effects: 6% vs. 5%). In published studies, terlipressin side effects were: abdominal cramps, diarrhoea, bradycardia, hypertension, dysrhythmias, angina, headache, facial pallor, ischemic colitis, bronchial constriction, peripheral vasoconstriction. Terlipressin has also been associated with nitrates to decrease the incidence of side effects. In a French study in which combined therapy was used, no serious side effect was reported [9].

Somatostatin is a 14 amino acid peptide, with vasoconstrictive properties when administered at pharmacological doses. It provokes splanchnic vasoconstriction, with a decrease in portal blood flow [10] and in portal-collateral blood flow (azygos blood flow). Five somatostatin receptors have been identified. The inhibition of the secretion of substances increasing splanchnic blood flow (glucagon, VIP, P substance) is considered the main mechanism of action of the drug, but it also has a direct venoconstrictive effects, mediated by the activation of the receptor subtype 2. It can also have a systemic effect, and indeed an increase in blood pressure has been reported during its use.

Octreotide is a synthetic octopeptide, sharing with somatostatin the 4 amino acids responsible for the biological effects. Octreotide mediates some of its effects via somatostatin receptors, but apart from the inhibition of vasodilating substances, a direct arterial vasoconstrictive action has been hypothesized [11].

On the whole, somatostatin and octreotide have a lower incidence of complications when compared with vasopressin or terlipressin. The incidence of side effects of somatostatin vs. vasopressin was 10% vs. 51%; odd ratio 0.11 (0.07–0.2) [4], and its use was followed by fewer serious side effects requiring drug withdrawal (2% vs. 20%). When compared with terlipressin, somatostatin showed the same incidence of complications (all complications: 21% vs. 29%; serious side effects requiring withdrawal of therapy: 4% vs. 4%), but in the largest among the published trials comparing the two drugs, a significant lower incidence of complications in the somatostatin group was reported [4,12]. Reported side effects of somatostatin were: bradycardia, hypertension, hyperglycemia, diarrhoea, fever, chest pain, flushing. The reported side effects of octreotide were: dizziness, fatigue, headache, diarrhoea, abdominal pain, bradycardia, dysrhythmias, blurred vision, nausea [5]. The acute administration of octreotide was followed by transient adverse effects on cardiac output, i.e. a decrease in heart rate and cardiac index, and an increase in mean arterial pressure and in pulmonary artery pressure [6,13]. Therefore, even though somatostatin and its analogue are all in all considered to have no or only minor side effects [7], they are not completely free of side

effects, and this should be taken into account when choosing pharmacological therapy.

In conclusion, among the vasoactive drugs available, terlipressin is probably the most effective pharmacological therapy for bleeding oesophageal varices, but somatostatin appears to be effective with fewer side effects [6].

Complications of TIPS

Transjugular intra-hepatic porta-systemic shunt, widely used in refractory bleeding from oesophageal varices, can be followed by numerous types of complications. Most of them are procedure-related accidents such as intraperitoneal haemorrhage, stent misplacement, haemobilia, acute renal failure, right-sided heart failure, sepsis and acute liver failure. These complications occur in 10–20% of patient in the reported series of the last 5 years; in only 2–4% did they result in the patient's death [14].

The most important consequence of emergency TIPS is a 30 day mortality rate, reported in a range varying from 15 to 40%. This is mostly related to early rebleeding, sepsis and impairment of hepatic function leading to liver failure [15].

Some efforts have been made to identify patients at high risk of dying after an emergency TIPS. In a series of 56 patients treated by Banares and coworkers [16], different results have been reported depending on the severity of the liver disease classified according to Child-Pugh. Thirty day mortality rate was reported as high as 28% in the whole series. However, a statistically significant difference in survival rate was observed in patients belonging to Child C class (Fig. 25).

Rubin and coworkers tried to make a risk assessment based on Child–Pugh classification and APACHE II score. This latter is a validated severity of disease classification that stratifies acutely ill patients giving them a score on the basis of three components: an acute physiology score, age points and chronic health points. The acute physiology score is determined on the worst value of 12 variables that are quite easy to measure: rectal temperature, mean arterial pressure, heart rate, respiratory rate, partial pressure of oxygen, arterial pH, serum sodium, serum potassium, serum creatinine, haematocrit, WBC count, coma score. In their paper, the authors reported the results obtained in 49 patients, 26 Child class A or B, 23 class C. Thirty days survival was 61% in the entire group, 80% in Child A or B patients, 39% in Child C. According to the APACHE II score, two patients had an assigned score of less than 10 and both survived; 28 patients had a score between 10 and 19 and 89% of them survived 30 days; 11 had a score between 20 and 29 and only 27% survived 30 days; out of eight patients with a score higher than 30, none survived.

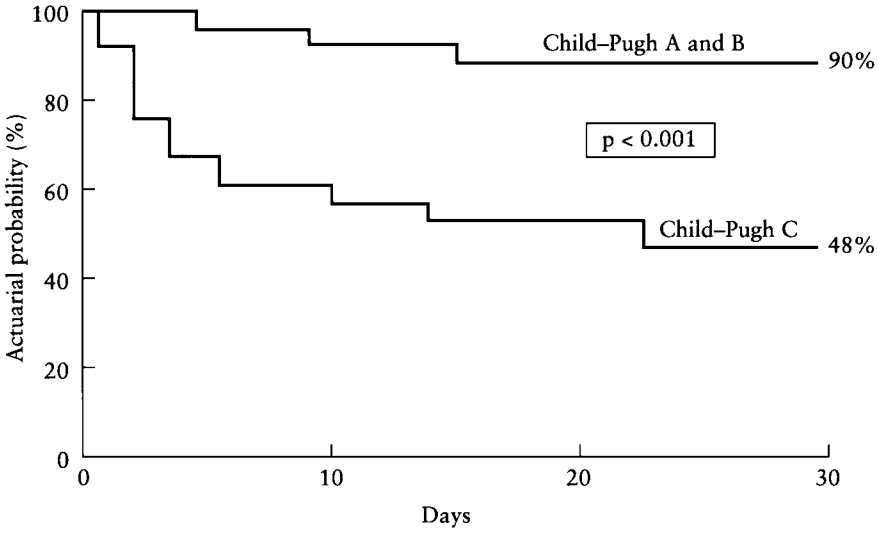

Fig. 25 Survival after emergency TIPS according to Child–Pugh classes.

A score of 18 stratified patients into those at low risk and those at high risk of mortality. Child C patients with APACHE II score higher than 18 had the lowest chance of surviving one month: 7.7%.

In a recent report from Emory University [17] the risk for emergency TIPS in advanced cirrhosis has been assessed in a different way. The authors made a retrospective analysis in a series of 147 patients who underwent TIPS, all belonging to Child classes B and C.

Active bleeding requiring emergent TIPS placement, pre-existing encephalopathy, ALT level > 100 IU/l. and bilirubin level > 3.0 mg/dl, where found to be independent predictors of overall mortality.

Each of these variables was given a weighted value based on hazard ratio: emergency TIPS, 2; ALT level > 100 IU/l, 1; bilirubin level > 3 mg/dl, 1; pre-TIPS encephalopathy, 1.

The study cohort was then stratified in three groups: high risk patients [13], score 4–5; medium risk patients [61], score 1–2; low risk patients [53], score 0. One year survival rate in the three groups was respectively 10%, 43% and 70%, low survival in the high risk patients depending on the very high mortality (90%) during the first post operative month (Fig. 26).

This prediction model has been tested on an independent cohort that consisted of 57 consecutive patients who underwent TIPS at Indiana University [18]. One year survival in this series was 30% in high risk, 49% in medium risk and 67% in low risk patients with statistically significant difference one from another group ($p = 0.037$).

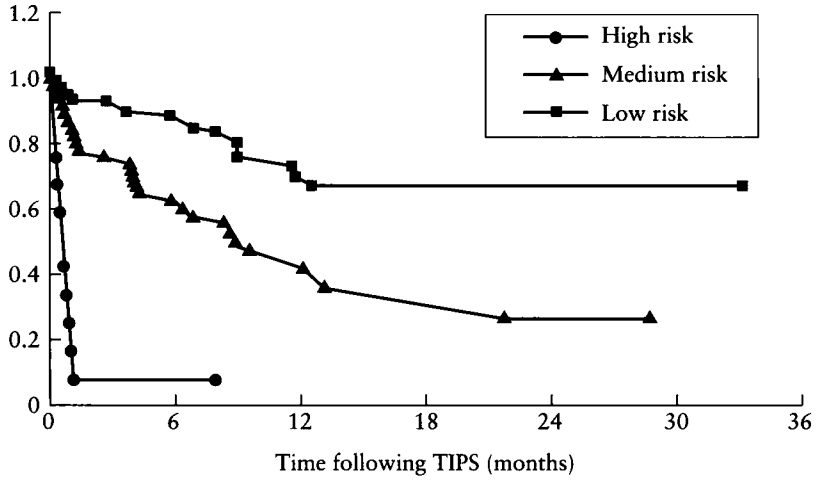

Fig. 26 Survival after TIPS by risk stratification.

All these studies demonstrated that it is possible to identify, among cirrhotic bleeders, patients who would probably die after an emergency TIPS. In these patients transjugular porta-systemic shunt should be avoided.

COMPLICATIONS OF ELECTIVE THERAPY

Complications of pharmacological treatment

Nonselective beta-blockers

Primary prophylaxis. Table 35 summarizes results of published trials of nonselective beta-blocker therapy in the prevention of first variceal haemorrhage. The first seven are trials of nonselective beta-blockers vs a placebo or other therapy (vitamin K, ranitidine, sclerotherapy) [19–25]. The last two trials compared propranolol vs isosorbide mononitrate [26] or nadolol alone vs nadolol plus isosorbide mononitrate [27] in the prevention of first haemorrhage. As can be seen in the table, approximately 7% of patients considered for entry into these trials were excluded because of contraindications to the use of beta-blockers.

Of 541 patients reported in seven trials in which the total number of side effects in the beta-blocker group is reported, 112 (20%) developed side effects. Two of the trials in which a placebo was used [21,24] showed that 5/104 (5%) patients in the placebo group had side effects. Of note, the only *double*-blind trial, that of Conn *et al.* [24] showed a 6% rate of side effects in the

Table 35 Randomized trials of nonselective beta-blockers for the prevention of first variceal haemorrhage.

First author	Year	*n* (*n* on beta-blocker)	Type of beta-blocker	Excluded (contraindicated)	Side effects		
					Control	Beta-blocker	Withdrawn due to side-effects
Pascal	1987	230 (118)	Propranolol	~6%	NR	20 (17%)	13 (11%)
Ideo	1988	79 (30)	Nadolol	7%	NR	NR	1 (3%)
Lebrec	1988	106 (53)	Nadolol	NR	2 (4%)	5 (9%)	2 (4%)
IMPP	1989	174 (85)	Propranolol	5%	NR	NR	23 (27%)
Andreani	1990	126 (43)	Propranolol	6%	NR	5 (12%)	3 (8%)
Conn	1990	102 (51)	Propranolol	20%*	3 (6%)	7 (14%)	7 (14%)
PROVA	1991	286 (141)	Propranolol	3%	NR	46 (33%)	21 (15%)
Angelico	1993	118 (61)	Propranolol	11%	2 (3%)†	19 (31%)	2 (3%)
Merkel	1996	146 (74)	Nadolol	12%	26 (36%)‡	10 (14%)	4 (5%)
TOTAL		1367 (656)			5/104 (5%)	112/541 (20%)	76/656 (12%)
Medians of studies				6.5%		14%	7.5%

* contraindicated or already receiving beta-blockers
† ISMN
‡ Nadolol plus ISMN
NR, not reported

placebo group vs 14% in the propranolol group. Therefore, the approximate rate of side effects from nonselective beta-blockers in cirrhotic patients who have not bled from varices is about 15%. Lack of a reported total number of side effects in the IMPP trial could underestimate this number.

In all nine trials, side effects led to withdrawal from the study in 12% (76/656) of the cases. However, if only the seven trials that reported total number of side effects is considered, only 9% (51/541) of the patients had to be withdrawn because of side effects.

The rate of side effects in trials in which nadolol was used (9% and 13%) appears to be lower than in trials in which propranolol was used (range 12–31%, median 17%), however direct comparisons have not been performed.

Table 36 shows the specific adverse events attributed to beta-blockers in these trials. Note that the most common are lightheadedness, asthenia and Raynaud's (or cold extremities). Also note that side effects such as encephalopathy and refractory ascites (which are most probably not related to beta-blockers) have been included.

Secondary prophylaxis. Beta-blockers have been shown to be effective in preventing rebleeding in patients who have bled from varices. These patients are sicker than patients who have never bled and could theoretically have a lesser tolerance to beta-blockers. However, this does not seem to be the case.

A recent meta-analysis [28] of 12 randomized trials comparing a nonselective beta-blocker vs a placebo or nonspecific therapy in patients with a recent variceal haemorrhage analysed the rate of adverse events. A total of 10 randomizations involving 617 patients (313 treated with beta-blockers) were analysed for the analysis of adverse events. The mean percentage of patients free of adverse events was 78% in patients treated with beta-blockers compared to 91% in the control group (the difference was significant). Considering trials in which adverse events were specifically mentioned, these occurred in 53/313 (17%) cases. Severe adverse events included cardiac failure, bradycardia and bronchospasm. Side effects led to withdrawal from the study by 18 (6%) patients.

Another meta-analysis by the same investigators [29] of nine selected randomized trials comparing propranolol vs sclerotherapy, also analysed the rate of adverse events. A total of eight randomizations involving 655 patients (324 treated with beta-blockers) were analysed. The mean percentage of patients free of adverse events was 76% in patients treated with beta-blockers compared to 56% in the sclerotherapy group (the difference was significant). Adverse events occurred in 52/324 (16%) cases. Severe adverse events included cardiac failure, bradycardia, bronchospasm and encephalopathy (?). Side effects led to withdrawal from the study by 15 (5%) patients.

Table 36 Specific side effects attributed to nonselective beta-blockers in randomized trials for the prevention of first variceal haemorrhage.

First author	Year	Dizziness or low BP	Asthenia	Raynaud's or cold feet	Dysrhythmia	Heart failure	Broncho-spasm	PSE	RA	Rash	Other
Pascal	1987	7		3	2	3	2	1			2
Ideo	1988				1						
Lebrec	1988	2		2							1
IMPP	1989	3	9		1		3	3	3	1	
Andreani	1990	3	2								
Conn	1990				1	2	1				3
PROVA	1991	19	3	8	4	4	3			2	3
Angelico	1993		18								1
Merkel	1996	5			2	1	1				1
TOTAL		39	32	13	11*	10	10	4	3	3	11†

* including six cases of bradycardia

† includes two cases of impotence, two cases of nightmares and one case each of depression, thrombocytopenia, diarrhoea, dysphagia, stroke, angina and abdominal discomfort

PSE, portal-systemic encephalopathy; RA, refractory ascites

Nitrates

Only one trial compares isosorbide mononitrate (ISMN) vs propranolol in the prevention of first variceal haemorrhage [26]. As shown in Table 35, adverse events in the beta-blocker group numbered 19/61 (31%) compared to only 2/57 (4%) in the ISMN group. However, withdrawal from the study due to adverse events occurred in only two patients in each group. Of the two patients in the ISMN with side effects, one had severe headache and one had hypotension that led to dizziness and weakness. In a follow-up of this trial [30], the investigators noted that no further withdrawals due to ISMN intolerance occurred, while five additional patients in the propranolol group had to be withdrawn (two heart failure, one bradycardia, one hypotension). However, there was a tendency for a higher mortality in the ISMN group, that achieved statistical significance in a subset of patients > 50 years of age. There was also a trend for a greater number of deaths due to liver failure in patients who remained compliant to ISMN therapy until the end of the study.

Nonselective beta-blockers plus nitrates

Only one published trial compares nadolol vs nadolol plus ISMN in the primary prophylaxis of variceal haemorrhage [27]. As shown in Table 35, the rate of side effects is higher in the combination group (26/72, 36%) than in the nadolol alone group (10/74, 14%) ($p = 0.002$). The adverse events in the combination group consisted of headache ($n = 16$, severe in 5), dizziness ($n = 6$), nightmares ($n = 1$) and unspecified in the rest. Withdrawal from the study due to adverse events also occurred in more patients in the combination group (8/72, 11%) than in the nadolol group (4/74 or 5%) however this difference is no longer significant.

One study compared the combination nadolol plus ISMN vs sclerotherapy in the secondary prophylaxis of variceal haemorrhage [31]. In this trial 7/43 (16%) patients in the medication group had adverse events, compared to 16/43 (37%) in the sclerotherapy group ($p = 0.03$). The adverse events in the medication group consisted of bradycardia ($n = 3$), weakness ($n = 3$), bronchospasm ($n = 1$) and impotence ($n = 1$). Nadolol had to be discontinued in four (9%) of the patients.

The discrepancies in the rate of adverse events in these two studies may be due to an under-reporting of headache in the second study. Results of as yet unpublished trials of combination therapy will settle whether this is accompanied by a higher rate of severe side effects in comparison to beta-blocker therapy alone.

Complications of endoscopic treatment (sclerotherapy and banding)

Endoscopic sclerotherapy

Early local complications associated with sclerotherapy are usually caused by technical errors. Pure mechanical perforation of the pharynx or oesophagus is uncommon using flexible endoscopes. Precipitation of massive bleeding by inadvertent laceration of a varix with the injection needle or penetration of the varix by the protective sheath of a flexible injection needle occasionally occurs and should be treated with additional sclerotherapy or balloon tamponade.

Aspiration pneumonia is more likely to occur in the setting of active haemorrhage. The overall incidence of x-ray defined pulmonary effects associated with sclerotherapy is as high as 85%; however, most patients have no meaningful clinical sequelae [32]. A study using nuclide scintigraphic techniques and intravariceal injections found that 60% of patients had embolization of injected sclerosant into the pulmonary circulation [33]. A cause and effect relationship between embolization of sclerosant and clinically significant pulmonary or systemic sequelae has not been proven.

Systemic effects of injected sclerosant include chest pain and fever lasting from 24 to 48 hours in up to 40% of patients. Post-sclerotherapy fever does not appear to be related to bacteremia, which may occur in up to 50% of patients [34, 35]. There is probably a greater risk for inducing bacterial peritonitis in patients with ascites when they are treated with sclerotherapy; however, the risk appears to be small.

Thrombotic complications associated with sclerotherapy include paralysis resulting from thrombosis of the anterior spinal artery and portal and mesenteric venous thrombosis [36]. These uncommon sequelae have been reported in small numbers.

Injection site ulceration is common and healing is slower in high-risk patients. Shallow ulcers are present in up to 100% of patients who have endoscopic re-examination of the oesophagus within 24 hours and up to 80% of those re-examined within 1 week [37,38]. Ulcers may result in secondary haemorrhage, which has been reported to occur in from 2 to 13% of patients [39]. Significant bleeding can occur if a deep ulceration occurs over a non-thrombosed varix or perforating vein.

Deep or full thickness ulcers may be associated with oesophageal stricture formation, a complication that occurs in from 10 to 25% of patients treated with multiple sclerotherapy sessions. Most sclerotherapy strictures respond to bougienage. Oesophageal wall necrosis and perforation may also result from deep sclerosant induced ulcers. Patients with advanced liver disease are more prone to this complication.

Sclerotherapy causes abnormalities in oesophageal primary peristaltic wave velocity, amplitude and in lower oesophageal sphincter pressures [40,41]. These changes are usually transient. In spite of the frequent occurrence of oesophageal stricture, sclerotherapy has little long-lasting adverse effect on oesophageal function.

Endoscopic variceal ligation (EVL)

Complications directly related to endoscopic ligation are uncommon. Ulceration is ubiquitous at ligated sites. These ulcers are shallower, have greater surface area, and heal faster than those caused by sclerosant injection [42].

Bleeding from ligation-induced ulceration probably accounts for less than 10% of recurrent bleeding episodes in patients treated with this method [43]. Most bleeding episodes from ligation induced ulcers are self-limited; however, significant haemorrhage, probably arising from ulcerations located over an oesophageal perforating vein or a nonthrombosed varix, can occur.

Web-like mucosal strictures are observed infrequently after multiple endoscopic ligation sessions. These can be treated with a single dilation. Transient acute obstruction of the oesophagus by boluses of ligated tissue has also been observed.

Bacteremia resulting from endoscopic ligation appears to be less common than after sclerotherapy and occurs in from 0 to 25% of patients [35]. The risk for bacteremia appears to be directly related to the severity of the liver disease. Patients with ascites may be at greater risk for bacterial peritonitis; however this has not been proven [44].

Portal hypertensive gastropathy (PHG) may be transiently worsened by endoscopic ligation as a result of decreased venous outflow from the stomach [45,46]. Most studies; however do not show any clinically apparent impact of this treatment on the appearance of PHG or subsequent bleeding events associated with PHG.

Like sclerotherapy, endoscopic ligation produces some transient effects on distal oesophageal function. Generally these effects are less pronounced than those caused by sclerotherapy and appear to have no long-term clinical significance [41,47]

The endoscopic overtube (now unnecessary as a result of the introduction of multiple-fire ligating devices) was the most common source of clinically significant endoscopic ligation related complications. These mishaps consisted of partial or complete oesophageal perforations or mucosal trauma causing bleeding. 'Pinching' of the oesophageal wall in the gap between the overtube and the endoscope when the latter is used as an obturator for introduction causes overtube trauma. The optimal solution is use of an oesophageal dilator, which completely fills the lumen of the overtube, as the obturator [48,49].

The overtube may also result in engorgement of distal oesophageal varices after passage of the overtube into the oesophagus. Withdrawal of the overtube until its distal end just protrudes through the cricopharyngeus into the oesophagus solves this problem.

Complications of TIPS

The use of the transjugular intrahepatic portosystemic shunt (TIPS) to obtain portal decompression in patients with complications of portal hypertension has become very popular in recent decades [50,51]. The widespread application and the increased experience in this procedure has led, as happens with most new techniques, to improved knowledge of the complications associated with TIPS.

Patients treated with TIPS may have complications related to the procedure itself, which occur during and/or shortly after TIPS placement, or, may present chronic complications, which generally occur later. Some of these complications are minor and probably underestimated because they resolve spontaneously and are not even recorded while others are very well known (i.e. shunt stenosis and hepatic encephalopathy) as they are rather frequent and may affect the efficiency of the shunt or the patients' quality of life.
Complications associated with TIPS implantation and their incidence are reported in Table 37. The overall rate of procedure related complications is 5–10%, while procedure-related mortality is 1–2% [52]. The greater risk for complications derives from the creation of the intraparenchymal connection. When the needle is advanced through the liver to puncture the portal vein it may injure portal, biliary and arterial structures causing intrahepatic haematoma or haemobilia. Capsular perforations may occur when the needle inadvertently reaches the extrahepatic portion of the portal vein. The risk of capsular perforation is increased by a smaller sized liver and by the presence of large amounts of ascites as both these factors alter the geometric relationship among the vessels inside the liver. However, even if it has been reported to be quite frequent, a capsular puncture spontaneously heals in most of cases and the overall risk of severe haemoperitoneum, which could be life-threatening for the patient, is considered low. Other factors influencing procedure related complications are the experience of the operator and the presence of severe coagulopathy or extremely low platelet count. Electrolyte abnormalities, prolonged hypotension, due to previous gastrointestinal bleeding, and/or preexisting cardiac pathologies may favour cardiac injury while nephrotoxicity, due to the contrast medium used during the angiographic procedure, may be enhanced in patients with refractory ascites.

The complications taking place after TIPS implantation are reported in Table 38. Shunt malfunctions, either caused by thrombotic occlusion or ste-

Table 37 Complications associated with TIPS placement.

Phase of the procedure	Complication	Percentage of cases
Initial venous puncture	Local haematoma	1–3%
	Accidental puncture of adjacent structures	1–3%
While the guidewire is advanced through the atrium	Cardiac dysrhythmias	1–4%
	Myocardial infarction	1–2%
	Injury to the right atrium and pericardial tamponade	<1%
During liver punctioning or balloon dilatation of the intrahepatic tract	Capsular perforation	35–40%
	Severe haemoperitoneum	1–2%
	Puncture of large bile ducts and haemobilia	2–5%
	Puncture of the hepatic artery and intrahepatic or subcapsular haematoma	2–7%
When TIPS is placed in the parenchymal tract	Dislodgement or rupture and migration of the stent	1–3%
	Acute thrombosis of the portal vein	3–6%
Twenty-four hours following the procedure	Nephrotoxicity causing acute renal failure	2–4%
	Fever within 24 hours	10–20%
	Sepsis and infection	4–10%

nosis due to intimal hyperplasia, have been reported with variable ranges (30–70% after 1 year and 47–83% after 2 years) [50,53–55]. Early malfunctions are generally due to thrombi inside the shunt and are related to technical problems when the stent is positioned or to bile leakage due to the sectioning of the biliary tract, or to activation of procoagulant factors. For this reason some authors propose the application of anticoagulant therapy during the first month after TIPS implantation [56].

Late shunt malfunctions are due to intimal hyperplasia inside the shunt or at the outflow hepatic vein. The pathogenesis of shunt stenosis is more complex because it involves platelet aggregation and endothelial injury causing

Table 38 Complications occurring after TIPS placement.

Shunt stenosis	33–66% at 1 year
Shunt thrombosis	5–15%
Hepatic encephalopathy	33–60%
Worsening of hepatic function	1–5%
Clinically relevant post-TIPS hemolysis	1–3%

the release of growth factors (PDGF and EGF) and other mediators which stimulate the proliferation of smooth muscle cells and collagen deposition. This process is intended to repair and re-endothelize the newly created vascular shunt but this leads to hyperplasia and shunt stenosis if the tissue continues to proliferate. Different mechanisms may take place in the pseudointimal hyperplasia inside the shunt, where hepatic sinusoidal cells are involved as shown by the elegant studies by Sanyal and coworkers [57,58], and the intimal hyperplasia occurring at the outflow hepatic vein, which seems to be triggered by the increased flow rate and turbulence of blood coming from the shunt.

Due to the high incidence of shunt stenosis, the monitoring and follow up of patients is very important for their management. When diagnosed, shunt malfunctions can be corrected by angiography in 90–98% of cases [53]. Almost all episodes of variceal rebleeding are caused by shunt malfunctions and recurrence of portal hypertension [50,53,59–64]. On the other hand, from controlled studies which used routine portography, we know that shunt malfunctions do not always cause rebleeding or ascites recurrence [50,53,59–62]. This observation may raise the question of whether therapeutic intervention is always needed in asymptomatic patients.

The pathogenesis of hepatic encephalopathy (HE) after TIPS is probably not different from that observed in patients treated with surgical porto-systemic shunts and is mainly caused by the portal flow diversion from the liver through the new shunt. Hepatic encephalopathy (HE) is a common complication after TIPS. In six different large uncontrolled studies reporting over 450 patients the rate of post-TIPS hepatic encephalopathy was between 23 and 45% [50,55,65–68] This wide range is probably related to the different methods used to evaluate HE and/or the criteria of definition applied. Similar numbers have been reported in randomized controlled studies comparing TIPS vs endoscopic therapies in the treatment of variceal bleeding [59–64]. However, these studies showed that when the enrolled patients presented a severe degree of liver disease (Child C), HE was also attributable to liver failure itself as occurred in 7–26% of patients treated with endoscopic sclerotherapy. All studies agree that episodes of HE are more frequent in the first months after a TIPS procedure, and in most cases medical treatment is efficacious to reverse the alterations in mental state. In time, these episodes may attenuate in severity and eventually completely disappear. It has been proposed that this may depend on the progressive narrowing of the shunt. Only a few patients (3–5%) experience a chronic impairment in their mental state after TIPS and some cases require a reduction in stent diameter [69]. Patients who are at higher risk to develop HE after TIPS procedure are those who have experienced previous episodes of hepatic encephalopathy, older patients (> 65 years) and those with severe liver insufficiency (Child Class C) [55,65–68]. In addition, the creation of a low porto-systemic gradient (< 10 mmHg) after the shunt may increase the incidence of HE [66].

Following TIPS, careful exploration may show signs of haemolytic anaemia in approximately 10% of patients [70]. This syndrome is recognized by the development of *de novo* haemolysis in the first weeks after TIPS implantation. Haemolysis is diagnosed according to the traditional stigmata: reduction in haemoglobin values not attributable to other causes, reticulocytosis and an increase in unconjugated bilirubin and decreased haptoglobin levels. No other causes of haemolysis are evidenced.

TIPS-associated haemolysis is asymptomatic in most cases but few patients experience a clinically relevant anaemia and may need blood transfusion [69,70]. The pathogenesis is likely to be related to red cell injury caused directly by the stent or indirectly by the accelerated flux in the shunt. Haemolysis may subside spontaneously after some weeks.

RESULTS OF THE QUESTIONNAIRE ON COMPLICATIONS OF TREATMENT OF PORTAL HYPERTENSION

Pharmacological treatment of acute variceal haemorrhage

1 The drugs used for the pharmacological treatment of acute variceal haemorrhage are: terlipressin, somatostatin and octreotide. Vasopressin is, at present, not recommended.

2 Terlipressin produces serious side effects in only 5% of the cases. These side effects include: abdominal cramps, diarrhoea, bradycardia, arterial hypotension, arrhythmia, angina, headache, facial pallor, ischaemic colitis, bronchial constriction and peripheral vasoconstriction.

3 Somatostatin and octreotide are reported to have side effects in only 4% of the patients. In all the studies reported the incidence of side effects with somatostatin and octreotide was lower than that found with the use of terlipressin. The side effects observed in patients receiving octreotide were: dizziness, fatigue, headache, diarrhoea, abdominal pain, bradycardia, arrhythmias, blurred vision and nausea. The side effects observed with somatostatin were: bradycardia, arterial hypertension, hyperglycemia, diarrhoea, fever, chest pain and flushing.

Use of beta-blockers in the primary and secondary prophylaxis of variceal bleeding in patients without contraindications

1 The overall median percentage of the side effects of beta-blockers is 15%. The most frequent side effects being fatigue, bradycardia and hypotension, shortness of breath and impotence.

2 Beta-blockers should be discontinued in about 10% of the cases because of side effects.
3 The incidence of portal thrombosis using beta-blockers is about 5%. Consequently the use of beta-blockers does not favour portal thrombosis.

Endoscopic techniques

1 The most frequent complications of sclerotherapy are oesophageal ulcers, oesophageal stricture and bleeding oesophageal ulcers. Other complications include dysphagia and fever, chest pain and pleural effusion.
2 Banding ligation does not increase the incidence of side effects.
3 There is no consensus on the use of antibiotic prophylaxis to prevent bacteremia in patients submitted to endoscopic therapy (21% positive using clindamycin plus gentamycin, ampicillin). Antibiotic therapy with quinolones should be used only in acute bleeding (11%).
4 Sixty-eight per cent do not favour the use of antibiotic prophylaxis.
5 There is no consensus on the prophylaxis of ulcers induced by sclerotherapy: 37% consider that oesophageal ulcers should be treated with omeprazole (20 mg/day) and 63% that prophylaxis of ulcers is not necessary.
6 The most frequent complications of banding ligation are bleeding from oesophageal ulcers, nonbleeding oesophageal ulcers, and dysphagia. Other complications are chest pain, fever, oesophageal stricture, and overtube-related complications.
7 There is no consensus in the acceptance that sclerotherapy may induce portal thrombosis: 30% consider that there is a risk for developing portal thrombosis and 65% consider that there is no risk.
8 There is no consensus as whether sclerotherapy favours portohypertensive gastropathy (PGH): 50% consider that sclerotherapy may favour PHG while 35% consider that it does not.
9 There is no consensus as to whether the multibanding device reduces the side effects of banding ligation: 53% consider that it does while 47% do not think so.

Transjugular intrahepatic portosystemic shunt (TIPS)

1 The most frequent complications of TIPS are hepatic encephalopathy and TIPS dysfunction. Other complications include sepsis, haemoperitoneum and biliary puncture.
2 The incidence of post-TIPS encephalopathy is about 30%.
3 TIPS dysfunction is very common, being about 50% at one year of follow-up. There is no consensus to establish therapy to prevent TIPS dysfunction:

32% use heparin, 63% do not give therapy and only 5% use treatment in patients with Budd–Chiari syndrome.

4 The most commonly used technique to assess TIPS dysfunction is Doppler ultrasonography (US) in 65%. Other techniques are Doppler US plus endoscopy (18%), Doppler US plus clinical criteria in 12% and portal pressure measurements in 5%.

5 Angiography is the technique used to confirm TIPS dysfunction by 38% and angiography plus portal pressure is performed in 38%. Portal pressure measurement alone is performed in 24%.

6 The incidence of technical complications during TIPS is about 5%. These technical complications include haemoperitoneum and arterial lesion.

7 There is no consensus as to the usefulness of US during the TIPS procedure. 50% of the investigations use US and 50% do not.

8 The incidence of technique-related mortality is about 1%.

9 The most frequent technical complications of TIPS are: haemoperitoneum, biliary puncture, stent migration, technical failure, jugular haematoma, capsule puncture, acute TIPS thrombosis, and liver haematoma, portal vein thrombosis and cardiopulmonary complications.

10 TIPS in noncandidate patients for liver transplantation is used in about 10%.

11 There is no consensus as to whether TIPS hinders liver transplantation. 47% consider TIPS hinders this procedure, while 53% do not believe so.

12 It is considered that in only 3.5% of the patients liver transplantation is difficult because of TIPS.

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Baveno III Consensus Statements: Complications of Treatment for Portal Hypertension

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DEFINITIONS OF COMPLICATIONS OF PHARMACOLOGICAL TREATMENTS

1 *Fatigue*: inability to perform regular physical activities carried out before treatment.
2 *Abdominal cramps*: abdominal pain starting after treatment that persists for more than 4 hours after other major causes of abdominal pain (i.e. bacterial peritonitis) have been ruled out.
3 *Severe bradycardia*: reduction of heart rate to a value below 50 b.p.m. during treatment, in the presence of symptoms.
4 *Arterial hypertension*: systolic blood pressure > 170 mmHg and/or diastolic blood pressure > 95 mmHg during treatment in a nonhypertensive patient.
5 *Arterial hypotension*: reduction in mean arterial pressure of 25% or greater with respect to baseline values with a final value of < 70 mmHg.
6 *Headache*: appearance of headache or worsening of pre-existing headache not responsive to usual analgesic drugs.

DEFINITIONS OF COMPLICATIONS OF ENDOSCOPIC TREATMENT

1 *Oesophageal ulcers*: large, confluent oesophageal ulcers two weeks or more after the last session of endoscopic treatment in the presence of symptoms.
2 *Bleeding from oesophageal ulcers*: upper GI bleeding with one of the following:
   (a) active bleeding at the ulcer site
   (b) adherent clot at the ulcer site
   (c) absence of other potentially bleeding lesions in the upper GI endoscopy.
3 *Dysphagia*: one week or more after treatment.
4 *Oesophageal stricture*: persistent narrowing of the oesophageal lumen, as diagnosed by oesophagogram or endoscopy, associated with dysphagia two weeks or more after treatment.
5 *Chest pain*: noncardiac chest pain requiring analgesics after treatment persisting for more than 48 hours.

DEFINITIONS OF COMPLICATIONS OF TIPS

1 *TIPS dysfunction*: there was agreement on the use of angiography and/or pressure measurement when there are clinical signs of TIPS dysfunction, such as reappearance of oesophageal varices or ascites. There was no agreement on whether or not TIPS dysfunction should be assessed in patients not developing oesophageal varices or ascites and which technique should be used.

2 *Hepatic encephalopathy post-TIPS*: in patients *without* hepatic encephalopathy before TIPS—the development of clinical episodes of encephalopathy. In patients *with* hepatic encephalopathy before TIPS—an increase in the frequency and/or intensity of episodes of encephalopathy.

LECTURE

Quality of Randomized Clinical Trials in Portal Hypertension and Other Fields of Hepatology

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INTRODUCTION

Quality of randomized clinical trials (RCTs) is difficult to define [1]. However, if one looks at quality from the point of view of patients, physicians, researchers, health care providers and societies, it should be possible to obtain a standard or a set of standards by which we can define and measure quality. In fact, what we all need is dependable information based on valid and exhaustive evidence. Further, this information ought to be presented in a clear and understandable manner.

The validity of RCTs may be divided into internal validity and external validity [2,3]. Internal validity deals with the following questions: is the presented information based on unbiased research results using the right design to answer the question and is the sample size large enough to reduce errors of type I and type II [2,3]? External validity deals with the question: can we as physicians use the information in the handling of our next patient with the disease or condition in question? Without internal validity, it is meaningless to consider external validity. During recent years it has been found that the degree of internal validity may be measured by components of methodological quality or composite scores reflecting the methodological quality [4–6].

We also want the information in reports of RCTs to be exhaustive. Reading a report on a RCT, we will, of course, evaluate the efficacy of the intervention based on the main outcome measures (e.g. mortality or bleeding). We will, however, also like to know of other consequences of the intervention, such as which specific patient groups the intervention works best for, the risk of adverse events and the impact on quality of life and health economics [7].

There are other aspects of the term 'quality' that may be of interest, such as the novelty of the topic addressed in a RCT, the relevance of the question addressed, the appropriateness of the statistical analyses, etc. [1]. This chapter, however, describes the methodological quality of the design and the reporting of hepato-biliary RCTs—focusing on RCTs within portal hypertension. We will examine whether the methodological quality of RCTs has improved

since the 1980s. Lastly, we will try to answer the provocative question: have the previous consensus workshops [8,9] within portal hypertension had any notable influence on the methodological quality of portal hypertension RCTs?

THE IMPORTANCE OF METHODOLOGICAL QUALITY IN RANDOMIZED CLINICAL TRIALS

The methodological quality of RCTs is here defined as the confidence that the design, conduct, and report of a RCT will restrict bias in the intervention comparison [11]. Methodological quality may be measured by separate components or by combining a number of components into composite scales.

Quality is a complicated and abstract construct and very difficult to appraise. A number of components and scales have been developed for the assessment of the methodological quality of RCTs [12]. Unfortunately, methods for quality assessment differ in purpose, scope, and coverage. No consensus seems to exist regarding which methods are the most reliable. If the efforts to assess the methodological quality of RCTs are to be founded on a sound scientific basis, then the methods used for this assessment must be both reproducible and valid. The issue has been dealt with within quality of life assessments and psychology. Researchers dealing with these issues have developed a set of guidelines for the use of tools to assess abstract and complex constructs such as quality. These psychometrical techniques include scale development and validation procedures [13,14]. Only few scales to assess the quality of RCTs have been developed or validated by these techniques [12, 15].

Quality components

Adequate generation of allocation sequence and adequate allocation concealment are prerequisites for the creation of a trial without selection bias. Adequate double blinding and follow-up of all patients are essential to avoid information bias. Adequate bias control in RCTs is important because it will secure dependable results.

Previous studies have examined the importance of methodological quality to the estimate of intervention efficacy in published RCTs [4,5,16]. The evidence indicate that RCTs with inadequate or unclear allocation concealment exaggerate intervention benefits significantly as compared to RCTs with adequately performed and reported allocation concealment [4,5]. One study also found that RCTs without adequate double-blinding lead to significantly exaggerated intervention benefits compared to double-blind RCTs [4], but a later study was unable to confirm these findings [5]. Surprisingly, none of these studies were able to demonstrate any association between biased

estimates of intervention efficacy and adequate generation of allocation sequence [4,5,16].

One major difficulty, not addressed in previous studies on the quality assessment of RCTs is the lack of a comparative 'gold-standard'. Which trials can be considered to reflect the true estimate of intervention efficacy?

To address these uncertainties, we have completed a study in which the results of very large RCTs including at least 1000 participants were used to obtain a comparative standard [6]. The reasons for this approach were that very large RCTs have a reduced risk of random error. Accordingly, large RCTs have a minimal risk of type I and type II error [2]. Furthermore, large RCTs are generally designed and conducted rigorously, i.e. with a high methodological quality. We based our analyses on the reports of 190 RCTs included in 14 meta-analyses from various medical fields [6]. The methodological quality of the included RCTs was assessed by components and a composite five-point scale developed by Jadad *et al.* [17] (Table 39).

There were 23 large RCTs and 167 small RCTs in the 14 meta-analyses, which could be assessed [6]. The median number of participants was 1741 (interquartile range 1290–4396) in the large RCTs and 165 (interquartile range 87–316) in the small RCTs. Based on an evaluation of the individual RCTs by the Jadad scale, 89% of the large RCTs were high quality RCTs (i.e. > 2 points) and 64% of the small RCTs were high quality RCTs. The median number of participants in the small RCTs of low and high quality were not significantly different (158 versus 171 participants, $p = 0.72$).

Table 39 Components and 5-point scale [17] used to assess the methodological quality of randomized clinical trials.

	Adequate	Inadequate
Generation of allocation sequence	Computer generated random numbers or similar (2 points)	Not described (1 point)
Allocation concealment*	Central randomization, sealed envelopes or similar	Not described or inadequate (by an open table or similar)
Double-blinding	Identical placebo tablets or similar (2 points)	Inadequate (e.g. tablets versus injection) or not described (1 point)
		No double-blinding (0 points)
Withdrawals and dropouts	The numbers and reasons were described (1 point)	The numbers and reasons were not described (0 points)

* Allocation concealment was not included in the scale [17], because of the low frequency of endorsement.

Components

Our analyses showed that the estimate of intervention efficacy obtained in small RCTs with adequate generation of the allocation sequence, adequate allocation concealment, and double-blinding were not significantly different compared with the intervention efficacy of the large RCTs [6].

However, the estimated intervention benefit obtained in the small RCTs with inadequate generation of allocation sequence was significantly different compared with the large RCTs (relative odds ratio (ROR) = 0.46 (95% confidence interval CI 0.28–0.78); $p = 0.002$). This corresponds to an exaggerated estimate of intervention efficacy by 54% in small RCTs with inadequate generation of allocation sequence. Compared with the large RCTs, intervention efficacy was exaggerated by 51% in small RCTs with inadequate allocation concealment (ROR = 0.49 (95% CI 0.29–0.80); $p = 0.005$), and by 48% in small RCTs with inadequate or no double blinding (ROR = 0.52 (95% CI 0.31–0.86); $p = 0.01$). In accordance with previous findings, we were unable to demonstrate any significant association between estimates of intervention efficacy and the description of dropouts and withdrawals.

Quality scales

The use of composite quality scales has been debated. A previous study indicates that the use of summary scores to identify trials of high quality has been regarded problematic and it has been suggested that relevant methodological aspects should only be assessed as separate components [18]. However, this contention is debatable. Most scales are not developed according to an established technique and very few are adequately validated. This means that the outcome of such scales will be unpredictable and variable as demonstrated in the study by Jüni *et al.* [18]. On the other hand, if a scale is developed and validated according to established psychometric techniques, it is possible that the measure can be both reliable and valid. Accordingly, both the use of components and scales may be employed [15]. As mentioned, the major difficulty to the assessment of the methodological quality of RCTs is the lack of an external gold standard. The two main questions are (a) what is being measured by the scale and (b) what is the relationship between the measurement and the purported reasons for the findings, i.e. does the scale assess the methodological quality and does methodological quality reflect the risk of bias in intervention comparisons?

We searched MEDLINE and reference lists of relevant articles for a quality scale developed and validated according to established psychometric methods [11,13,14]. We identified a five-point scale, which fulfilled these criteria [17] (Table 39). A previous study has demonstrated that RCTs scoring 1 or 2 points

on this scale exaggerate intervention efficacy significantly compared to RCTs scoring 3, 4 or 5 points [5].

In accordance with these results we found that the estimated intervention effect obtained in large RCTs and small RCTs with a low quality score (≤ 2 points) was significantly different (ROR = 0.52 (95% CI 0.31–0.86); $p = 0.01$) [6]. This corresponds to an increased estimate of intervention efficacy of 48% by small, low quality RCTs. The estimated intervention effect obtained in large RCTs and small RCTs with a high quality score (> 2 points) did not differ significantly [6].

METHODOLOGICAL QUALITY OF HEPATO-BILIARY RANDOMIZED CLINICAL TRIALS

In order to identify and quality assess hepato-biliary RCTs, we have performed handsearches and electronic searches for RCTs published in three journals *Liver*, *Journal of Hepatology*, and *Hepatology* [11,19,20]. An assessment of the methodological quality of the published RCTs demonstrated ample room for improvement [11,19,20] (Table 40).

Guidelines for good clinical research practice were introduced during the 1970s and 1980s. However, we were unable to demonstrate any substantial improvement in the methodological quality of hepato-biliary RCTs during the last 20 years [11,20,21].

The risks of both type I and type II error increase when a small number of patients are randomized [2]. Hepato-biliary RCTs seldom (7–26% depending on the journal) report sample size estimation (Table 41). Further, the median number of patients randomized in hepato-biliary RCTs is only about 40 patients (Table 41). Accordingly, a significant number of hepato-biliary RCTs are designed with a significant risk of finding false positive effects (due to skewed distribution of prognostic factors) and of overlooking significant intervention benefits (Table 41). There were no signs of an increasing number of patients being randomized with time [11,19,20].

Table 40 Number of randomized clinical trials (RCTs) and the proportion of RCTs with adequate generation of allocation sequence, allocation concealment, and double-blinding in three hepato-biliary journals [11,19,20].

	Liver	*Journal of Hepatology*	*Hepatology*
Number of RCTs	32	171	235
Adequate generation of allocation sequence	21%	28%	52%
Adequate allocation concealment	5%	13%	34%
Adequate double-blinding	28	30	34%

Table 41 Number of randomized clinical trials (RCTs), the proportion of RCTs reporting sample size calculations and number of patients per intervention arm in three hepatobiliary journals [11,19,20].

	Liver	*Journal of Hepatology*	*Hepatology*
Number of RCTs	32	171	235
Sample size calculations	7%	19%	26%
Number of patients per intervention arm			
Median	18	19	26
Interquartile range	10–36	11–31	14–44
Range	2–169	5–519	3–542

METHODOLOGICAL QUALITY OF PORTAL HYPERTENSION RANDOMIZED CLINICAL TRIALS

From the first year of publication in 1981 until August 1998, 235 RCTs were published in *Hepatology* [11]. This number made it possible for us to perform an analysis of the methodological quality and aspects possibly associated with high methodological quality.

The median quality score (Table 39) [17] of the 235 RCTs was 3 points (interquartile range 2–4 points), 41 RCTs scored 5 points (17.4%) and 27 RCTs scored 1 point (11.5%). Adequate allocation concealment was described in 80 RCTs (34.0%), of which 28 RCTs (35.0%) employed central randomisation and 52 RCTs (65.0%) sealed envelopes.

Our analyses showed that multicentre RCTs obtained significantly higher quality scores compared to single centre RCTs (OR = 3.4 (95% CI 1.3–8.9); $p = 0.01$). RCTs with external funding by profit and/or nonprofit organisations obtained significantly higher quality scores compared with RCTs without external funding (OR = 4.2 (95% CI 2.1–8.6); $p = 0.0001$). The methodological quality of RCTs funded by profit and nonprofit organisations did not differ significantly.

We also explored the association between methodological quality and the therapeutic area of the RCTs. All RCTs were classed within one of five therapeutic areas (miscellaneous, alcoholic liver disease, hepatitis, gallstones, portal hypertension, and primary biliary cirrhosis). The group consisting of portal hypertension RCTs dealt with varices, gastropathy, ascites, or hepatic encephalopathy. A multivariate logistic regression analysis was performed in order to adjust for the possible predictors of quality (i.e. the number of clinical sites, funding, year of publication, and country of origin). The analysis showed that the therapeutic area was a significant predictor of methodological quality and that the proportion of high quality RCTs was significantly higher in portal

hypertension compared to RCTs classed as miscellaneous (OR = 2.42 (95% CI 1.06–5.52); $p = 0.03$).

However, the assignment of therapeutic areas into groups was arbitrary. The observation could be a chance finding and RCTs within primary biliary cirrhosis actually demonstrated a higher odds ratio for high quality. Accordingly, we decided to expand our analyses by assembling a larger sample of hepato-biliary RCTs. We combined electronic and hand searches of 11 journals, including *Liver*, *Journal of Hepatology*, *Hepatology* and other journals likely to publish hepato-biliary RCTs in order to identify all hepato-biliary RCTs published in these 11 journals between 1985–1996 [22]. We excluded trials that were quasirandomized, published as abstracts or referred to previous articles for an account of the study design. In total, 530 RCTs were included.

Therapeutic areas with less than 10 RCTs were grouped as miscellaneous. The methodological quality of all RCTs were assessed by separate components and the Jadad scale [17] (Table 39). The association between the therapeutic area and methodological quality was analysed by multiple logistic regression analysis adjusting for the year of publication, statistical significance of the primary study outcome, funding and the number of clinical sites.

The analysis showed that the therapeutic area was a significant predictor of the proportion of RCTs with adequate generation of allocation sequence ($p < 0.001$), adequate allocation concealment ($p < 0.001$), double-blinding ($p < 0.001$) and the proportion of high-quality trials ($p < 0.001$). The proportion of high-quality RCTs was 72% (98 of 136 RCTs) in portal hypertension, whereas the proportion of high quality trials was only 27% in fulminant hepatic failure RCTs, 60% in miscellaneous RCTs, but 90% in noncalcolous cholestasis RCTs [22].

The median number of patients randomized per intervention arm in all 530 RCTs was 22 (interquartile range 12–42; range 3–2294). The association between the therapeutic area and the number of patients per intervention arm was not significant when analysed by univariate analysis of variance with or without adjustments for the year of publication, statistical significance of the primary study outcome, funding, and number of clinical sites [22].

Table 42 shows the proportions with adequate methodological quality of the 136 portal hypertension RCTs compared to the 35 RCTs on miscellaneous hepato-biliary diseases [22]. The group of miscellaneous RCTs was chosen as the comparison group, as the miscellaneous RCT group had a proportion of high quality RCTs (60%) close to the mean of all 530 hepato-biliary RCTs evaluated [22]. The portal hypertension RCTs had significantly more often described adequate generation of allocation sequence than the miscellaneous RCTs (Table 42). However, the two groups of RCTs did not differ significantly regarding the proportion of RCTs with adequate allocation concealment, ad-

Table 42 Proportion of portal hypertension and miscellaneous hepato-biliary randomized clinical trials (RCTs) with adequate methodology [22].

	Portal hypertension (n = 136 RCTs)	Miscellaneous (n = 35 RCTs)
Adequate generation of allocation sequence	94 (69.1%)	14 (40.0%)*
Adequate allocation concealment	63 (46.3%)	10 (28.6%)†
Adequate allocation concealment by a central independent unit	12 (8.8%)	6 (17.1%)†
Adequate double-blinding	41 (30.1%)	12 (34.3%)†

* $p = 0.001$
† no significant difference

equate allocation concealment using a central, independent unit, or adequate double-blinding. The two groups of RCTs did not differ significantly regarding funding and number of single centre trials (data not shown).

OTHER QUALITY ASPECT OF PORTAL HYPERTENSION RANDOMIZED CLINICAL TRIALS

In the following, we will address three other quality aspects (stratified randomization, quality of life and health economics) of the 136 portal hypertension RCTs and compare the results with those of the 35 RCTs dealing with miscellaneous hepato-biliary topics [22].

Stratified randomization

The principle of randomization implies that known and unknown prognostic factors are equally distributed to the intervention groups. In order to ensure equal distribution of known prognostic factors, stratified randomization may be employed either by random permuted blocks within strata or by minimization [2]. There are three main reasons for not using stratified randomization: (a) if the RCT is very large (e.g. $n > 500$ participants); (b) if the organizational resources of the randomization are limited; (c) if there is uncertainty about the known prognostic factors [2].

Most portal hypertension RCTs are small, have the possibility of attaining the appropriate organization for performing the stratified randomization, and factors significantly influencing prognosis are known (e.g. portal pressure, variceal size, ascites, hepatic encephalopathy).

Of the 136 identified portal hypertension RCTs published from 1985 through 1995 [22], only 23 (16.9%) RCTs used stratified randomization compared to four RCTs (11.1%) of the 35 miscellaneous RCTs (Table 43). The

Table 43 Proportion of portal hypertension and miscellaneous hepato-biliary randomized clinical trials (RCTs) using stratified randomization and reporting quality of life and health economic measures [22].

	Portal hypertension (n = 136 RCTs)	Miscellaneous (n = 35 RCTs)
Stratified randomization	23 (16.9%)	4 (11.4%)*
Quality of life	1 (0.7%)	0 (0%)*
Health economics	3 (2.2%)	1 (2.8%)*

* No significant difference

proportion of portal hypertension RCTs using stratified randomization decreased from 22.2% during 1985–1990 to 13.6% during 1991–1996. The proportion of miscellaneous hepato-biliary RCTs reporting stratified randomization increased from 6.3% during 1985–1990 to 15.0% during 1991–1996.

Quality of life

Focus has increasingly centred upon patients' quality of life. However, the term has often been used without a clear definition [23–25].

Quality of life may be examined by generic measures (such as the short form health survey SF-36 [26]), which assess physical, mental and social health. Generic measures can be supplemented by disease specific measures or they may be used independently [27]. Other measures focus on a single aspect, such as mental health functioning, e.g. in patients with hepatic encephalopathy, or use of individualized measures, in which the patients themselves define the most important aspect or aspects of their quality of life [28].

The difficulties in defining quality of life measures are witnessed by the plethora of measurements developed over the time [29]. In spite of this diversity, several well functioning and validated generic quality of life measures have been developed [29]. Concurrent with this development, quality of life has become an increasingly reported outcome measure in RCTs during the recent years [30]. By searching The Cochrane Controlled Trials Register from 1980 to 1997 on the Cochrane Library [31] (which represents the largest collection of trials in the world), Sanders *et al.* [30] observed an increase in the proportion of trials reporting on quality of life from 0.6% in 1980 to 4.2% in 1997. This may be seen as a positive development. However, they also demonstrated that the reporting quality was often poor. Based on an evaluation of 67 selected full reports of trials, 71.1% used at least one established quality of life instrument, but 22.3% used instruments or indicators developed for the study. Second, response rates for quality of life was only given in 56.7% of

the trials, with response rates ranging from 51 to 100%. Response rates are critical as differential nonresponse can introduce bias. Third, in 46 reports (68.7%) the patients provided information on quality of life, whereas the remaining articles were unclear to what extent the information originated from patients, carers, or relatives. This is important, as only patients can make a valid assessment of their quality of life [32]. Finally, complete reporting of all items and scales occurred only in 46.3% of the trials. Selective reporting of favourable or statistically significant results may thus have occurred [30].

In the sample of portal hypertension RCTs [22], only one RCT reported quality of life (see below) corresponding to a proportion of 0.7%. This is not significantly better than the absence of quality of life reports in the 1985 through 1995 miscellaneous hepato-biliary RCT sample (Table 43). However, it is less than the reported proportion of cancer trials reporting on quality of life in 1997 of 8.2% [30].

The only portal hypertension RCT reporting on quality of life by Orloff *et al.* [33] compared emergency portacaval shunt versus emergency medical therapy (intravenous vasopressin and oesophageal balloon tamponade) followed by elective portacaval shunt. The quality of life measures used by Orloff *et al.* were confined to 'length of hospital stay, presence of hepatic encephalopathy, and abstention from alcohol'. It is debatable if these outcomes can be considered quality of life.

Health economics

Regardless of the health care system, there is a need for reliable information on the costs of clinical interventions [34]. However, economic analyses currently available are often incomplete or fail to provide relevant cost information to practitioners. In addition to provide evidence about major outcome variables, RCTs can serve as reliable sources on cost information [35]. RCTs in which cost measures (direct costs, indirect costs, cost-benefit analyses, cost-effectiveness analyses and cost-utility analyses [29,36] are built into the trial are likely to estimate more precisely costs than trials where measuring costs is an afterthought.

Adams *et al.* [37] assessed the prevalence and completeness of economic analyses in RCTs from all fields of medicine published during 1966–1988. Only 121 of over 50 000 RCTs identified in MEDLINE (0.2%) included economic analyses. There were several deficiencies among the economic analyses, including improper allocation of overhead costs, absence of sensitivity analyses and the fact that only about 28% of the analyses included some form of aggregation of treatment costs and consequences. However, Adams *et al.* [37] noted a significant correlation between an economic completeness score and later date of publication ($r = 0.28$; $p < 0.05$).

Comparing the proportion of RCTs from portal hypertension versus miscellaneous hepato-biliary RCTs [22] reporting health economics demonstrated no significant difference (2.2% versus 2.8%) (Table 43). During the 1985–1990 period, 1.8% of portal hypertension RCTs reported health economics and this figure increased to 2.5% during the 1991–1996 period. These figures should be compared with 0% reporting health economics among the miscellaneous RCT group from 1985–1990 and 5.0% among the miscellaneous RCT group published during 1991 through 1995.

Although it may seem as if portal hypertension and miscellaneous hepato-biliary RCTs have a higher proportion of health economic evaluations than RCTs published within all fields of medicine, one should note that we do not have comparative data from the same time period. Other fields of medicine may also have seen a similar increase as observed within hepatology.

Trying to assess the completeness of the health economic evaluations presented during the 1985 through 1995 period within portal hypertension and miscellaneous hepato-biliary RCTs some room for improvement seemed available. It was not possible to evaluate from where the figures for expenses were derived in all cases and some analyses only considered intervention costs [38–41].

Although cost-effectiveness analyses and other health economic analyses do not reflect every element of importance in health care decisions, the information they provide is critical to informing decisions about allocation of scarce health care resources [42]. A panel on cost-effectiveness in health and disease [43, 44] has developed methodological recommendations, which address

- components belonging to the numerator and denominator of a cost-effectiveness ratio;
- measuring resource use in the numerator of the ratio;
- valuing health consequences in the denominator of the ratio;
- estimating effectiveness of interventions;
- incorporating time preferences and discounting; and
- handling of uncertainty.

If researchers follow standard methods in cost-effectiveness analyses and other health economic analyses, the quality and comparability of studies as well as their utility can be improved.

DISCUSSION AND CONCLUSIONS

In this review, we have demonstrated that the low methodological quality of RCTs—assessed either by components or a scale—is significantly associated with an over-estimation of intervention efficacy in various fields of medicine. Further, the methodological quality problems seem to stick to RCTs irrespec-

tive of the field of medicine the RCT originates from. In this sense, hepato-biliary RCTs are no exception. We have not presented data demonstrating that hepato-biliary RCTs of low methodological quality overestimate intervention efficacy. On the other hand, we have no evidence demonstrating that this is not the case. In fact, we do not see why this dangerous association between low methodological quality and overestimation of intervention efficacy should not exist within the hepato-biliary field.

Hepato-biliary RCTs differ significantly regarding methodological quality. Multicentre RCTs and RCTs with external funding seem to achieve the highest methodological quality. Although portal hypertension is a field in which many RCTs have been performed [45] and in which many workshops on how to conduct RCTs have been held, portal hypertension RCTs still have room for improvement. The impact of the previous workshops has at best been small, although the potential impact of the Baveno II workshop [10] cannot yet be assessed.

Portal hypertension RCTs also suffer from inadequate sample sizes and infrequent use of stratified randomization. Further, quality of life and health economics are seldom reported—and when reported it does not seem to be with sufficient detail. In patients with cardiovascular diseases, it has been calculated that the sample size needed for RCTs employing years of healthy life as primary outcome measure is in fact less than RCTs using survival as the primary outcome measure [46]. This may also be true for portal hypertension and other hepato-biliary diseases.

In conclusion, portal hypertension RCTs still need improvement [7]. Such improvement can be obtained by expanding the collaborative efforts so that more trials are conducted as multicentre RCTs. Organizations that can assist in the conduct of multicentre RCTs have been established, such as The Copenhagen Trial Unit [47]. Until large hepato-biliary RCTs are being conducted, we have to rely on meta-analyses preferably conducted as systematic reviews [48,49]. The combined efforts could lead to a more rapid development of better and more evidence based interventions, which can help our patients.

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SESSION 9

Methodology of Future Trials: Prognostic Stratification, Health-Related Quality of Life and Health Economics

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INTRODUCTION

In this chapter, we address three important aspects of the methodology of randomized clinical trials (RCTs) in portal hypertension—prognostic stratification, health-related quality of life (HRQOL) and health economics, all of which have been only briefly dealt with in previous consensus conferences [1–3], and in which the experience so far is very limited. However, there is a growing recognition of the need to take these aspects into account in order to further improve the evidence for sound clinical practice in the field of portal hypertension as in other fields [4].

In the first section, the current experiences in the field, standards and recommendations are presented, the latter being based on the International Conference on Harmonization—Guidance on Statistical Principles for Clinical trials [5]. The principles of stratified randomization are presented in this section, and the following section deals with prognostic stratification in analysis of the data from portal hypertension RCTs with emphasis on the aim of identifying differential treatment effects [6]. The last two sections address principles, methods, problems and limitations of assessment of HRQOL and health economics.

Current experiences, standards, and recommendations

Christian N. Gluud

Portal hypertension RCTs are very small with a median inclusion of only about 44 patients [7,8]. Hence, they are subject to both type I and type II errors [9]. The use of stratified randomization as well as HRQOL and health economic assessments are very infrequent in portal hypertension RCTs [10].

STRATIFIED RANDOMIZATION

In any RCT it is desirable that the intervention groups are as similar as possible at inclusion with regard to relevant patient characteristics. To ensure such comparability, stratified randomization may be employed either through the use of random permuted blocks within strata or minimization (dynamic randomization) [5,9]. There are three main reasons for *not* using stratification: (a) if the RCT is very large (e.g. $n > 500$ patients); (b) if the organizational resources for carrying out the randomization are limited; (c) if there is uncertainty about which patient characteristics might influence prognosis [9]. Portal hypertension RCTs are mostly very small, they may easily get an appropriate organization to perform the stratified randomization or minimization for each RCT [11], and factors significantly influencing prognosis are known.

The proportion of portal hypertension RCTs employing stratified randomization decreased from 22% during 1985–1990 to 14% during 1991–1996 [10].

The International Conference on Harmonisation—Guidance on Statistical Principles for Clinical Trials [5] recommends that stratified randomization is carried out in order to increase the comparability of the intervention groups.

Accordingly, increased use of stratified randomization can be recommended for future portal hypertension RCTs unless they are planned to be very large.

HEALTH-RELATED QUALITY OF LIFE

HRQOL measures have been hard to define, which is witnessed by the plethora of instruments developed over time [12]. In spite of this diversity, several well functioning and validated generic HRQL measures are currently available [12]. Concurrent with this development, quality of life has become an increasingly reported outcome measure in RCTs [13]. Eight per cent of cancer RCTs reported on HRQOL in 1997 [13].

Based on a sample of portal hypertension RCTs ($n = 136$), only one RCT (0.7%) reported HRQOL [10]. Even this single trial did not report what is usually understood by a HRQOL measure [10].

The International Conference on Harmonization—Guidance on Statistical Principles for Clinical Trials [5] points to HRQOL assessments as potential primary (or secondary) outcome measures in RCTs.

Therefore, increased use of HRQOL measures can be recommended for future portal hypertension RCTs. These should include both generic as well as disease-specific measures of HRQOL. The disease-specific measures have to be developed and validated and checked for reliability.

HEALTH ECONOMICS

Regardless of the health care system, there is a need for reliable information on the costs of clinical interventions [12,14]. However, economic analyses currently available are often incomplete or fail to provide relevant cost information to practitioners [15].

The proportion of portal hypertension RCTs reporting health economics is only 2% [10]. Further, the methodology used leaves ample room for improvement [10].

The International Conference on Harmonization—Guidance on Statistical Principles for Clinical Trials [5] points to health economics assessments as potential primary (or secondary) outcome measures in RCTs.

Therefore, increased use of health economics assessments can be recommended for future portal hypertension RCTs. They ought to comply with international recommendations for measuring health economics [12,16].

Prognostic stratification in analysis of RCT data

Gennaro D'Amico

RCTs provide estimates of the average treatment effect in the trial population. However, the response to the treatment of individual patients may be different from the average response shown by RCTs.

In fact, patients with a specific disease may differ greatly from one another and treatment effects may differ according to their baseline clinical characteristics. For this reason, RCTs frequently report results by subgroups within which treatment effects are expected to be similar, but between which the treatment effects are suspected to differ [17]. The importance of prognostic stratification of patients included in RCTs, both for description of patient characteristics and for reporting results in major prognostic subgroups, was also outlined in previous consensus conferences on diagnosis and treatment of portal hypertension [1,2,18]. However, anticipated differential effects of therapy in different subgroups are often absent or hard to establish, whereas unanticipated differences, when found, are difficult to interpret.

RESULTS FROM META-ANALYSES

It has recently been shown in RCTs of treatment of HIV infection that the treatment effect may be markedly different in populations with a different proportion of high and low-risk patients [19].

In the field of portal hypertension, an example of this was provided by the RCTs of endoscopic variceal sclerotherapy for the prevention of first bleeding from oesophageal varices in cirrhosis. Previous meta-analyses showed that prophylactic sclerotherapy was beneficial only in patients with a baseline bleeding risk higher than 40%, whereas it had no effect in patients with risk between 20% and 40% and it was harmful with a baseline risk of lower than 20% [20]. This has been confirmed by the last update of this meta-analysis including 21 RCTs (Fig. 27a).

It has recently been argued that the analysis of variations of the treatment effect based on the proportion of events in controls may be seriously misleading [21]. In fact, since in such analyses the outcome in the control group contributes to the measure of the treatment effect, a relation is expected as an expression of regression to the mean. However, a more appropriate analysis using a Bayesian approach on the same data has convincingly confirmed that the apparent benefit from prophylactic sclerotherapy is significantly related to the underlying bleeding risk [22].

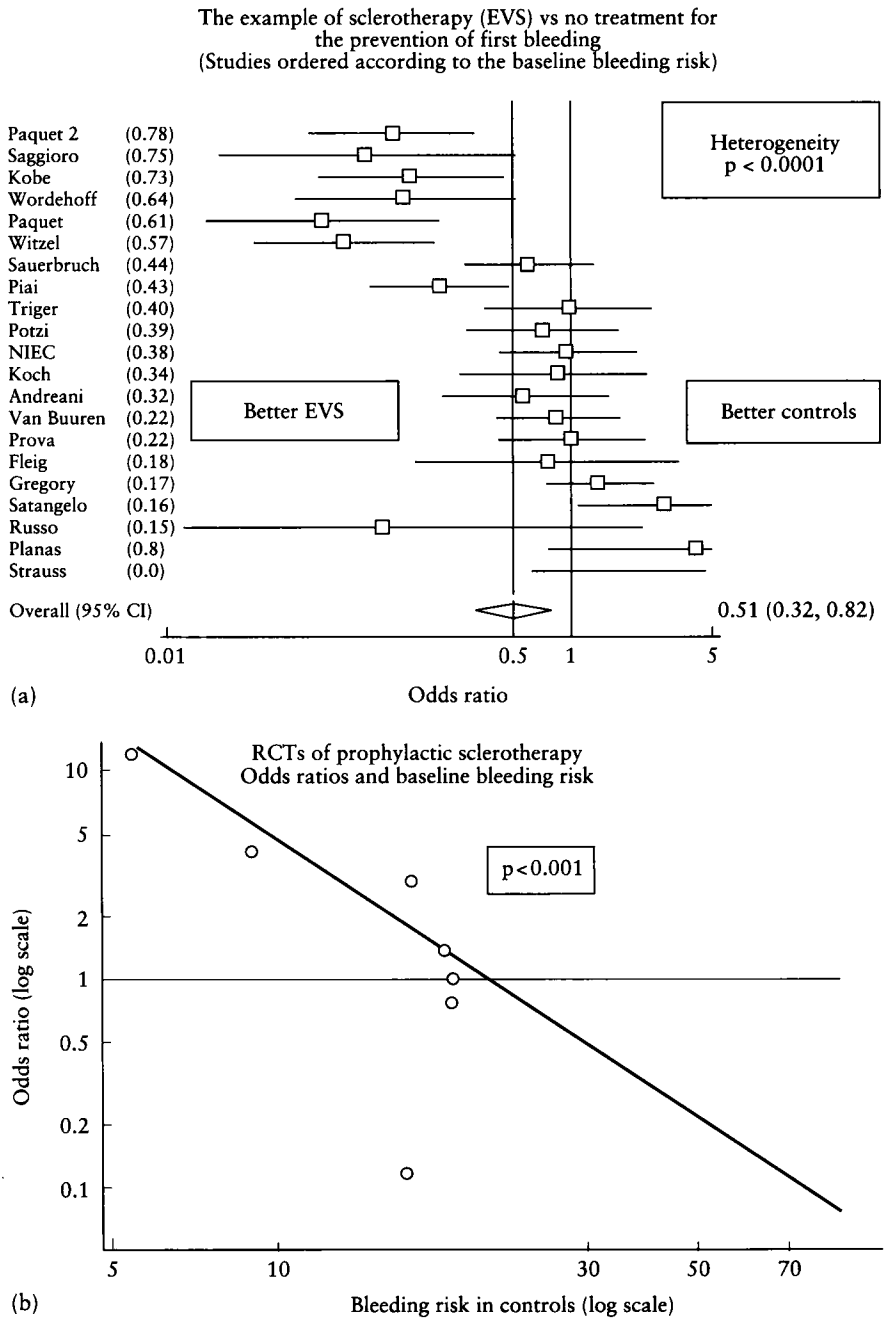

Fig. 27 Meta-analysis of RCTs of endoscopic variceal sclerotherapy (EVS) for the prevention of first variceal bleeding in cirrhosis. RCTs are arranged according to the bleeding risk in untreated control patients (the baseline bleeding risk). A significant benefit from EVS was found only in RCTs with baseline bleeding risk higher than 40%, whereas no benefit or even harm was found in RCTs with baseline risk lower than 20%.

PREDICTION OF UNDERLYING RISK

It is therefore important to know the clinical predictors of the underlying risk in order to identify prognostic subgroups of patients in which the treatment effects may be substantially different. Besides the statistical reasons, showing that the attempt to relate the underlying risk to the treatment effect may be misleading, the underlying risk *per se* is not clinically relevant if it is not predictable by prognostic indicators, being otherwise measurable only *a posteriori* both in clinical trials and in clinical practice. Accordingly, it has been suggested that a preferable approach is to relate the treatment effect to some measurable patients characteristics [21].

This approach may allow the identification of prognostic subgroups of patients with potentially (or existing) different treatment effects, and it is sensible in meta-analyses as well as in individual RCTs. In this regard it may be interesting to note that a recent re-analysis of beta-blockers RCTs for the prevention of first bleeding in cirrhosis, based on relevant patients' characteristics, showed that patients with large varices and no ascites benefit from beta-blockers more than those with large varices and ascites and that no significant benefit may be expected in patients with small varices [23].

PRIOR AND *POST HOC* APPROACH

Although a different treatment effect may be suspected in prognostically different subgroups of patients, this is rarely anticipated in clinical trials [17] and it is difficult to establish, requiring a specific study design and sample size calculation, frequently yielding requests for larger sizes.

Conversely, different treatment effects in different prognostic subgroups defined *a posteriori* (data derived) should be considered potentially misleading, since they usually result from multiple tests with an inherent high risk of false significant estimates. However, even the analysis of treatment effects according to *post hoc* stratification of patients may provide useful information, particularly when the results have been corrected for multiple testing, when they are supported by significant interaction tests and, most importantly, when they are based on clinical and biologically plausible hypotheses.

It should be noted that interactions in which the treatment is beneficial in some subgroups of patients and harmful in others, are usually more difficult to explain by a plausible hypothesis and that they are rarely reproduced in other trials. For this reason, such interactions are generally less reliable than interactions that show a different size of treatment effects in different subgroups of patients, but in the same direction as the overall trial result. These interactions should be regarded as the better guide to the direction of the treatment effect [24].

The above-mentioned results from RCTs on prophylactic sclerotherapy (Fig. 27b) may be a reasonable exemption. If the specific treatment effect—here on variceal bleeding—declines with decreasing baseline risk whereas the frequency of adverse effects, including serious complications decline less, or is independent of the base-line risk, then such qualitative interactions may be expected. If such interactions exist, they obviously contribute to setting the indications for treatment.

However, even when supported by proper statistical analysis and by clinical and biologically plausible hypotheses, different treatment subgroup effects derived from *post hoc* patients stratification should, in general, only be considered as a basis for hypotheses to be tested in future, specifically designed studies.

A measure of the reliability of different subgroup treatment effects derived from *post hoc* analyses is provided by reproducibility in several trials: a spurious effect is unlikely to be replicated. Therefore, meta-analysis is probably the most appropriate approach to subgroup analysis if the relevant data are adequately and homogeneously reported in individual RCTs, particularly when individual RCTs do not reach sufficient power.

IMPLEMENTATION

The above considerations suggest, in accordance with the results of previous consensus conferences in portal hypertension [1–3,18], that patients included in clinical trials should be stratified according to some relevant clinical characteristics both for patients description and for the reporting of results. Also, it is worthwhile to note that although a consensus previously was reached on this issue, prognostic stratification has only been used for patient description and to achieve comparability of trial groups, whereas subgroup results have not been reported. This also applies to the most recently published trials. Although it was among the principal objectives, two recent meta-analyses of trials on transjugular intrahepatic portosystemic shunt (TIPS) compared with endoscopic therapy failed to assess potential differences of subgroup treatment effects, because data were insufficient in the trial reports.

TIME-DEPENDENT PROGNOSTIC STRATIFICATION

The prognosis of the patient with portal hypertension varies strikingly over time, both because of changes of prognostic factors and because of new events such as bleeding. This course may be taken into account in analysis of RCTs using appropriate statistical techniques that reduce the statistical variation in the risk of occurrence of the end-points at any given point in time, and thereby increase the statistical power. Changes in prognostic factors may be

introduced in models with time-dependent updating of the level of prognostic factors [25]. The time of new end-point events during the course may be considered as new time zero [26].

CONCLUSION

Knowledge of different treatment effect according to patient characteristics may be clinically important. Stratification of patients according to few important prognostic variables allows proper evaluation of different subgroup treatment effects, either in single trials or in meta-analyses if single RCTs do not reach adequate power. Such a stratified analysis is justified if prior hypotheses are specified in the study plan on the basis of a clinically and biologically plausible basis or on hypotheses derived from previous studies. It must be made explicit if such an analysis is a *post hoc* analysis. In any case, data-derived subgroup analyses may be considered only explorative and subgroup effects should be replicated in other studies and/or confirmed by meta-analysis before being accepted for clinical practice.

Health-related quality of life measures

Robert F. Yacavone and Patrick S. Kamath

HRQOL is increasingly being recognized as an important outcome measure. However, HRQOL measurement has not been widely reported in the hepatology literature [10]. Hepatologists need to be familiar with the various HRQOL measures in order to understand this literature and use the instruments in clinical trials.

HRQOL—DEFINITION AND MEASUREMENT

HRQOL may be defined as 'the net consequence of a disease and its treatment on the patient's perception of his ability to live a useful and fulfilling life.' It represents 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient' [27]. HRQOL is a multidimensional construct with four basic components (or 'domains'): physical/occupational function, psychological state, social interaction, and somatic sensation. Overall HRQOL, therefore, is seen as the synthesis of these four domains. Because many of these components cannot be directly measured, we measure them indirectly by asking patients a series of questions (or 'items'). The patient's answers are converted to numerical scores, which in summation yield domain scores and/or overall HRQOL scores, depending on the instrument used. The main goals of HRQOL measurement are 'discrimination' (i.e. differentiating persons with a better vs. worse health related quality of life) and 'evaluation' (i.e. quantifying how much change has occurred in HRQOL following treatment) [28].

PROPERTIES OF HRQOL INSTRUMENTS

HRQOL instruments are judged based on their fulfilment of criteria for *validity*, *reliability*, *responsiveness*, and *coverage*.

Validity indicates the degree to which an instrument measures what it intends to measure. In other words, it measures the accuracy of the instrument and includes subtypes such as face validity, content validity, criterion validity, and construct validity.

The *reliability* of an HRQOL instrument is a measure of its reproducibility or consistency, and includes subtypes such as test-retest reliability and internal consistency. Test-retest determines whether similar scores are obtained over short periods of time (1–2 weeks) under constant clinical conditions. Internal consistency measures the degree to which items within each domain correlate with each other.

Responsiveness measures the association between changes in the score on an instrument and underlying changes in the patient's clinical condition. A responsive instrument, for example, should be able to detect a relative change in a patient with compensated liver disease that has decompensated.

Coverage is an index of the spectrum of quality of life issues an instrument measures, which is important in deciding which instrument(s) are most appropriate in studies of different disease processes and clinical interventions.

HRQOL MEASURES

Two basic approaches to HRQOL measurement include: (1) *generic* instruments, which provide a summary measure of HRQOL; and (2) *disease-specific* instruments, which focus on those problems characteristic of a given disease or patient group [28]. Generic measures can be used in any patient population, and provide data comparable across disease groups or interventions. However, they may not focus adequately on the most relevant aspects of HRQOL for given disease states, and may lack adequate responsiveness. Disease-specific instruments, in contrast, relate more closely to traditional clinical disease measures, and have the potential for increased responsiveness [28]. Disease specific HRQOL measures are most often used in clinical trials evaluating specific therapeutic interventions. Due to their complementary nature, generic and disease-specific measures are often most effectively utilized in concert.

GENERIC HRQOL MEASURES

Generic instruments can be single indicators (example: grading quality of life on a scale of 1–10), instruments which generate health utilities (time trade-off), and health profiles (Sickness Impact Profile, Medical Outcome Study Short Form 36 [SF-36], etc). Typically, the generic instruments measure the following domains: physical, cognitive, social and role functioning; psychological well-being and distress; energy/fatigue; pain; sleep/rest; and general health perceptions [29]. The characteristics of the most commonly used generic health profiles are as follows:

Sickness Impact Profile

The Sickness Impact Profile is a comprehensive, behaviourally-based health status measure with 136 items in physical and psychosocial domains as well as miscellaneous categories. SIP has been used in patients with multiple types and severity of illnesses, and has been applied extensively in clinical trials. SIP is useful in distinguishing a sick from a healthy population, and assessing ben-

efits of treatment. The Sickness Impact Profile fails to detect true differences in HRQOL among groups with little disease burden.

Medical Outcomes Study SF-36

The SF-36 is a comprehensive measure of general health status originally used in the Medical Outcomes Study and covers 36 items. This instrument is the most widely used health status measure, particularly in the gastroenterology literature. Normative data for the US population as well as from several other nations are available. Abbreviated versions of this instrument are the SF-20 and SF-12. The reliability and validity of the SF-12 and SF-20 are slightly lower than for the SF-36, but are superior to those for single item measures. In the hepatology literature, the SF-36 has been used to measure HRQOL in patients with chronic hepatitis C [30].

The Nottingham Health Profile

The Nottingham Health Profile was originally intended for use in comparing health status between populations and identifying areas of unmet need for care. The Nottingham Health Profile has two parts, of which Part II is less frequently used. The advantage of the Nottingham Health Profile is that it is simple to use and score, and is available and comparable across numerous languages. However, the Nottingham Health Profile has limited responsiveness and has to be used with caution in the clinical trial setting.

The Nottingham Health Profile was used in a study of patients with primary biliary cirrhosis who were studied in the two years following liver transplantation [31]. Because the Nottingham Health Profile data were not available pre-transplant, this study is useful only in describing the state of primary biliary cirrhosis patients post-transplant. The data do not help optimize the timing of liver transplantation in patients with primary biliary cirrhosis.

Quality of Well-Being Scale

The Quality of Well-Being Scale calculates a person's well-being score (or utility index) ranging from 0 (death) to 1.0 (optimal functioning) using the patient's symptoms and functional level on mobility, physical activity and social activity scales [32]. This instrument is unique in that it not only describes a patient's current health status, but it weighs that health state by its desirability. The Quality of Well-Being Scale can be used as a time-specific functional measure. In addition, Quality of Well-Being Scale scores, multiplied by the expected length of time to be spent at each functional level, yield a form of

quality-adjusted life year (QALY) measurement. The Quality of Well-Being Scale is useful in longitudinal patient assessment and clinical trials.

Psychological Well-Being Index

The Psychological Well-Being Index targets primarily the psychological or emotional domain of HRQOL. Both negative and positive affective states are covered. The questionnaire has been adapted in many different languages. Caution needs to be applied in interpreting results from clinical trials which use this instrument, since reproducibility is limited.

DISEASE-SPECIFIC HRQOL MEASUREMENT

Disease-specific instruments in the field of hepatology are limited and have not been put to widespread use. The instruments available are as follows:

Hepatitis quality of life questionnaire

This questionnaire was developed by Quality Metric, Inc. and combines generic and disease-specific instruments for the assessment of HRQOL in patients with chronic hepatitis C [33]. The Hepatitis Quality of Life Questionnaire combines eight domains of the SF-36 with three additional generic scales (positive well-being, sleep/somnolence, and health distress). These instruments are believed to be pertinent to the impact of chronic hepatitis C on quality of life. Also included are two chronic hepatitis C-specific scales (health distress because of chronic hepatitis C, and limitations because of chronic hepatitis C). In patients treated for hepatitis C, the trade-offs between limited efficacy, side effects, and potential benefits of antiviral therapy warrant the use of an outcome measure such as the Hepatitis Quality of Life Questionnaire in clinical trials.

NIDDK liver transplantation quality of life instrument

This form was developed for the United States National Institute of Health Liver Transplantation Database and is a composite of generic measures of HRQOL, namely the Karnofsky Performance Status Scale, The Sickness Impact Profile, The Medical Outcomes Survey, and The Nottingham Health Profile. In addition, specific questions have been introduced to assess liver disease symptoms. The instrument has not been validated as an HRQOL measure in patients with liver disease.

Liver Disease Quality of Life

The Liver Disease Quality of Life was developed for individuals with chronic liver disease based on input from a focused group of patients with chronic liver disease awaiting liver transplantation, and expert hepatologists [34]. The LDQOL is a self-report measure which includes 21 multi-item scales, including physical functioning, role limitations, pain, liver disease-related symptoms, emotional well-being, stigma of liver disease, social function, sexual function, impact of liver disease, and several other parameters. This instrument measures significant impairment of daily functioning not detected by more traditional methods (Example: Child–Pugh Classification). The Liver Disease Quality of Life should prove useful in portal hypertension-related studies.

Chronic Liver Disease Questionnaire

The Chronic Liver Disease Questionnaire was based on responses of patients with chronic liver disease, expert hepatologists, and from a literature search which identified potential items which might affect health-related quality of life [35]. Of the 156 items of potential importance, factor analysis suggested six domains. The final Chronic Liver Disease Questionnaire includes 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. The Chronic Liver Disease Questionnaire is short and easy to administer, and correlates with the severity of liver disease. The questionnaire includes questions which might be important in patients with hepatic encephalopathy. However, items important to patients with variceal bleed or ascites are lacking.

PATIENT CHOICES

Unfortunately, neither the generic measures nor the disease-specific measures take into consideration the patient's perception of quality of life. Instruments currently in use measure HRQOL based on what investigators think it should be, and generally ignore patient preferences for various health states. Two value measures that address this issue are the Time Trade-Off and the Standard Gamble.

The Time Trade-Off is a health status value measure. A trained investigator discusses with the patient the following choices: The patient could continue in his/her present state of health for time (T), or could live in a state of full health for a shorter period of time (X). The patient's value of the current state is expressed as X/T and ranges between 0 and 1. A value of 1 indicates a perfect value measure.

The Standard Gamble is a health status utility measure. It measures the patient's choice when the outcomes are uncertain. Here, the patient's choices are either to continue to live in the current health state for the remainder of life, or to take a gamble. The gamble here is the choice between immediate death versus full health for the remainder of life with an assigned probability. A trained observer varies the probability until the patient is indifferent between the current state and the gamble.

The utility of current health state ranges between 0 and 1 with 1 indicating perfect utility. While the advantages of these value/utility measures are that they incorporate patient preferences, they are time-consuming, often difficult for patients to understand, and have not been administered in questionnaire format.

CONCLUSIONS

Portal hypertension is a disease state where quality of life is of obvious clinical importance and therefore should be measured. HRQOL in chronic liver disease may not be adequately measured using existing instruments. Issues related to social stigma, encephalopathy, and fatigue are not evaluated by generic instruments [36]. The burden of the portal hypertension, which involves both the disease as well as its treatment, translates into significant morbidity and change in the quality of life of the patient. Since many of the treatment measures do not prolong survival, and since treatments can be associated with significant side effects (for example, trade-off between bleeding risk and risk of hepatic encephalopathy), HRQOL should be measured in these patients. None of the currently available instruments have been validated in patients of portal hypertension. In our experience, the NIDDK liver transplantation instrument is not sensitive enough to detect changes in HRQOL following a variceal bleed. An ideal instrument for measurement of HRQOL in patients of portal hypertension would be a composite of a generic instrument such as the SF-36, a liver disease specific instrument, a portal hypertension specific instrument and patient choice. This instrument would need validation before it can be widely used in clinical trials.

Health economics

Oliviero Riggio

The introduction of new health technologies together with limited health-care resources has generated a growing interest in the economic assessment as a way of guiding the health-care decision-making processes. The cost-effectiveness analysis, which compares medical interventions in terms of extra costs per unit of health outcome obtained, is becoming increasingly common in medical journals. Despite this, clinical studies reporting on health economics are still very few. For example, the proportion of RCTs on portal hypertension reporting health economic evaluations is only 2% [10]. Moreover, analysis and reports are often incomplete and not always in keeping with international recommendations for measuring health economics [12]. Out of 45 RCTs published with an economic evaluation and cost variables suitable for statistical analysis, only 20% reported measures of variability, 56% gave results of statistical tests and 16% gave conclusions justified by the results [15]. Very similar results were recently obtained by Briggs *et al.* on 492 reviewed studies [37]. Although information about the impact of new therapies on costs within a health-care system should be essential for improving health-care decisions, the relevance of health economic information to decision makers has not been demonstrated.

DEFINITIONS

Health economics is a relatively new research discipline without a strong consensus on methodology. This discretionary nature of the methods used to analyse cost-effectiveness, has prompted journals, such as the *British Medical Journal* or the *New England Journal of Medicine*, to issue guidelines for authors and reviewers of economic evaluations to be published in those journals [38,39]. The existence of language and definitional barriers prevents the effective communication between users and suppliers of health economic information.

Health economic terminology may be a problem among those who are alien to the field and may be unaware of the differences between *costs* (the resources required to provide a service) and *charges* (which may be regulated by the market and may therefore not reflect the true cost of providing a service), *direct medical costs* (which comprise hospital care, laboratory tests, radiological procedures, etc.), *indirect costs* (the cost of loss of life, absenteeism from work, etc.—which are difficult to measure) and *intangible costs* (the costs of pain, suffering, etc.—which are never included in economic analysis). There are also several types of economic analysis: *cost-identification* is aimed

at finding the least expensive way of treating the disorder while *cost-effectiveness* considers the outcome obtained, i.e. cost per life-year gained, and *cost-utility* which combines the quantity and quality of the outcome, i.e. cost per quality-adjusted life year gained.

METHODOLOGICAL ISSUES IN ECONOMIC EVALUATION

Several major organizations which run trials such as the European Organization for Research and Treatment of Cancer (EORTC) have a policy of always considering health economics and quality of life implications when a new RCT is designed. The health economic information, which derives from RCTs, has the advantage of good interpretability of the results, statistical rigour, improved control of bias and well established methodology for clinical outcomes.

However, the fundamental question is: to what extent we can generalize costs as observed in the context of a RCT [4]. Are we dealing with the true costs of treatment or with the cost of the RCT protocol? RCTs usually demand close and frequent monitoring of patients to detect side effects and clinical outcomes as well as compliance with therapy. If a treatment is new, non-routine monitoring of outcomes and side-effects is necessary while, with experience, clinicians learn to minimize and manage side-effects more efficiently. Other problems with RCTs are the exclusion of many types of patients (especially the vulnerable patients), the limited duration of follow-up and the high cost.

Health economic information can derive from the retrospective analysis of an existing database. This method is relatively inexpensive and can be carried out quickly. Specific populations can be studied and the sample size is generally larger than that of RCTs. On the other hand, selection bias and confounding factors may be an unsolvable problem in a retrospective study. The quality of the database used should always be checked.

A cost-effectiveness analysis is often performed by developing a model of the outcomes of alternative treatments, selecting published data on the probability of the outcomes to enter in the model, identifying the expenses associated with each therapy and then comparing the results. The data can be derived from a single RCT, meta-analyses or from many sources. Modelling studies may be extended to different geographic areas or different treatment settings. However, no model perfectly represents reality. Moreover, this approach is usually not well suited to represent recurrent events over time. Cost (derived from Diagnosis-Related Groups, DRGs) and outcomes (e.g. the length of hospital stay) are averaged, while outliers usually have a major impact on the results. Sensitivity analysis can explore the impact of increasing or decreasing estimates of the various parameters affecting costs, but it is difficult

to discover what variations are really important. Therefore, an ideal method does not exist. RCTs have high internal validity and are relatively bias-free for the assessment of the most effective of two or more treatments.

Higher survival rates and effectiveness are the primary reasons for choosing a treatment. However,when survival is similar or when advantages of a given treatment are balanced by the side effects, the costs (and even more the quality of life) may have an important impact in determining the preferred procedure. Therefore, comparing two treatments in terms of costs may be more important than establishing the real cost of a given treatment. If this is the aim, a RCT is potentially better than an analysis based on decision models. Therefore, considering health economics in future trials on portal hypertension is recommended. The economic assessment in future portal hypertension studies needs to follow international recommendation [40].

DESIGN, ANALYSIS AND INTERPRETATION OF ECONOMIC EVALUATION

In particular, important issues to be addressed are: choice of a comparator, definition of the time horizon and perspective (social vs. individual perspective) and sample size. Because the variability of economic end-points usually is larger than the variability of primary clinical endpoints, the sample size needed to detect economic benefits is usually greater. Power calculations based on economical end-points, instead of clinical ones, may therefore be unethical as one may submit some patients to potentially inferior treatments just to establish a costs difference.

Finally, valid unit cost estimates must be determined for resources consumed. Moreover, the protocol-driven costs must be identified and distinguished from the cost of the standard treatment. It takes little effort and should be routine to record basic details on the cost of a therapy such as the number of interventions or nights as in-patients in order to establish at least the minimal costs of a treatment. Censoring is another challenge: often the resource consumption commences when the patient reaches the clinical endpoint. Lastly, appropriate statistical analysis should be used by taking into consideration that economic data often do not follow a normal distribution [41].

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Baveno III Consensus Statements: Methodological Requirements for Future Trials

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1 Portal hypertension RCTs should:
(a) Include a sufficient number. of patients, based on appropriate sample size calculation
(b) Preferably be multicentre
(c) Preferably use stratified randomization/minimization
(d) Preferably report quality of life
(e) Preferably report health economics.

2 Previous consensus statements:
(a) Groningen, 1986. Prognostic stratification at randomization needed at least for description of patients
(b) Baveno, 1990. Prognostic stratification in randomization and analysis
(c) Baveno, 1995. RCTs results in major prognostic subgroups should be reported
(d) Reston, 1996. RCTs results in major prognostic subgroups should be reported. Therapeutic benefit and harm should be interpreted according to baseline risk.

3 Prognostic stratification:
(a) Knowledge of different treatment effect according to the patient characteristics may be clinically important
(b) Stratification of patients according to few important prognostic variables allows to properly evaluate different subgroup treatment effects in meta-analyses if single RCTs do not reach adequate power
(c) Stratified analysis is justified if:
- a prior hypothesis is made in planning the study
- to validate hypotheses from previous studies
- it is made explicit that it is a *post-hoc* analysis.

(d) *Post-hoc* subgroup analyses may be considered only explorative of plausible hypotheses
(e) Subgroup effects should be replicated in other studies and/or confirmed by meta-analysis before being accepted for clinical practice.

4 Quality of life evaluation:
(a) In patients with portal hypertension, both the disease, as well as its treatment are likely to have a significant impact on quality of life
(b) Future studies on portal hypertension should, thus, measure Health-Related Quality of Life as one of the (major) outcomes

(c) At present, there is no disease-specific instrument for patients with portal hypertension that has all the essential properties for measurement of HRQOL (validity, reliability, responsiveness/sensitivity, and coverage)
(d) While instruments to measure HRQOL are being developed and validated for patients with portal hypertension generic and chronic liver disease specific instruments may be used in trials.

5 Health-economics:
(a) Higher survival and effectiveness are the primary reasons for choosing a treatment for portal hypertension
(b) Future RCTs on portal hypertension should be planned to record at least the event-based basic details about the cost of therapy. The adequacy of the time horizon, sample size and the protocol driven costs should be clearly stated
(c) The methodology for health economic assessment in portal hypertension should be a topic of a future consensus conference.

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References to tables are shown in **bold**; figures in *italics* and plates in ***bold italics***. RCTs refer to randomized clinical trials.