ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2013 January 27; 5(1): 1-45

Baishideng Publishing Group
www.wjgnet.com

WJH World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

Editorial Board

2009-2013

The *World Journal of Hepatology* Editorial Board consists of 585 members, representing a team of worldwide experts in hepatology. They are from 46 countries, including Argentina (4), Australia (7), Austria (2), Bangladesh (2), Belgium (4), Botswana (2), Brazil (8), Brunei Darussalam (1), Bulgaria (1), Canada (10), Chile (1), China (90), Denmark (1), Egypt (3), Finland (1), France (15), Gambia (1), Germany (28), Greece (9), Hungary (3), India (20), Ireland (1), Israel (8), Italy (65), Japan (44), Malaysia (1), Mexico (4), Netherlands (4), Pakistan (2), Philippines (1), Poland (1), Portugal (1), Romania (1), Saudi Arabia (1), Singapore (5), South Korea (18), Spain (23), Sri Lanka (1), Sudan (1), Switzerland (2), Thailand (6), Tunisia (2), Turkey (13), United Kingdom (18), United States (148), and Venezuela (1).

Chile

Luis A Videla, *Santiago*

China

Peng Bing, *Chengdu*
Chiranjib Chakraborty, *Beijing*
Stephen Lam Chan, *Hong Kong*
George G Chen, *Hong Kong*
Min-Shan Chen, *Guangzhou*
Yang Cheng, *Shanghai*
Siu Tim Cheung, *Hong Kong*
Thomas Yau Chung Cheung, *Hong Kong*
Yick-Pang Ching, *Hong Kong*
William Chi-shing Cho, *Hong Kong*
Chui Chung-Hin, *Hong Kong*
Shuang-Suo Dang, *Xi'an*
Yi-Tao Ding, *Nanjing*
Jian-Gao Fan, *Shanghai*
Yuen Man Fung, *Hong Kong*
Zuo-Jiong Gong, *Wuhan*
Tian-Quan Han, *Shanghai*
Jin-Yang He, *Guangzhou*
Garrett Chi Lai Ho, *Hong Kong*
Ji-Ming Hu, *Wuhan*
Can-Hua Huang, *Chengdu*
Zhi-Yong Huang, *Wuhan*
Jian-Hui Jiang, *Changsha*
Dong-Yan Jin, *Hong Kong*
Hsiang-Fu Kung, *Hong Kong*
Wan Yee Joseph Lau, *Hong Kong*
Nancy Wai Yee Leung, *Hong Kong*
Jin-Qing Li, *Guangzhou*
Li-Ying Li, *Beijing*
Shu-Chen Li, *Harbin*
Xin-Wei Li, *Shanghai*
Yu-Yuan Li, *Guangzhou*
En-Qi Liu, *Xi'an*
Yin-Kun Liu, *Shanghai*
Chung-Mau Lo, *Hong Kong*
Lun-Gen Lu, *Shanghai*
Ming-De Lu, *Guangzhou*
John M Luk, *Hong Kong*
Guang-Hua Luo, *Changzhou*
Shuang Mei, *Shanghai*
Kelvin Kwok-Chai Ng, *Hong Kong*
Qin Ning, *Wuhan*
Qin Pan, *Shanghai*
Bo San Lai Paul, *Hong Kong*
Qi-Jun Qian, *Shanghai*
Jian-Min Qin, *Shanghai*
Xian-Jun Qu, *Jinan*
Qin Su, *Beijing*
Xue-Ying Sun, *Harbin*
Wu-Yi Sun, *Hefei*
Hui-Ru Tang, *Wuhan*
Peng Tao, *Nanning*
Eric Wai Choi Tse, *Hong Kong*
Bin Wang, *Weifang*
Xiao-Zhong Wang, *Fuzhou*
Xiu-Jie Wang, *Chengdu*
Zhen-Xia Wang, *Huhhot*
Grace Lai-Hung Wong, *Hong Kong*
Nathalie Wong, *Hong Kong*
Xiong-Zhi Wu, *Tianjin*
De-Xiang Xu, *Hefei*
Rui-An Xu, *Quanzhou*
Xun-Di Xu, *Changsha*
Xiao Yang, *Beijing*
Zhen-Fan Yang, *Hong Kong*
Boon Hun Yong, *Hong Kong*
Ting-He Yu, *Chengdu*
Benny Chung-Ying Zee, *Hong Kong*
Jia-Ning Zhang, *Dalian*
Xiao-Dong Zhang, *Tianjin*
Xiao-Lan Zhang, *Shijiazhuang*
Xiao-Yan Zhang, *Shanghai*
Hong-Chuan Zhao, *Hefei*
Xiao-Ping Zhao, *Beijing*
Jiang-Fan Zhu, *Shanghai*
Yi-Ping Zou, *Wuhan*

Denmark

Henning Gronbaek, *Aarhus*

Egypt

Nabil Mohie Abdel-Hamid, *Minia*
Laila Ahmed Farag Eissa, *Mansoura*
Mona Mostafa Fahmy Nosseir, *Giza*

Finland

Thomas Kietzmann, *Oulu*

France

Aramando Abergel, *Clermont-Ferrand*
Henri Bismuth, *Villejuif Cedex*
Ana C Ferreira Netto Cardoso, *Pairs*
Nicolas Chignard, *Paris*
Claude Caron de Fromentel, *Lyon*
Victor de Ledinghen, *Pessac*
Zdenko Herceg, *Lyon*
Nathalie Janel, *Paris*
Antoinette Lemoine, *Villejuif*
Marcellin Patrick, *Pairs*
Raoul Poupon, *Paris*
Rodrigue Rossignol, *Bordeaux*
Christian Trépo, *Lyon*
Dominique Angèle Vuitton, *Besancon*
Virginie Wautot, *Pierre Benite Cedex*

Gambia

Maimuna Ebirunkeh Mendy, *Banjul*

Germany

Thomas Bock, *Tuebingen*
Ali Canbay, *Essen*
Enrico Narciso De Toni, *München*
Joachim Drevs, *Freiburg*
Volker Fendrich, *Marburg*
Peter R Galle, *Mainz*
Erich Gulbins, *Essen*
Sebastian Hinz, *Kiel*
Roland Kaufmann, *Jena*
Philipp Kobbe, *Aachen*
Michael Kremer, *Heidelberg*
Aachen Christian Liedtke, *Aachen*
Martin Loss, *Regensburg*
Arun Kumar Mankan, *Munich*
Michael D Menger, *Saarbrucken*
Lars Müller, *Kiel*
Andreas K Nussler, *Munich*
Margarete Odenthal, *Koeln*
Claus Petersen, *Hannover*
Andrej Potthoff, *Hannover*
Thomas Pusl, *München*
Elke Roeb, *Giessen*
Stefan Rose-John, *Kiel*
Frank Tacke, *Aachen*
Andreas Teufel, *Mainz*
Lothar Thomas, *Frankfurt*
Jens James Walter Tischendorf, *Aachen*
Arndt Vogel, *Hannover*

Greece

Alex P Betrosian, *Athens*
Spiros G Delis, *Athens*
Johanna Kassianie Delladetsima, *Athens*
Ioannis Diamantis, *Athens*
Papandreou Dimitrios, *Athens*
Moses S Elisaf, *Ioannina*
Elias A Kouroumalis, *Crete*
George Papatheodoridis, *Athens*
Stamatios E Theocharis, *Athens*

Hungary

Gábor Bánhegyi, *Budapest*
Subhamay Ghosh, *Ifjusag*
Peter Nagy, *Budapest*

India

Anjali Deepak Amarapurkar, *Mumbai*
Deepak Narayan Amararpurkar, *Mumbai*
Runu Chakravarty, *Kolkata*
Pronobesh Chattopadhyay, *Moradabad*
Puneet Chopra, *Gurgaon*
Tanya Das, *Kolkata*
Radha Krishan Dhiman, *Chandigarh*
Ajay Duseja, *Chandigarh*
Devendra K Gupta, *New Delhi*
P Kar, *New Delhi*
Sudhir Kumar, *Lucknow*
Vijay Kumar, *New Delhi*
Anoop Misra, *New Delhi*
Devendra Parmar, *Lucknow*
Rajendra Prasad, *Chandigarh*
Pallu Reddanna, *Hyderabad*
K Rajeshwari, *New Delhi*
Barjesh Chander Sharma, *New Delhi*
Sarman Singh, *New Delhi*
Ajith TA, *Thrissur*

Ireland

Matthew William Lawless, *Dublin*

Israel

Yaron Ilan, *Jerusalem*
Yaakov Maor Kendler, *Tel-Hashomer*

Ran Oren, *Tel Aviv*
Shimon Reif, *Karnei-Shomron*
Rifaat Safadi, *Jerusalem*
Shira Zelber Sagi, *Tel Aviv*
Amir Shlomai, *Modiin*
Yehuda Julius Shoenfeld, *Tel Hahsomer*

Italy

Luca Aasaloni, *Via Massarenti*
Giovanni Addolorato, *Rome*
Luigi E Adinolfi, *Naples*
Pietro Andreone, *Bologna*
Marialuisa Appetecchia, *Rome*
Antonio Ascione, *Napoli*
Ferruccio Bonino, *Milano*
Savino Bruno, *Milano*
Melchiorre Cervello, *Palermo*
Claudio Chiesa, *Rome*
Stefano Colagrande, *Firenze*
Massimo Giuseppe Colombo, *Milan*
Bruno Daniele, *Benevento*
Samuele De Minicis, *Ancona*
Massimo Di Maio, *Rossano*
Fabio Farinati, *Padova*
Paolo Feltracco, *Padova*
Domenico Ferri, *Bari*
Amalia Gastaldelli, *Pisa*
Domenico Girelli, *Verona*
Fernando Goglia, *Benevento*
Alessandro Grasso, *Savona*
Ignazio Grattagliano, *Bari*
Pietro Invernizzi, *Milan*
Francesco Izzo, *Naples*
Amedeo Lonardo, *Modena*
Malaguarnera Lucia, *Catania*
Melania Manco, *Rome*
Andrea Mancuso, *Milan*
F Marotta, *Milano*
Fabio Marra, *Florence*
Roberto Mazzanti, *Florence*
Giulia Morsica, *Milan*
Antonio Moschetta, *Bari*
Massimo Negrini, *Ferrara*
Andrea Nicolini, *Pisa*
Giuseppe R Nigri, *Rome*
Valerio Nobili, *Rome*
Valentina Pallottini, *Rome*
Adriano M Pellicelli, *Rome*
Marcello Persico, *Naples*
Massimo Pinzani, *Firenze*
Giovanni Polimeni, *Messina*
Camillo Porta, *Pavia*
Piero Portincasa, *Bari*
Emilio Quaia, *Trieste*
Giuseppe Remuzzi, *Bergamo*
Domenico Ribatti, *Bari*
Massimo Roncalli, *Rozzano*
Carlo Sabbà, *Bari*
Orazio Schillaci, *Rome*
Gaetano Serviddio, *Foggia*
Aurelio Sonzogni, Bergamo
Paolo Sorrentino, *Salerno*
Enea Spada, *Rome*
Giovanni Tarantino, *Naples*
Luciano Tarantino, *Naples*
Claudio Tiribelli, *Trieste*
Pierluigi Toniutto, *Udine*
Pietro Vajro, *Naples*
Luca Vigano, *Torino*
Alessandro Vitale, *Paodva*

Japan

Yuichiro Eguchi, *Saga*
Munechika Enjoji, *Fukuoka*
Jiro Fujimoto, *Osaka*
Atsushi Hosui, *Osaka*
Kazuo Ikeda, *Nagoya*
Toru Ishikawa, *Niigata*
Yoshiaki Iwasaki, *Okayama*
Satoru Kakizaki, *Gunma*
Naoya Kato, *Tokyo*
Takumi Kawaguchi, *Kurume*
Tsuneo Kitamura, *Chiba*
Keiichi Kubota, *Tochigi*
Sabina Mahmood, *Okayama*
Hitoshi Maruyama, *Chiba*
Sachiko Matsuhashi, *Saga*
Toshihiro Mitaka, *Sapporo*
Eiji Miyoshi, *Suita*
Zenichi Morise, *Aichi*
Ryuichi Morisihita, *Osaka*
Yoshiki Murakami, *Kyoto*
Satoru Murata, *Tokyo*
Atsushi Nakajima, *Kanagawa*
Yasuni Nakanuma, *Kanazawa*
Waka Ohishi, *Hiroshima*
Morikazu Onji, *Matsuyama*
Toshiji Saibara, *Nankoku*
Hiroaki Shiba, *Tokyo*
Ikuo Shoji, *Hyogo*
Ryo Sudo, *Yokohama*
Yoshio Sumida, *Nara*
Shinji Tanaka, *Tokyo*
Takuji Tanaka, *Gifu*
Akihiko Tsuchida, *Tokyo*
Shinichi Ueno, *Sakuragaoka*
Takato Ueno, *Kurume*
Kiyohito Yagi, *Osaka*
Yo-ichi Yamashita, *Hiroshima*
Teruyoshi Yanagita, *Saga*
Shuang-Qin Yi, *Kanazawa*
Hiroshi Yoshida, *Tokyo*
Hitoshi Yoshiji, *Nara*

Malaysia

Kamsiah Jaarin, *Kuala Lumpur*

Mexico

Javier Lizardi Cervera, *Tlalpan*
Norberto Carlos Chavez-Tapia, *Tlalpan*
Saúl Villa-Treviño, *Mexico City*
Florencia Vargas Vorackova, *Tlalpan*

Netherlands

Robert Jacobus de Knegt, *Rotterdam*
TU Hoogenraad, *Heidelberglaan*
Maarten E Tushuizen, *Amsterdam*
Robert Christiaan Verdonk, *Groningen*

Pakistan

Syed Hamid Ali, *Karachi*
Huma Iftikhar Qureshi TI, *Islamabad*

Philippines

Janus P Ong, *Manila*

Poland

Maria E Sobaniec Lotowska, *Bialystok*

Portugal

Felix Dias Carvalho, *Porto*

Romania

Eugen Georgescu, *Craiova*

Saudi Arabia

Ahmed Helmy, *Riyadh*

Singapore

Wei Ning Chen, *Singapore*
Pierce Kah-Hoe Chow, *Singapore*
Si-Shen Feng, *Singapore*
Chun-Tao Wai, *Singapore*
Lang Zhuo, *Singapore*

South Korea

Sang Hoon Ahn, *Seoul*
Byung Ihn Choi, *Seoul*
Seok Joo Han, *Seoul*
Sun Pyo Hong, *Yongin*
Kyung Lib Jang, *Busan*
Bum-Joon Kim, *Seoul*
Dong Goo Kim, *Seoul*
Kyung Sik Kim, *Seoul*
Meehyein Kim, *Yongin*
Young Chul Kim, *Seoul*
In Kyoung Lim, *Gyunggi-do*
Mi-Kyung Lee, *Jeonnam*
Young-Ik Lee, *Taejon*
Kwan-Kyu Park, *Daegu*
Taesung Park, *Seoul*
Hyunchul Rhim, *Seoul*
Dae-Yeul Yu, *Daejeon*
Jong Won Yun, *Kyungbuk*

Spain

Jose AG Agundez, *Avda de Elvas*
Maria Angeles, *Madrid*
Agustin Castiella, *Mendaro*

Ruben Ciria, *Cordoba*
Joan Clari, *Barcelona*
Miguel López de Heredia, *Barcelona*
Maria Buti Ferret, *Barcelona*
Puri Fortes, *Pamplona*
Joan Genescà, *Barcelona*
María josé Gómez-Lechón, *Valencia*
Arias Jaime, *Madrid*
Jose JG Marin, *Salamanca*
Jordi Muntane, *Cordoba*
Julia Peinado Onsurbe, *Barcelona*
Ángeles Pajares María, *Madrid*
Albert Parés, *Barcelona*
Sonia Ramos, *Madrid*
Cristina Ripoll, *Madrid*
Isabel Fabregat Romero, *Barcelon*
Marta Rodriguez Romero, *Salamanca*
Juan Macias Sanchez, *Sevilla*
Juan Sastre, *Valencia*
Manuel Vázquez-Carrera, *Barcelona*

Sri Lanka

EG Don Shaman Rajindrajith, *Ragama*

Sudan

Hatim M Yousif Mudawi, *Khartoum*

Switzerland

Maurer Andreas Christoph, *Liestal*
Beat Mullhaupt, *Zurich*

Thailand

Nattiya Hirankarn, *Bangkok*
Somchai Pinlaor, *Khon Kaen*
Yong Poovorawan, *Bangkok*
Abhasnee Sobhonslidsuk, *Bangkok*
Chanitra Thuwajit, *Bangkok*
Sopit Wongkham, *Khon Kaen*

Tunisia

Olfa Bahri, *Tunis*
Chadli Dziri, *Tunis*

Turkey

Inci Alican, *Istanbul*
Ahmet Atessahin, *Elazig*
Yasemin Hatice Balaban, *Ankara*
Hayrullah Derici, *Bornova*
Cigdem Ulukaya Durakbasa, *Istanbul*
Muhsin M Muhip Harputluoglu, *Malatya*
Adnan Kabaalioglu, *Antalya*
Abdurrahman Kadayifci, *Gaziantep*
Ali Sazci, *Kocaeli*
Ilker Tasci, *Etlik*
Mehmet Yalniz, *Elazig*
Serkan Yener, *Inciralti*
Yusuf Yilmaz, *Istanbul*

United Kingdom

Alastair David Burt, *Newcastle*
David O Cosgrove, *London*
Anil Dhawan, *London*
Indra Neil Guha, *Nottingham*
Phillip Macdonald Harrison, *London*
Stefan G Hübscher, *Birmingham*
Long R Jiao, *England*
Anastasios T Koulaouzidis, *Edinburgh*
Patricia Lalor, *Birmingham*
David A Lomas, *Cambridge*
Rajeshwar Prosad Mookerjee, *London*
Gareth John Morris-Stiff, *Wales*
Kathryn Louise Nash, *Southampton*
Derek Anthony O'Reilly, *Manchester*
Christian Philipp Selinger, *Bolton*
Konstantinos Tziomalos, *London*
Feng Wu, *Oxford*
Emmanouil Zacharakis, *London*

United States

Gary A Abrams, *Montgomery*
Hans-Olov Adami, *Boston*
Joseph Ahn, *Maywood*
Hassan Hesham A-Kader, *Tucson*
Shannon Marie Bailey, *Alabama*
Numan Cem Balci, *Alabama*
Linas A Bieliauskas, *Ann Arbor*
Edmund J Bini, *New York*
Anupam Bishayee, *Rootstown*
Victor Ephraim Buckwold, *Frederick*
Roniel Cabrera, *Gainesville*
Guoqing Cao, *Indiana*
Disaya Chavalitdhamrong, *New York*
Chien-Shing Chen, *Loma Linda*
Fei Chen, *Morgantown*
Su Chen, *San Antonio*
Youhai H Chen, *Philadelphia*
Jinah Choi, *Merced*
Anne Mara Covey, *New York*
Mark J Czaja, *Bronx*
Srikanta Dash, *New Orleans*
Michael E de Vera, *Pittsburgh*
Anthony Jacob Demetris, *Pittsburgh*
Sridevi Devaraj, *Sacramento*
Lisa Ross Dixon, *Gainesville*
Terrence M Donohue, *Omaha*
Q Ping Dou, *Detroit*
Murray N Ehrinpreis, *Detroit*
Marwan Ghazi Fakih, *Buffalo*
Shengyun Fang, *Baltimore*
Claus J Fimmel, *Maywood*
Robert Anthony Fisher, *Richmond*
Samuel W French, *Torrance*
Phillip Allen Furman, *Princeton*
M Eric Gershwin, *Davis*
Jalal K Ghali, *Detroit*
Grace Liejun Guo, *Kansas*
Dieter Haemmerich, *Charleston*
Young S Hahn, *Charlottesville*
James Paul Hardwick, *Ohio*
Stephen A Harrison, *Fort Sam Houston*
Dee Harrison-Findik, *Omaha*
Sidhartha Hazari, *New Orleans*
Thomas Sacher Helling, *Jackson*
Alan William Hemming, *Gainesville*
Iryna S Hepburn, *Evans*
Ai-Xuan Le Holterman, *Chicago*
Ke-Qin Hu, *Orange*
Guang-Cun Huang, *Columbus*
Wendong Huang, *Duarte*
Rachel Mary Hudacko, *New Brunswick*
Michael John Jacobs, *Rochester*
Hartmut Walter Jaeschke, *Kansas City*
Ravi Jhaveri, *Durham*
Lynt B Johnson, *Washington*
Neil Louis Julie, *Bethesda*
Sanjay Kakar, *San Francisco*
Sanjeeva P Kalva, *Boston*
Jing X Kang, *Charlestown*
Hetal Karsan, *Atlanta*
Emmet B Keeffe, *Palo Alto*
Nancy Ellen Kemeny, *New York*
Andrew Scott Kennedy, *Cary*
Kusum K Kharbanda, *Omaha*
David H Kirn, *San Francisco*
Hyam Lerner Leffert, *La Jolla*
Stacee Marie Lerret, *Milwaukee*
Fengzhi Li, *New York*
Wei Li, *Houston*
Shuang Liu, *Indiana*
Su Hao Lo, *Davis*
Daniel G Maluf, *Richmond*
Jose E Manautou, *Storrs*
Richard S Mangus, *Indianapolis*
Mary Ko Manibusan, *Springfield*
Paul Martin, *Miami*
Jochen Mattner, *Cincinnati*
James Andrew McCubrey, *Greenville*
Valentina Medici, *Sacramento*
George Michalopoulos, *Pittsburgh*
Smruti Ranjan Mohanty, *Chicago*
John Tomlin Moore, *Research Triangle Park*
Ravi Murthy, *Houston*
Laura E Nagy, *Cleveland*
Sagar U Nigwekar, *Rochester*
Kevin F Staveley O'Carroll, *Hershey*
Eileen M O'Reilly, *New York*
Melissa Kay Osborn, *Atlanta*
Helieh Saatara Oz, *Lexington*
Igor P Pogribny, *Jefferson*
Daniel S Pratt, *Boston*
Ratna Bhattacharyya Ray, *St. Louis*
Raymund R Razonable, *Rochester*
Nancy Reau, *Chicago*
Janardan K Reddy, *Chicago*
Martin J Ronis, *Little Rock*
Phillip Ruiz, *Miami*
Tanios Bekaii Saab, *Columbus*
Adnan Said, *Madison*
Neeraj Saxena, *Atlanta*
Ann Scheimann, *Baltimore*
Timothy M Schmitt, *Charlottesville*
Bernd Schnabl, *La Jolla*
Kunwar Shailubhai, *Doylestown*
Muhammad Y Sheikh, *Fresno*
Perry Shen, *Winston-Salem*
Viji Shridhar, *Rochester*
Shivendra D Shukla, *Missouri*
Ashwani K Singal, *Stanford*
Keshav K Singh, *Buffalo*
Omar Skalli, *Shreveport*
Byoung-Joon Song, *Bethesda*
Branko Stefanovic, *Tallahassee*
Stephen Strom, *Pittsburgh*
Xiao Su, *San Francisco*
Wing-Kin Syn, *North Carolina*

WJH

World Journal of Hepatology

Contents

Monthly Volume 5 Number 1 January 27, 2013

REVIEW

1 Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation
Paolo F, Marialuisa B, Stefania B, Helmut G, Moira M, Cristiana C, Carlo O

16 Diagnosis and management of bacterial infections in decompensated cirrhosis
Pleguezuelo M, Benitez JM, Jurado J, Montero JL, De la Mata M

ORIGINAL ARTICLE

26 Outcomes following liver transplantation in intensive care unit patients
Sibulesky L, Heckman MG, Taner CB, Canabal JM, Diehl NN, Perry DK, Willingham DL, Pungpapong S, Rosser BG, Kramer DJ, Nguyen JH

BRIEF ARTICLE

33 Pancreatic fistula: A proposed percutaneous procedure
Pradella S, Mazza E, Mondaini F, Colagrande S

38 Treatment of Budd-Chiari syndrome with a focus on transjugular intrahepatic portosystemic shunt
Neumann AB, Andersen SD, Nielsen DT, Holland-Fischer P, Vilstrup H, Grønbæk H

CASE REPORT

43 Hepatitis B reactivation related to everolimus
Sezgin Göksu S, Bilal S, Coşkun HS

Contents

World Journal of Hepatology
Volume 5 Number 1 January 27, 2013

APPENDIX I-V Instructions to authors

ABOUT COVER Editorial Board Member of *World Journal of Hepatology*, John M Luk, MD, Department of Surgery and Center for Cancer Research, The University of Hong Kong, 21 Pokfulam Road, Pokfulam, Hong Kong, China

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ ABSTRACTING

World Journal of Hepatology is now indexed in PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

FLYLEAF I-V Editorial Board

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITOR-IN-CHIEF
Masatoshi Kudo, MD, PhD, Professor, Department of Gastroenterology and Hepatology, Kinki University School of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama, 589-8511 Osaka, Japan

EDITORIAL OFFICE
Jian-Xia Cheng, Director
Jin-Lei Wang, Vice Director

World Journal of Hepatology
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Bulding, No.90 Jaffe Road, Wanchai, Hong Kong, China
Telephone: +852-58042046
Fax: +852-31158812
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
January 27, 2013

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5182/g_info_20100316080002.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i1.1

World J Hepatol 2013 January 27; 5(1): 1-15
ISSN 1948-5182 (online)

REVIEW

Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation

Feltracco Paolo, Brezzi Marialuisa, Barbieri Stefania, Galligioni Helmut, Milevoj Moira, Carollo Cristiana, Ori Carlo

Feltracco Paolo, Brezzi Marialuisa, Barbieri Stefania, Galligioni Helmut, Milevoj Moira, Carollo Cristiana, Ori Carlo, Department of Medicine UO Anesthesia and Intensive Care, University Hospital of Padova, Via Cesare Battisti, 256, 35128 Padova, Italy

Author contributions: Paolo F and Marialuisa B performed the literature search and drafted the article; all other authors made substantial contributions in completing the manuscript, revising it for important intellectual content, and approving the version to be submitted.

Correspondence to: Feltracco Paolo, MD, Department of Medicine UO Anesthesia and Intensive Care, University Hospital of Padova, Via Cesare Battisti, 256, 35128 Padova, Italy. paolofeltracco@inwind.it
Telephone: +39-49-8218285 Fax: +39-49-8218289
Received: August 9, 2012 Revised: January 7, 2013
Accepted: January 18, 2013
Published online: January 27, 2013

Abstract

Blood loss during liver transplantation (OLTx) is a common consequence of pre-existing abnormalities of the hemostatic system, portal hypertension with multiple collateral vessels, portal vein thrombosis, previous abdominal surgery, splenomegaly, and poor "functional" recovery of the new liver. The intrinsic coagulopathic features of end stage cirrhosis along with surgical technical difficulties make transfusion-free liver transplantation a major challenge, and, despite the improvements in understanding of intraoperative coagulation profiles and strategies to control blood loss, the requirements for blood or blood products remains high. The impact of blood transfusion has been shown to be significant and independent of other well-known predictors of posttransplant-outcome. Negative effects on immunomodulation and an increased risk of postoperative complications and mortality have been repeatedly demonstrated. Isovolemic hemodilution, the extensive utilization of thromboelastogram and the use of autotransfusion devices are among the commonly adopted procedures to limit the amount of blood transfusion. The use of intraoperative blood salvage and autologous blood transfusion should still be considered an important method to reduce the need for allogenic blood and the associated complications. In this article we report on the common preoperative and intraoperative factors contributing to blood loss, intraoperative transfusion practices, anesthesiologic and surgical strategies to prevent blood loss, and on intraoperative blood salvaging techniques and autologous blood transfusion. Even though the advances in surgical technique and anesthetic management, as well as a better understanding of the risk factors, have resulted in a steady decrease in intraoperative bleeding, most patients still bleed extensively. Blood transfusion therapy is still a critical feature during OLTx and various studies have shown a large variability in the use of blood products among different centers and even among individual anesthesiologists within the same center. Unfortunately, despite the large number of OLTx performed each year, there is still paucity of large randomized, multicentre, and controlled studies which indicate how to prevent bleeding, the transfusion needs and thresholds, and the "evidence based" perioperative strategies to reduce the amount of transfusion.

Key words: Transplantation surgery; Liver dysfunction; Liver transplant; Intraoperative bleeding; Intraoperative transfusion; Autotransfusion; Autologous transfusions; Transfusion requirements; Blood salvage; Cell salvage

Paolo F, Marialuisa B, Stefania B, Helmut G, Moira M, Cristiana C, Carlo O. Blood loss, predictors of bleeding, transfusion practice and strategies of blood cell salvaging during liver transplantation. *World J Hepatol* 2013; 5(1): 1-15 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i1/1.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i1.1

INTRODUCTION

Bleeding in major surgical procedures involving the liver, such as partial liver resection and liver transplantation (OLTx), occurs almost inevitably and still represents a daunting problem when massive. Although the origin of bleeding during OLTx is multifactorial, technical difficulties and pre-existing abnormalities of the hemostatic system represent the principal causes of significant perioperative hemorrhages. Since there is minimal consensus on transfusion guidelines during OLTx, massive volume empirical transfusion was the standard practice until a few years ago, and blood products accounted for approximately 10% of the total cost of transplantation[1,2].

As anesthesiologic and surgical teams have gained experience blood loss in patients undergoing liver transplantation has decreased substantially and in recent years the procedure is occasionally performed without intraoperative blood transfusion.

A variety of strategies, including acute isovolemic hemodilution, appropriate surgical and anesthesiologic management, and the use of autotransfusion devices have been adopted during the last decade to limit the amount of allogenic blood transfusion. In addition, the extensive utilization of thromboelastogram (TEG) has improved the understanding of intraoperative coagulation profiles of these patients and led to a reduction in blood requirements[3].

However, the intrinsic coagulopathic features of end stage cirrhosis make transfusion-free liver transplantation a major challenge, and despite the improvement in strategies to control blood loss, most patients still bleed extensively. This requires the transfusion of variable amount of blood or blood products and may be associated with increased rates of morbidity and mortality.

Blood bank demands in complicated liver transplant surgery are still high and even though the quality and safety of blood products continue to improve they remain costly and increase the risks encountered by the patient.

The relationship between intraoperative blood use, the effects on immunomodulation and an increased risk of postoperative complications, such as infections, gastrointestinal, intra-abdominal, and/or pulmonary complications, prolonged recovery, and a higher rate of reoperation has been repeatedly demonstrated[4,5].

Among the various strategies to substantially reduce the amount of blood product transfusions and the associated side effects, intraoperative blood salvage has been considered and still is an important method of blood conservation. However, controversy still surrounds its usefulness during OLTx, with studies demonstrating either an increase or a decrease in blood transfusion.

Since the clinical conditions of the candidates who undergo liver transplant surgery are increasingly critical and therefore we cannot predict with accuracy which patients will bleed, in our personal view a cell saver machine should be instituted in all OLTx.

BLOOD LOSS DURING LIVER TRANSPLANTATION

The liver is a highly vascular organ and the transplant procedure usually involves a recipient with severe coagulopathy, portal hypertension, and sometimes previous abdominal surgery. Blood losses and transfusion requirements remain difficult to predict in the intraoperative course of OLTx and many studies have shown discordant results and no uniform conclusions[6]. In general the predictions are based on the severity of liver disease, preoperative coagulation function, recipient's clinical status, quality of the donor liver, and experience of the transplantation team. Blood losses are frequently difficult to measure during OLTx, and quite often they are quantified indirectly by calculating the amount of blood necessary to maintain or reach a predetermined hematocrit (Ht) or hemoglobin (Hb) value. As previously stated, advances in surgical technique and anesthetic management, as well as a better understanding of the risk factors, have resulted in a steady decrease in intraoperative bleeding and transfusion requirements[7]. However, the risk of bleeding still seems to vary from centre to centre depending on various factors such as the severity of recipient's clinical conditions, surgeon's preferred technique, the duration of surgery, the duration of the anhepatic phase, and the time to graft function. Many preoperative conditions and unforeseen intraoperative events impart complex changes to the recipient's spontaneous hemostasis; the potential occurrence of technical difficulties which require massive fluid resuscitation may alter the substantial intraoperative coagulopathy and predispose to further extensive bleeding. Contributing factors to blood loss during OLTx can be categorized as preoperative and intraoperative.

PREOPERATIVE HEMATOLOGIC AND COAGULATION DEFECTS

Hemostatic function is determined by the interaction of the vascular wall, platelets, coagulation factors, and fibrinolytic function. All these components may be abnormal in patients who have a compromised liver function. Anemia is common in these patients as a result of chronic disease, malnutrition, or occult bleeding. Bleeding complications may not be primarily related to impaired coagulation; alterations in haemodynamics and vessel wall function may play a more important role. The hyperdynamic circulation and the presence of portal hypertension are among the most important causes of perioperative bleeding tendency[8]. The aetiology of impaired haemostasis in the advanced liver failure is often multifactorial and may include impaired coagulation factor synthesis, synthesis of dysfunctional coagulation factors, their increased consumption, altered clearance of activated factors, hyperfibrinolysis, disseminated intravascular coagulation (DIC), and platelet disorders.

The reduced hepatic synthesis of clotting factors is also associated with a significant deficit of natural anticoagulants, particularly protein C and antithrombin.

Commonly, the vitamin K-dependent factors decrease first, starting with factor Ⅶ and protein C owing to their short half-life (6 h), followed by reductions_in factor Ⅴ, Ⅱ and Ⅹ levels[9].

Impaired synthesis and altered clearance of the fibrinolytic factors cause complex abnormalities in the fibrinolytic system. One of the most striking mechanisms is an imbalance between tissue plasminogen activator (t-PA) and its specific inhibitor plasminogen activator inhibitor-1 (PAI-1)[10]. Quantitative (thrombocytopenia) and/or qualitative platelet abnormalities (thrombocytopathies) such as impaired platelet adhesion and aggregation are often attributed to splenic sequestration (hypersplenism), but may also occur as a result of platelet destruction mediated by platelet-associated immunoglobulins, impaired hepatic synthesis and/or increased degradation of thrombopoietin by platelets sequestered in the congested spleen[11].

Additional risk factors for extensive bleeding include the injury of collateral vessels developing as a result of portal hypertension, some from the raw surface of the liver, inflammatory adhesions, as well as previous abdominal surgery.

INTRAOPERATIVE FACTORS CONTRIBUTING TO BLOOD LOSS

Complex coagulation disorders may occur during liver transplantation due to the underlying liver disease and haemostatic changes associated with the transplantation. The latter may result from hemodilution, platelet consumption, disordered thrombin regulation, and fibrinolysis. Haemodilution secondary to fluid replacement and the preservation solution from the donor liver can additionally reduce plasma levels of coagulation factors. Variable intraoperative blood loss may ensue in the form of brisk bleeding through a vascular injury and/or appear as diffuse continuous microvascular bleeding mixed with the peritoneal ascites. Technical difficulties predisposing to bleeding include portal vein thrombosis, post-surgical adhesions, and, in children with biliary atresia, previous portoenterostomy. Bleeding is greatly potentiated by the activation of the fibrinolytic system, which occurs both during the anhepatic and reperfusion phases. During the anhepatic phase, circulating levels of PAI-1 are reduced leading to an increase in t-PA. Some patients develop severe coagulopathy early after the reperfusion phase due to an accelerated release of t-PA from the graft endothelium which causes generalized fibrinolysis and significant bleeding[12]. Release of exogenous heparin from the harvested graft after donor heparinization or endogenous heparin-like substances from the damaged ischaemic graft endothelium may also play a role in the coagulopathy at reperfusion[13]. Other intraoperative factors contributing to prolonged hemorrhage include hypothermia, hypocalemia and citrate toxicity. Bleeding during the postanhepatic phase may also be related to disseminated intravascular coagulation and platelet trapping. Platelet trapping has been documented by simultaneous measurement of arterial and venous platelet counts. DIC has been correlated with ischemic damage of the graft liver[14]. Transplantation of an optimal graft restores the patient's clotting function. A dysfunctional graft may not immediately produce clotting factors, thereby leading to prolonged coagulopathy mandating massive transfusions[15].

PREDICTORS OF TRANSFUSION REQUIREMENTS

The most important variables affecting transfusion requirements include the severity of disease [Child-Turcotte-Pugh Score, United Network for Organ Sharing priority for transplantation or in recent years model for end-stage liver disease (MELD) classification], preoperative prothrombin time (PT), history of abdominal operations, and Factor Ⅴ levels. The Child classification is a measure of disease severity that includes assessments of ascites, encephalopathy and measurements of serum bilirubin and albumin. MELD gives a score based on how urgently the patient needs a liver transplant within the next three months. Its impact on transfusion requirements at the time of transplantation may be difficult to predict. The length of cold ischemia time has also been associated with short-term graft dysfunction and negative effects on perioperative red blood cell (RBC) transfusion requirements. Other variables include cholestasis, splenomegaly, the preoperative haematocrit value, use of the piggyback transplantation method, and operative time[16]. Patients with chronic active hepatitis have more advanced disease and require more blood products than patients with primary biliary cirrhosis[17]. Previous upper abdominal surgery tends to have vascularised adhesions which may render liver dissection hemorrhagic. Portal vein hypoplasia and decreased donor liver size, presenting a technical challenge for the surgeons, were predictive of blood loss[16]. Use of a partial liver graft, as in living-donor liver transplantation, creates a graft with a raw surface that can bleed after reperfusion[14]. The risk of primary nonfunction after transplantation of poor quality cadaveric graft increases proportionately with the degree of steatosis. Graft dysfunction further necessitates massive transfusions[18]. Inadequate graft-recipient body weight ratio, poor graft preservation and prolonged cold ischemia time have also been associated with increased intraoperative bleeding tendency[14]. Massicotte *et al*[6] in a retrospective study of 206 successive liver transplants found that the three most important variables related to the number of RBC units transfused were: the starting international normalized ratio (INR) value, the starting platelet count, and the duration of surgery.Plasma transfusion did not decrease the amount of RBC transfusions.

Deakin *et al*[19] showed that in their population of 300 adult liver transplantations, blood urea nitrogen level and platelet count had an independent correlation with transfusion necessity. Ramos *et al*[20] looking for useful variables for the preoperative identification of patients likely to require transfusion of RBCs could not show a statistically significant relationship between preoperative coagulation parameters and need for intraoperative blood products. However, age, Child class, diagnosis, INR, Hb level and the effect of intraoperative portacaval shunt placement were close to significance on the amount of blood transfusion. They concluded that preoperative normalization of Hb level and placement of intraoperative portacaval shunt could diminish the need for RBC transfusion during OLTx. In a multivariate linear regression analysis of 526 liver transplants Mangus *et al*[21] demonstrated that predictors of estimated blood loss were age, MELD score, preoperative hemoglobin, initial fibrinogen, initial central venous pressure, and total anesthesia time. Specific predictors of RBCs usage were age, MELD score, preoperative hemoglobin, initial fibrinogen, and anesthesia time. On the contrary, Massicotte *et al*[22] found that only two variables were linked to RBC transfusion: starting hemoglobin value and phlebotomy. In their study the MELD score did not predict blood losses and blood product requirement during OLTx.

Steib *et al*[23] looking at the preoperative factors associated with high blood loss in 510 consecutive patients undergoing OLTx, were unable to correctly identify patients at risk for intraoperative hemorrhage. In the recent study by Roullet *et al*[24], MELD score did not appear as a risk factor for bleeding or transfusion requirements during OLTx, nor did previous upper abdominal surgery, preoperative coagulation defects, or Hb level. They concluded that the preoperative risk factors for bleeding and transfusion during OLTx were of little clinical usefulness and therefore blood products should always be available during the procedure. Given the poor predictive value of the single preoperative variable even in a homogeneous population some authors recommend that centres evaluate their practice individually in order to identify the centre-specific risk factors and high risk patients for perioperative transfusion[25].

TRANSFUSION PRACTICE DURING OLTx

Blood transfusion therapy has remained a critical feature in OLTx and various studies have shown a large variability in the use of blood products among different centers and even among individual anesthesiologists within the same center[2]. The decision of when a patient should be transfused with RBCs still remains a greatly discussed issue, in part because there is scant evidence supporting one practice over another. For example, conflicting results derive from the adoption of different triggers for blood transfusion or different inter-centre protocols or protocols not driven by coagulation monitoring or with or without the use of antifibrinolytics. Evidence that liberal RBCs transfusion thresholds are associated with better outcomes than a more restrictive approach is still lacking, and a remarkable variability in this practice continues to be observed. In particular, there is little published data in support of RBCs transfusion when the Hb level is above 7 g/dL, even if the patient has cardiac comorbidities[15,26]. Some authors recommend to keep the hematocrit between 30% and 35%; others think it advisable and acceptable to maintain it between 26% and 28%[27,28]. In the study by Steib *et al*[23] RBCs were administered to maintain Ht levels at 30%. Even though OLTx surgery is widely seen as a highly specialized procedure, strict guidelines for optimal use of packed red blood cells have not been developed. The influence of the amount of transfusion of various blood components on clinical outcome after liver transplantation has not been studied in detail. Blood transfusion is generally considered a surrogate marker for sicker patients and complex surgery, and its role on outcome has not been precisely defined in large trials[7].

Fresh frozen plasma transfusion

The standard indication for fresh frozen plasma (FFP) infusion is clotting improvement; in some centres FFP is still administered for volume replacement in case of hemodynamic derangement. Many consider transfusing FFP while waiting for laboratory results reasonable and preferable to not giving coagulation factors in time[29]. Freeman *et al*[30] support the view that FFP administration is not essential during OLTx and that platelets and fibrinogen concentrates may be given when platelet count and fibrinogen level fall to below 50.000 mm^3 and 1 g/L, and human serum albumin can be used as a volume expander. Liver removal during surgery leaves the patient anhepatic for a period of time, which further complicates the coagulation. This phase is associated with a decrease in Factors Ⅷ and Ⅴ, a decrease in fibrinogen, and an increase in fibrinolysis. FFP is expected to improve complex coagulation disorders in case of severe bleeding as it contains all coagulation factors and inhibitors. FFP should be treated with solvent-detergent to inactivate viral particles and decrease the risk of viral infection. Treated plasma has lower factor Ⅷ and alpha-2 antiplasmin activity, but patients who receive treated FFP demonstrate a similar correction of the INR and activated partial thromboplastin time (aPTT), and they have transfusion requirements similar to those of patients who receive untreated FFP[30]. Whether FFP should always be used for treating a patient with major blood loss during OLTx is still not completely defined. In addition there is currently no consensus on the volume of FFP or rate of infusion required to prevent or treat intraoperative persistent bleeding; in the common practice 10-15 mL/kg are usually administered. Because of the lack of universally shared guidelines, beside some centre-specific indications[28], both the amount and timing of FFP administration during OLTx still seem guided by experienced clinical judgment, local practices

and the assistance of timely coagulation tests (including near-patient tests).

Platelets transfusion during OLTx

Although there is no consensus regarding the appropriate threshold, platelet concentrates are frequently administered during OLTx for the prevention or treatment of bleeding. However, intraoperative platelet transfusions have been identified as a strong independent risk factor for patient survival after OLTx, in addition to RBCs[31]. The negative impact of platelet transfusions is independent from other well known risk factors, in accordance with the adverse effects of platelets discovered in experimental studies. In animal models of liver transplantation, studies have demonstrated that platelets are involved in the pathogenesis of reperfusion injury of the liver graft by inducing endothelial cell apoptosis. This effect is independent of ischemia-related endothelial cell injury and cannot simply be explained by activation of the coagulation system and aggregation of platelets at the site of endothelial cell injury[32]. In addition, platelets contain many cytokines and vasoactive and inflammatory mediators which are rapidly released on activation by various stimuli after reperfusion. The specific causes that lead to a worse outcome following platelet transfusion have not been examined, however, several factors have been considered such as the risk of viral transmission, the potential for bacterial contamination especially for platelets stored at room temperature[33], the risk of alloimmunization, graft *vs* host disease, nonspecific immunosuppressive effects, and acute lung injury (ALI) or adult distress respiratory syndrome (ARDS). Recent studies show that it is not RBC, but, in fact, plasma-rich blood products, such as FFP and platelet transfusions, that are linked to the development of ALI/ARDS[34]. Pereboom *et al*[35] demonstrated that platelet transfusion during OLTx is associated with increased postoperative mortality due to heavy lungs because of severe lung edema in accordance with the clinical diagnosis of transfusion-related acute lung injury (TRALI)/ARDS. The increased rate of graft loss after platelet transfusion did not result from the specific adverse effects of transfused platelets such as an increased occurrence of graft-related thrombotic complications, but it was caused by higher rate of patients' death with a well functioning graft. Due to the difficulty in discerning whether a bleeding complication during OLTx is a result of the lack of platelets or defects in other hemostatic systems it seems reasonable not to transfuse patients based on a low platelet count alone. Given the reported detrimental effects of platelet transfusion, it is advisable to transfuse them only if significant bleeding complications do occur which are mostly attributable to low platelet count or dysfunctional platelets as demonstrated by on-site coagulation monitoring. Considering that the appropriateness of different blood components administration schemes has not been evaluated in randomised studies, a specific approach targeted to the individual needs may be reasonable. In addition to surgical and anesthetic measures to minimize intraoperative blood loss, a conservative and more targeted use of blood products, weighing the short-term benefits *vs* increased postoperative risk for adverse events in each individual patient, should be considered.

OLTx WITHOUT BLOOD/BLOOD PRODUCTS

For many uncomplicated recipients OLTx has been safely performed without transfusion of any blood products, especially when maximum blood loss was limited to 2500-3500 mL[36]. Even though, as aforementioned, the reports from various centres attest to the high variability of transfusion requirements, a confirmed trend toward a significant reduction in the use of blood products is being observed nowadays[2]. Massicotte *et al*[6] reported that up to 79% of their patient population did not need any red cell transfusion during surgery. Transfusion-free OLTx in Jehovah's witnesses, in combination with preoperative stimulation of red cell production using recombinant human erythropoietin and iron, cell salvage, volemic replacement and tolerance of moderate anemia, have been associated with favourable results[37]. Limiting transfusions to situations where clinical bleeding and/or severe anemia are present has been shown to reduce many perioperative complications. Bloodless strategies also include meticulous surgical technique and the intraoperative hemodilution procedure, where the patient's blood is removed and replaced with non-blood products (5% albumin and crystalloid solution) whenever feasible. The patient's blood is later reinfused during the operation as needed or routinely after liver implantation. Acute normovolemic hemodilution preserves the integrity of the red blood cells and clotting factors, ensuring the availability of safe, fresh autologous blood. Contraindications to the hemodilution procedure include coronary heart disease, significant anemia, and severe pulmonary hypertension. Both prophylactic (prior to incision) and intraoperative administration of recombinant activated Factor Ⅶa has been considered by some authors to prevent intraoperative blood transfusion in Jehovah's witnesses or markedly reduce it in non-Jehovah's witnesses[36,37].

INTRAOPERATIVE BLOOD TRANSFUSION, COMPLICATIONS AND OUTCOME

The impact of blood transfusion has been shown to be important and independent of other well-known predictors of posttransplant outcome, such as recovery of graft function, infectious disease, renal failure, and other comorbidities. Older studies have observed that an increased blood requirement was associated with many adverse events in the postoperative period, including higher rates of graft failure and patient mortality[18]. Cacciarelli

et al[38] reviewed 225 adult OLTx recipients and showed a significant improvement in both patient and graft survival when less than 5 U of RBCs were transfused intraoperatively. Ramos *et al*[20] showed that even a moderate number of blood transfusions was associated with a longer hospital stay and that transfusion of more than 6 U of PRBCs was associated with diminished survival. In pediatric patients, increased blood product administration appeared as a significant independent negative predictor of long-term patient survival[39]. As Hendriks *et al*[39] stated intraoperative transfusion of RBCs was the sole predictor of surgical reintervention after OLTx. Patients with reinterventions had a three-fold higher mortality during the observation period and had significantly longer hospital stay compared with patients without reinterventions. Whether the difference in outcome is related to the transfusion as an independent risk factor or whether the transfusion is a marker for a technically more difficult surgery remains unclear[14]. However, multiple observations underline that every attempt to control blood loss and reduce transfusion requirements should be practiced in order to lessen the probability of surgical reintervention and improve in-hospital morbility and overall outcome. The immunosuppressive effect and the induction of several complications may account for the negative correlation between the intraoperative blood transfusion and postoperative outcome. Common complications of massive transfusions are immunologic adverse effects, metabolic derangement, infectious exposure with increased septic episodes, and acute lung injury. Transfusion-related immunological adverse effects include anaphylactic reactions, hemolysis, graft *vs* host disease, and nonspecific immunosuppressive effects. Large volumes of allogenic blood result in the infusion of large amounts of foreign antigens in both soluble and cell-associated forms. The persistence of these antigens in the circulation of the recipient is considered to result in impaired cell-mediated and natural killer cell activity, and deterioration in liver regeneration[40,41]. Severe metabolic derangement from massive transfusion may occur as a consequence of dilutional coagulopathy, dilutional thrombocytopenia, DIC, citrate toxicity, metabolic alkalosis, hypocalcemia, hypomagnesemia, hyperkalemia, acid/base disturbances and hypothermia[42]. Blood products transfusions have been identified as a risk factor for TRALI, ALI and ARDS[43].

ARDS is a serious multifactorial complication after OLTx most likely caused by fluid overload from crystalloid liquid infusion or massive transfusion and reperfusion syndrome[44]. The risk of developing ALI/ARDS seems to be higher after transfusion of FFP or platelets than after RBC[34]. Other postoperative complications associated with blood transfusion include perioperative myocardial infarction, postoperative low-output cardiac failure, and increased tumor recurrence[45-47]. In addition, exposure to multiple units of allogenic blood increases the risk of developing abnormal antibodies which makes future crossmatching more difficult and time-consuming[48].

INTRAOPERATIVE STRATEGIES TO REDUCE BLOOD LOSS

Anesthesiologic management

Properly balanced intraoperative fluids, use of predefined or "individualized" transfusion triggers, and prophylactically administered pharmacologic agents capable of reducing blood loss may have a positive impact on amount of bleeding and transfusion requirements. Avoiding excessive fluid administration and maintaining relative hypovolemia have been firmly advocated. As demonstrated during hepatic resections, maintaining a low central venous pressure (CVP) *via* volume restriction, phlebotomy, or both, has been shown to decrease surgical blood loss and promote graft decongestion. A low CVP has been recommended to minimize blood loss during explantation of the liver. With the "classical" cava-cava technique severe hemodynamic instability may ensue when inferior vena cava is clamped in the presence of hypovolemia; on the other hand with the wider application of the "piggy-back" technique measures to maintain CVP below 5 cm H_2O have become possible. Massicotte *et al*[49,50] reported that maintaining a low CVP before the anhepatic phase was of utmost importance to decrease blood loss and transfusion rate. However, the debate on an optimal CVP value to prevent major bleeding during OLTx is still not solved; in fact, although a low CVP is associated with reduced blood loss, it also carries a higher risk of complications such as air embolism, systemic tissue hypoperfusion, and renal failure. Schroeder *et al*[51] demonstrated that intentionally lowering the CVP to decrease blood loss during OLTx was associated with significant morbidity and mortality; the postoperative peak serum creatinine level, the need for dialysis, and 30-d mortality were higher in patients who had low CVP. Many transplant surgeons prefer that the CVP be kept "low" after reperfusion of the graft to avoid venous congestion of the new graft, but any quantification of this "low" number is futile. During liver transplantation there is no evidence to support decreasing CVP and effective circulating blood volume to levels currently practiced during hepatic resections surgery; this practice might compromise vital organ perfusion[52]. Diuretics also often play a role in achieving euvolemia and can help in reducing transfusion requirements. The osmotic activity of mannitol can aid in removing free water within abdominal organs, particularly in the setting of hepatorenal syndrome, thus preventing hepatic distension once the graft is reperfused. Due to the lack of adequately powered, randomized, prospective controlled trials further investigations are needed to determine which patients would benefit from restrictive volume management in the intraoperative period of OLTx. Intraoperative coagulation abnormalities have long been thought of as major culprits for blood loss and transfusion requirements. They may be aggravated by unrecognized hypothermia and acidosis. Hypothermia likely occurs when large volumes of unheated fluids are admin-

istered; acidosis affects hemostasis as well, probably by inhibition of platelet function[53]. Among the strategies to attenuate surgical bleeding by reducing both graft and portal vein pressure the use of lower tidal volumes (6-8 mL/kg) and very low positive end-expiratory pressure, have also been advocated[3].

Thromboelastography

Besides standard coagulation tests (i.e., PT, aPTT, fibrinogen levels), TEG allows a rapid on-site assessment of the functional clotting status. Its use permits the assessment of both cellular and humoral components of whole blood coagulation and fibrinolysis, instead of a single procoagulation or anticoagulation parameter. Results can be obtained fairly quickly, the onset of clot formation within a few min and platelet function within 45 min. The prognostic value of intraoperative standard tests on bleeding or blood component requirements is poorly documented and controversial.

TEG, on the other hand, can assist anesthesiologists in treating intraoperative bleeding by identifying the cause and facilitate selective use of blood components and specific drug treatments[54]. In various studies the amount of blood usage was significantly reduced when TEG monitoring was compared to the conventional "clinician-directed" transfusion management. Wang *et al*[55] demonstrated that the same was true for FFP administration during OLTx as well. Fewer units of FFP were required to keep the TEG reaction time within an accepted transfusion threshold compared with the PT/INR. TEG may also diagnose a heparin-like effect after reperfusion and determine the lowest efficient dose of protamine to correct the prolongation of the reaction time representing the rate of initial fibrin formation[28].

In addition, TEG may help document the prothrombotic state that sometimes occurs in post liver transplant patients because of deficiencies in antithrombin Ⅲ and protein C causing potentially disastrous hepatic artery thrombosis[56].

Even though the usefulness of TEG in complex coagulation defects has been questioned[57], recent literature does reaffirm that the use of TEG and rotation thromboelastometry in more rational transfusion algorithms can reduce the number of blood products transfused[58].

Surgical techniques to reduce blood loss

The importance of surgical experience and skill during hepatic dissection and meticulous hemostasis has long been recognized as important in determining the amount of intraoperative blood loss. One of the first techniques introduced to reduce intraoperative bleeding was the application of the venovenous bypass (VVB) during the anhepatic phase of "classic" OLTx. By decompressing the splanchnic and retroperitoneal circulations, venovenous bypass contributes to reduce blood loss and avoids important hemodynamic changes caused by a variable reduction in venous return to the heart. Another extensively adopted method is the piggy-back technique, which consists of performing the anastomosis of the retrohepatic inferior vena cava of the donor liver directly to the recipient inferior vena cava, thus avoiding extensive dissection of the retroperitoneum in this area. In recipients with portal hypertension and multiple venous collaterals this technique may reduce the anhepatic time and the amount of bleeding. Another advantage of the piggy back technique is the shorter warm ischemia time during implantation of the graft as only one cavo-caval anastomosis has to be performed, compared to the two end-to-end anastomoses of the inferior vena cava in the "classic" technique. While the proponents of the extensive use of venovenous bypass claim that it improves hemodynamic stability, reduces blood loss, and reduces the incidence of postoperative acute renal failure[59], many authors have shown an association between VVB and an increased transfusion of blood products. This increase in the amount of intraoperative bleeding during VVB has been attributed to fibrinolysis, hemolysis, and platelet activation by bypass tubing[60-62]. Miyamoto *et al*[63] demonstrated significantly lower blood transfusion requirements in patients in whom the "piggyback" technique was used, compared with patients transplanted using the "classic" technique. According to the recent statements from the Cochrane database[64] no superiority of one over another technique seems to emerge from the examined trials. Based on the available studies there is currently no evidence to recommend or refute the use of piggy-back method during OLTx as far as the amount of bleeding and blood product consumption is concerned.

PHARMACOLOGICAL STRATEGIES TO REDUCE BLOOD LOSS

Antifibrinolytic drugs

Hyper-fibrinolysis plays a significant role in non-surgical blood loss requiring massive transfusion. Antifibrinolytics will decrease bleeding only in cases where it is caused by enhanced fibrinolysis but they are potentially harmful in patients with prothrombotic states like Budd-Chiari syndrome, retransplantation, fulminant liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, transplant for malignant disease, portal vein thrombosis[65]. Of the two groups of antifibrinolytics available, lysine analogues [epsilon aminocaproic acid (EACA) and tranexamic acid] and serine protease inhibitors (aprotinin), tranexamic acid (TA) is more commonly used. EACA is a synthetic lysine analogue that competitively inhibits the binding of plasminogen to lysine residue on the surface of fibrin and prevents conversion of plasminogen to plasmin. It may also prevent plasmin degradation of platelet glycoprotein Ib receptors, thus preserving platelet function[66]. EACA has demonstrated less antifibrinolytic potency than tranexamic acid. In a prospective, double-blinded, placebo-controlled, randomized study by Dalmau *et al*[67], prophylactic EACA did not reduce intraoperative total red blood cell transfusion during OLT. In addition its use may be associated

with renal complications such as acute tubular necrosis, renal infarction, myopathy, pigment-induced renal complications, glomerular capillary thrombosis and elevated excretion of beta-2 microglobulin. Tranexamic acid prevents plasmin-mediated conversion of fibrinogen to fibrinogen split products by competitively binding to the lysine binding sites on the plasminogen molecule. As compared to EACA, its antifibrinolytic activity is 6-10 times more potent, and higher in peripheral compartments like kidney, intestines, and prostatic tissues. Strong evidence that TA reduces blood transfusion in various types of surgery has been provided in a recent review, even though its effects on thromboembolic events and mortality remains uncertain[68]. In liver transplant surgery the effectiveness of TA in reducing blood transfusion is still under critical evaluation. Years ago, Boylan *et al*[69] demonstrated that administration of tranexamic acid (20 mg/kg) was associated with significantly less intraoperative blood loss and reduced transfusion requirements. No patient had hepatic artery or portal vein thrombosis. More recently, Dalmau *et al*[70] did not find any significant difference in blood loss and transfusion requirements with TA (10 mg/kg per hour) or aprotinin. Thromboembolic events, reoperations and mortality were similar in both groups. Massicotte *et al*[71] compared the efficacy of TA *vs* aprotinin during OLTx. They found no intergroup difference in intraoperative RBC transfusion per patient, final Hb concentration, and the percentage of OLTx cases requiring no blood product administration. In their experience, administration of aprotinin was not superior to TA with regards to blood loss and blood product transfusion requirement.

A study published in 2011 by the Cochrane Hepato-Biliary Group[72], which included all randomised clinical trials that compared various methods of decreasing blood loss and blood transfusion during OLTx, reported that there were no significant differences in the allogenic blood transfusion requirements, amount of platelets, FFP, or cryoprecipitate transfused between the tranexamic acid and control groups.

Aprotinin

Even though a reduction in intraoperative bleeding and transfusion requirement with aprotinin has very frequently been reported, aprotinin use has recently been reduced and criticized as it was related to an increased mortality in cardiac surgery[73].

Antifibrinolytic effect of aprotinin is complex and includes inhibition of plasmin, contact activation system (*via* kallikrein inhibition) and inhibition of tissue-plasminogen activator production. In addition to antifibrinolysis, aprotinin also has antithrombotic effects, which may be due to selective blockade of proteolytically activated thrombin receptors on platelets[74]. The European Multicentre Study of Aprotinin in Liver transplant showed that both high dose and regular dose of aprotinin attenuated fibrinolytic activity, and decreased blood loss and red blood cell transfusion requirements during OLTx[75]. The blood-saving effect of aprotinin was particularly evident when surgery was complicated with significant blood loss. Subsequently, several other reports supported these findings[76,77]. However, parallel to its widespread utilization, concerns arose about the safety of aprotinin and an increased risk of thrombotic complications has been reported[78]. Thromboembolic phenomena are among the most undesirable complications during liver transplantation manifesting as hepatic artery thrombosis, venous thromboembolism, and pulmonary thromboembolism. Lentschener *et al*[78] reported that prophylactic use of large dose aprotinin decreased blood loss and transfusion requirement only when OLTx was associated with significant blood loss, but it did not alter the postoperative outcome. Because of its potential side effects, they recommend that aprotinin should not be systematically administered to patients undergoing OLTx.

It should be noted that most of the data contributing to the increased thromboembolic risk with aprotinin came from a single study - the BART trial[74], whereas in the recent years its negative side effects have been consistently reconsidered.

Molenaar *et al*[79] demonstrated that both aprotinin and TA significantly reduce RBC transfusion requirements; intraoperative use of FFP was significantly reduced with aprotinin but not with TA. No increased risk of hepatic artery thrombosis, venous thromboembolic events or mortality was detected in patients who received antifibrinolytics. No significant difference in the proportion of thromboembolic episodes or other serious adverse events between the aprotinin-treated groups and controls was also reported in the recent review by Gurusamy *et al*[72] and Liu *et al*[80] performed a meta analysis to study the effect of aprotinin on the intraoperative requirement for blood products and the postoperative outcomes. They observed that aprotinin can reduce the intraoperative requirement of blood product, and has no significant effect on the incidence of laparotomy for bleeding, thrombotic events and mortality. A Cochrane Intervention Review (2011)[81] on anti-fibrinolytic use for minimising perioperative allogenic blood transfusion concluded that anti-fibrinolytic drugs provide worthwhile reductions in blood loss and the receipt of allogenic red cell transfusion. Aprotinin appears to be slightly more effective than the lysine analogues in reducing blood loss. The lysine analogues are effective in reducing blood loss during and after surgery, and appear to be free of serious adverse effects.

However, given the high risk of type I and type Ⅱ statistical errors because of few trials and the small sample size in some trials, the authors stated that further large clinical randomized multicentre controlled trials are likely needed to confirm the specific advantages of aprotinin in liver transplantation surgery.

Recombinant factor Ⅶa

Recombinant activated Factor Ⅶa (rFⅦa) complexes directly with tissue factor (TF) released from the subendothelium at sites of vascular disruption. The TF-rFⅦ

a complex then activates the remainder of the common coagulation cascade *via* activated factor X. Additionally, rFVIIa may bind to activated platelets, which also concentrates factor X activation to sites of tissue injury. The factor Xa generated by these two mechanisms ultimately drives the thrombin burst, which cleaves fibrinogen to fibrin, thus initiating the formation of the fibrin meshwork critical to secondary coagulation and clot stabilization[82].

Nieman *et al*[83] demonstrated that in a selected group of patients with prolonged PT and high MELD score, the prophylactic application of rFVIIa at the start of the OLTx may reduce perioperative transfusion requirements. However, the prophylactic administration of rF VIIa during orthotopic liver transplantation has lead to inconclusive results; there was a trend across studies toward reduced red blood cell transfusion requirements with prophylaxis, but neither operating room time nor length of stay in the intensive care unit was reduced[84-86]. Nowadays the strength of evidence is low or moderate for intraoperative blood saving capability when given as prophylaxis; furthermore use of rFVIIa has been associated with an increased rate of thromboembolic events in intracerebral hemorrhage and cardiac surgery[87]. Therefore the prophylactic administration may not be the most efficient use of this drug; it should instead be seen more as a "rescue therapy" to control bleeding in situations of major perioperative bleeding where other therapies have failed[88]. Case reports and studies with small number of patients found this drug beneficial in correcting clotting alterations, reducing frank surgical bleeding, controlling clotting failure due to graft reperfusion, or stabilizing clotting functions before the closure of the abdomen[89,90].

Recombinant activated factor VIIa is not a substitute of clotting factors; in addition, it can also induce other negative pharmacological effects. It seems to be useful in improving coagulation in transplant recipients with refractory hemorrhagic complications serving as a bridge to definitive treatment. Safety of rFVIIa in OLTx has been demonstrated in many reports; no effects on thromboembolism or mortality have been found in various trials[87]. However, the experience with this drug is still too limited and the benefit/risk ratio not completely evaluated. The role of recombinant factor VIIa during OLTx still remains to be completely defined. Its administration provides a novel way to increase the thrombin burst and acutely improve coagulation in the presence of rapid factor consumption. It is advisable that TEG monitoring be performed before rFVIIa administration[91].

BLOOD SALVAGE DURING OLTx

The use of intraoperative blood salvage and autologous blood transfusion has been for a long time an important method to reduce the need for allogeneic blood and the associated complications[92].

By reducing the demand for heterologous transfusion this strategy can prevent or diminish the exposure to transmissible infectious diseases. The use of cell salvage has become an important part of intraoperative management of Jehovah's Witnesses who refuse allogeneic blood or blood products transfusion on religious grounds[93].

The principle of cell salvage consists of collecting RBCs from the operative fields, storing the blood in a reservoir, separating the components, and transfusing. Blood collection is carried out with a dedicated double-lumen device, one for suction and the other for adding a predetermined volume of anticoagulant to the aspirated blood. After storage the blood is centrifuged and the RBCs are washed and filtered across a semi-permeable membrane which removes free haemoglobin, plasma, white blood cells, platelets and heparin. The process of concentration by centrifugation enables the plasma, platelets, and irrigating solutions to be removed, as well as 70%-90% of the soluble contaminants and the so called "biochemical debris" present in the salvaged blood. The salvaged blood may then be transfused after being re-suspended in normal saline. The resultant hematocrit ranges between 50%-80%[15]. Although the safety of cell-salvaging procedure has been widely demonstrated[94] intraoperative red blood cell salvage and autologous transfusion is not routinely used in major liver surgery as cost-effectiveness is still an unsolved concern[95].

Blood salvaging techniques are controversial during OLTx as well, since some studies demonstrated their effectiveness in reducing allogeneic RBCs requirements and safety, while others reported higher blood loss, mainly through fibrinolysis, and increased costs[7,96,97]. Hendriks *et al*[98] reported a remarkable increase in transfusion requirements in liver transplant recipients where cell saver blood was returned. They hypothesised that excessive blood loss was a consequence rather than a cause of transfusion of cell saver blood. The need for an increased amount of RBCs, FFP, cryoprecipitate, and platelets in autotransfused patients was also demonstrated by other studies[99,100]. The increased blood loss in recipients receiving cell saver blood has been attributed to the release of fibrinolytic compounds from blood cells in the collected blood and/or from the transplanted liver, that are not washed out by the cell saver[99]. As opposed to the above-mentioned reports many other studies underline that cell salvage is efficacious in reducing the need for allogeneic blood transfusion in adult elective surgery, as evidenced by a recent Cochrane Collaboration meta-analysis of various studies[101]. Waters *et al*[102] in a review of the cell salvage data from 2328 surgical patients suggested that cell salvage can be significantly less expensive than allogenic blood. Older experiences in patients undergoing liver transplantation with large volumes of blood loss, demonstrated that besides its medical benefits intraoperative autologous transfusion was also cost-effective. Use of intraoperative autologous transfusion resulted in conservation of erythrocytes and reduction in exposure to homologous blood and blood components[103]. Similar observations were also reported in a prospective study on 660 adult liver transplant pa-

tients published more recently[104].

Sankarankutty *et al*[105] demonstrated that when cell saver was used during OLTx more than half of the blood lost was recovered and was almost entirely available for reinfusion after processing. Substantial reduction in FFP and a lesser reduction in platelet requirement was also seen.

Nowadays the use of cell salvage to collect and reinfuse shed, autologous blood during OLTx is a common practice when high blood loss is anticipated. It is, in fact, a complementary method that can replace blood in proportion to the volume lost. However, when compared with the cost of providing allogenic blood, it becomes cost effective when at least two or more units of blood can be salvaged and reinfused. Massicotte *et al*[95] demonstrated that when cell salvage autotransfusion was used systematically for every patient (75 OLTx) there was enough blood salvage to retransfuse 65% of the cases; in their centre with a low transfusion rate, it saved a mean of 21 g/L of Hb per patient or two RBC unit transfusions.

Even though the collection of a recipient own blood from surgical sites may result an effective, safe and cost-effective procedure, there are some relative contraindications due to the presence of certain materials incorporated into the salvaged blood that could potentially harm the patient upon readministration[106]. These include contaminants such as stool, urine, or blood aspirated from contaminated or septic wounds, intestinal leaks, intra-abdominal infections, and malignant cells.

Bacterial contamination

Bacterial contamination of intraoperatively cell salvaged and processed blood is a known phenomenon even if the technique is applied to so-called "sterile" operations[107,108].

Contamination may occur during blood sampling and washing. It may originate from intestinal flora or it may be blood-borne in the recipient. Retrograde contamination of the shed blood from the bile duct has been demonstrated as well[101]. The most common source of contamination is thought to be the skin and the environment. The use of cell salvage has been contraindicated in cases where there is potential contamination with enteric contents, however, the relationship between the transfusion of contaminated cell-salvaged blood and an increased risk of systemic infection is not clear. Feltracco *et al*[109] in a prospective observational study of 38 patients undergoing OLTx found samples of processed salvaged blood positive for microorganisms in 68.4% cases. A variety of microorganisms were cultured, i.e., *Staphylococcus* (73%), *Escherichia coli* (4%), *Propionibacter* (4%) and *Candida* (8%). All the patients in this study had blood cultures obtained on postoperative days 1 and 3, and none was positive for the organisms previously cultured from the salvaged blood. Studies on transfusion of microbiologically contaminated salvaged blood have demonstrated no adverse outcomes nor an increase in postoperative infectious complications[109,110]. Therefore, potential contamination should no longer be considered an absolute contraindication to the use of intraoperative cell salvage during OLTx.

Blood salvaged from patients with liver tumor

The presence of hepatocellular carcinoma has been considered a contraindication for the use of blood salvaging techniques due to the theoretical risk of reintroducing neoplastic cells into the circulation and disseminating the tumor. In 1986 the American Medical Councils stated that cell salvage was contraindicated in cases of malignancy[111].

However, in clinical practice the use of autologous transfusion from salvaged blood of patient with malignant disease has been diffusely reported in different surgical settings, such as urological cancer and gynaeoncology surgery[112,113]. In various studies on surgical patients with malignant disease autologous transfusion with cell salvaged blood did not increase recurrence rates and was effective at reducing allogenic blood requirements. The use of leucocyte depletion filters (LDFs) has been proposed to improve cell salvage safety, to reduce the number of malignant cells in the blood recovered during cancer surgery, and to attenuate the side-effects[114]. In a prospective observational study on 32 patients undergoing OLTx for hepatocellular carcinoma, Liang *et al*[115] investigated the presence of tumour cells in shed blood and the efficiency of cell salvage in combination with a LDF at removing them. Tumour cells were present in the cell saver reservoir in 62.5% of patients and after processing tumour cells were still detected in 75% of those. After passing through an LDF, tumour cells were only detected in 10% of samples where the tumour had ruptured intraoperatively. Because of the incomplete elimination of tumour cells in the autologous blood, in circumstances where the potential rupture of the tumor may occur intraoperatively the authors raise concerns on the opportunity of reinfusing the salvaged blood. In the report by Catling *et al*[116], the cell saver used in combination with LDFs significantly reduced the number of tumour cells from salvaged blood. After collecting the blood from the field and processing it, viable cells were demonstrated in 62% of samples, but once the processed salvaged blood was passed through an LDF no tumor cells were found, only tumour cell fragments, which were unable to cause metastases. Muscari *et al*[117] reported no difference in the incidence of neoplastic recurrence with the use of cell saver during liver transplantation for hepatocarcinoma. Various authors also confirm that the use of cell salvage is useful to reduce the exposure to allogenic blood during liver transplantation for hepatocellular carcinoma and is cost-effective as well[95,115]. Filtration through leucodepletion filters in association with irradiation (25 Gy) prior to transfusion of recovered blood has also been proposed to increase the safety of blood salvaging procedure in cancer surgery[118]. Other potential complications associated with cell salvage include non-immune haemolysis, air embolus, febrile non-haemolytic transfusion reactions, coagulopathy, contamination with cleansing solutions and incomplete

washing leading to contamination with activated leucocytes, cytokines, and other microaggregates[92]. Abnormal suctioning of RBCs may cause sheer stress injury, which can result in haemolysis and therefore reduction in return of RBCs[119]. Saline washing of red cells increases sodium levels and decreases potassium and calcium levels; potassium and calcium continuous monitoring and supplementation may be necessary during autologous transfusion of salvaged blood. An inadeguate washing of administered blood could result in renal insufficiency and failure. As the washing process discards all platelets and clotting factors leaving only the red cells re-suspended in normal saline, the reinfusion of large amount of blood from the cell saver machine may determine coagulation disturbances. Large volume transfusion of salvaged blood can, in fact, cause postoperative hypofibrinogenemia, thrombocytopenia, prolonged prothrombin and partial thromboplastin time and elevated fibrin split products[120]. FFP, platelet and cryoprecipitate administered in association with reinfusion of salvaged blood may prevent the cell saver induced coagulopathy.

CONCLUSION

Improvements in organ preservation, surgical technique, anesthesiologic care, as well as in postoperative intensive care management have contributed to a steady reduction of transfusion requirements in the perioperative period and have increased the number of patients undergoing OLTx without any need for blood products[92,121].

Because of the progressive increased severity of end stage liver disease of candidates undergoing OLTx with the "MELD rules" for graft allocation, and the poor quality of many donor livers, the bleeding risk correlated with the surgical manoeuvres may be relevant with inevitable consequences on the amount of transfusions. Even though the transfusion practices still vary greatly from centre to centre, considerable progress has been made on properly balancing intraoperative fluid, preventing and treating clotting abnormalities as well as on "individualizing" the transfusion triggers. The understanding that perioperative blood loss and blood transfusions have a negative impact on postoperative outcome has led to emphasize the need for a critical reappraisal of the traditional heterologous transfusion policies and a re-evaluation of cell salvage as part of a blood conservation strategy in anaesthesia.

REFERENCES

1 **Liu LL**, Niemann CU. Intraoperative management of liver transplant patients. *Transplant Rev* (Orlando) 2011; **25**: 124-129 [PMID: 21514137 DOI: 10.1016/j.trre.2010.10.006]

2 **Ozier Y**, Pessione F, Samain E, Courtois F. Institutional variability in transfusion practice for liver transplantation. *Anesth Analg* 2003; **97**: 671-679 [PMID: 12933381 DOI: 10.1213/01.ANE.0000073354.38695]

3 **Hannaman MJ**, Hevesi ZG. Anesthesia care for liver transplantation. *Transplant Rev* (Orlando) 2011; **25**: 36-43 [PMID: 21126662 DOI: 10.1016/j.trre.2010.10.004]

4 **Maxwell MJ**, Wilson MJA. Complications of blood transfusion. Continuing Education in Anaesthesia. *Crit Care Pain* 2006; **6**: 225-229 [DOI: 10.1093/bjaceaccp/mkl053]

5 **Romero FA**, Razonable RR. Infections in liver transplant recipients. *World J Hepatol* 2011; **3**: 83-92 [PMID: 21603030 DOI: 10.4254/wjh.v3.i4.83]

6 **Massicotte L**, Sassine MP, Lenis S, Roy A. Transfusion predictors in liver transplant. *Anesth Analg* 2004; **98**: 1245-1251, table of contents [PMID: 15105195 DOI: 10.1213/01.ANE.0000111184.21278.07]

7 **de Boer MT**, Molenaar IQ, Hendriks HG, Slooff MJ, Porte RJ. Minimizing blood loss in liver transplantation: progress through research and evolution of techniques. *Dig Surg* 2005; **22**: 265-275 [PMID: 16174983 DOI: 10.1159/000088056]

8 **Martell M**, Coll M, Ezkurdia N, Raurell I, Genescà J. Physiopathology of splanchnic vasodilation in portal hypertension. *World J Hepatol* 2010; **2**: 208-220 [PMID: 21160999 DOI: 10.4254/wjh.v2.i6.208]

9 **Kerr R**, Newsome P, Germain L, Thomson E, Dawson P, Stirling D, Ludlam CA. Effects of acute liver injury on blood coagulation. *J Thromb Haemost* 2003; **1**: 754-759 [PMID: 12871412 DOI: 10.1046/j.1538-7836.2003.00194.x]

10 **Castelino DJ**, Salem HH. Natural anticoagulants and the liver. *J Gastroenterol Hepatol* 1997; **12**: 77-83 [PMID: 9076629 DOI: 10.1111/j.1440-1746.1997.tb00351.x]

11 **Sanjo A**, Satoi J, Ohnishi A, Maruno J, Fukata M, Suzuki N. Role of elevated platelet-associated immunoglobulin G and hypersplenism in thrombocytopenia of chronic liver diseases. *J Gastroenterol Hepatol* 2003; **18**: 638-644 [PMID: 12753144 DOI: 10.1046/j.1440-1746.2003.03026.x]

12 **Yost CS**, Niemann CU. Miller's Anesthesia. Anesthesia for Abdominal Organ Transplantation. 7th ed. Philadelphia: Churchill Livingstone Elsevier, 2010: 2155-2184

13 **Bayly PJ**, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; **73**: 840-842 [PMID: 7880678 DOI: 10.1093/bja/73.6.840]

14 **Murthy TVSP**. Transfusion support in liver transplantation. *Indian J Anaesth* 2007; **51**: 13-19. Available from: URL: http://www.ijaweb.org/text.asp?2007/51/1/13/61108

15 **Massicotte L**, Lenis S, Thibeault L, Sassine MP, Seal RF, Roy A. Reduction of blood product transfusions during liver transplantation. *Can J Anaesth* 2005; **52**: 545-546 [PMID: 15872137]

16 **Devi AS**, Ogawa Y, Shimoji Y, Ponnuraj K. Cloning, expression, purification, crystallization and preliminary X-ray diffraction analysis of the collagen-binding region of RspB from Erysipelothrix rhusiopathiae. *Acta Crystallogr Sect F Struct Biol Cryst Commun* 2010; **66**: 156-159 [PMID: 20124711 DOI: 10.4103/0972-5229.58536]

17 **Spence RK**, Maurer J. Transfusion requirements in liver transplantation. 2006

18 **Palomo Sanchez JC**, Jimenez C, Moreno Gonzalez E, Garcia I, Palma F, Loinaz C, Gonzalez Ghamorro A. Effects of intraoperative blood transfusion on postoperative complications and survival after orthotopic liver transplantation. *Hepatogastroenterology* 1998; **45**: 1026-1033 [PMID: 9756002]

19 **Deakin M**, Gunson BK, Dunn JA, McMaster P, Tisone G, Warwick J, Buckels JA. Factors influencing blood transfusion during adult liver transplantation. *Ann R Coll Surg Engl* 1993; **75**: 339-344 [PMID: 8215151]

20 **Ramos E**, Dalmau A, Sabate A, Lama C, Llado L, Figueras J, Jaurrieta E. Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. *Liver Transpl* 2003; **9**: 1320-1327 [PMID: 14625833 DOI: 10.1016/jlts.2003.50204]

21 **Mangus RS**, Kinsella SB, Nobari MM, Fridell JA, Vianna RM, Ward ES, Nobari R, Tector AJ. Predictors of blood product use in orthotopic liver transplantation using the

piggyback hepatectomy technique. *Transplant Proc* 2007; **39**: 3207-3213 [PMID: 18089355]
22 **Massicotte L**, Beaulieu D, Roy JD, Marleau D, Vandenbroucke F, Dagenais M, Lapointe R, Roy A. MELD score and blood product requirements during liver transplantation: no link. *Transplantation* 2009; **87**: 1689-1694 [PMID: 19502961 DOI: 10.1097/TP.0b013e3181a5e5f1]
23 **Steib A**, Freys G, Lehmann C, Meyer C, Mahoudeau G. Intraoperative blood losses and transfusion requirements during adult liver transplantation remain difficult to predict. *Can J Anaesth* 2001; **48**: 1075-1079 [PMID: 11744582 DOI: 10.1007/BF03020372]
24 **Roullet S**, Biais M, Millas E, Revel P, Quinart A, Sztark F. Risk factors for bleeding and transfusion during orthotopic liver transplantation. *Ann Fr Anesth Reanim* 2011; **30**: 349-352 [PMID: 21353450 DOI: 10.1016/j.annfar.2011.01.008]
25 **Findlay JY**, Rettke SR. Poor prediction of blood transfusion requirements in adult liver transplantations from preoperative variables. *J Clin Anesth* 2000; **12**: 319-323 [PMID: 10960206]
26 **Hébert PC**, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001; **29**: 227-234 [PMID: 11246298]
27 **Klink JR**. Liver Transplantation: Anesthesia. In: Klink JR, Lindop MJ, editors. Anesthesia and Intensive Care for Organ Transplantation. London: Chapman and Hall, 1998: 169-199
28 **Kang Yg**, Gasior TA. Blood coagulation during liver, kidney, pancreas, and lung transplantation. In: Spiess BD, Counts RB, Gould SA, editors. Perioperative Transfusion Medicine. Baltimore, MD: Williams and Wilkins, 1998; 471-492
29 **Dupont J**, Messiant F, Declerck N, Tavernier B, Jude B, Durinck L, Pruvot FR, Scherpereel P. Liver transplantation without the use of fresh frozen plasma. *Anesth Analg* 1996; **83**: 681-686 [PMID: 8831303]
30 **Freeman JW**, Williamson LM, Llewelyn C, Fisher N, Allain JP, Bellamy M, Baglin TP, Klinc J, Ala FA, Smith N, Neuberger J, Wreghitt T. A randomized trial of solvent/detergent and standard fresh frozen plasma in the treatment of the coagulopathy seen during Orthotopic Liver Transplantation. *Vox Sang* 1998; **74** Suppl 1: 225-229 [PMID: 9789533 DOI: 10.1046/j.1423-0410.1998.7440225.x]
31 **de Boer MT**, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HG, Slooff MJ, Porte RJ. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. *Anesth Analg* 2008; **106**: 32-44, table of contents [PMID: 18165548 DOI: 10.1213/01.ane.0000289638.26666.ed]
32 **Sindram D**, Porte RJ, Hoffman MR, Bentley RC, Clavien PA. Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. *Gastroenterology* 2000; **118**: 183-191 [PMID: 10611167]
33 **Kopko PM**, Holland PV. Mechanisms of severe transfusion reactions. *Transfus Clin Biol* 2001; **8**: 278-281 [PMID: 11499977]
34 **Khan H**, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest* 2007; **131**: 1308-1314 [PMID: 17400669 DOI: 10.1378/chest.06-3048]
35 **Pereboom IT**, de Boer MT, Haagsma EB, Hendriks HG, Lisman T, Porte RJ. Platelet transfusion during liver transplantation is associated with increased postoperative mortality due to acute lung injury. *Anesth Analg* 2009; **108**: 1083-1091 [PMID: 19299765 DOI: 10.1213/ane.0b013e3181948a59]
36 **Hendriks HG**, Meijer K, de Wolf JT, Klompmaker IJ, Porte RJ, de Kam PJ, Hagenaars AJ, Melsen T, Slooff MJ, van der Meer J. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation* 2001; **71**: 402-405 [PMID: 11233901]
37 **Jabbour N**, Gagandeep S, Mateo R, Sher L, Genyk Y, Selby R. Transfusion free surgery: single institution experience of 27 consecutive liver transplants in Jehovah's Witnesses. *J Am Coll Surg* 2005; **201**: 412-417 [PMID: 16125075]
38 **Cacciarelli TV**, Keeffe EB, Moore DH, Burns W, Busque S, Concepcion W, So SK, Esquivel CO. Effect of intraoperative blood transfusion on patient outcome in hepatic transplantation. *Arch Surg* 1999; **134**: 25-29 [PMID: 9927126 DOI: 10.1001/archsurg.134.1.25]
39 **Hendriks HG**, van der Meer J, de Wolf JT, Peeters PM, Porte RJ, de Jong K, Lip H, Post WJ, Slooff MJ. Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. *Transpl Int* 2005; **17**: 673-679 [PMID: 15717214 DOI: 10.1111/j.1432-2277.2004.tb00493.x]
40 **Blumberg N**. Deleterious clinical effects of transfusion immunomodulation: proven beyond a reasonable doubt. *Transfusion* 2005; **45**: 33S-39S; discussion 39S-40S [PMID: 16086785 DOI: 10.1111/j.1537-2995.2005.00529.x]
41 **Yuasa T**, Niwa N, Kimura S, Tsuji H, Yurugi K, Egawa H, Tanaka K, Asano H, Maekawa T. Intraoperative blood loss during living donor liver transplantation: an analysis of 635 recipients at a single center. *Transfusion* 2005; **45**: 879-884 [PMID: 15934985 DOI: 10.1111/j.1537-2995.2005.04330.x]
42 Transfusions for massive blood loss. Related Resucitation Critical Care. Available from: URL: http: //www.trauma.org/
43 **Brander L**, Reil A, Bux J, Taleghani BM, Regli B, Takala J. Severe transfusion-related acute lung injury. *Anesth Analg* 2005; **101**: 499-501, table of contents [PMID: 16037167 DOI: 10.1213/01.ANE.0000159375.26910.9C]
44 **Li GS**, Ye QF, Xia SS, Chen ZS, Zeng FJ, Lin ZB, Gong NQ, Zhang WJ, Wen ZX, Sha P, Jiang JP. Acute respiratory distress syndrome after liver transplantation: etiology, prevention and management. *Hepatobiliary Pancreat Dis Int* 2002; **1**: 330-334 [PMID: 14607702]
45 **Davis M**, Sofer M, Gomez-Marin O, Bruck D, Soloway MS. The use of cell salvage during radical retropubic prostatectomy: does it influence cancer recurrence? *BJU Int* 2003; **91**: 474-476 [PMID: 12656896 DOI: 10.1046/j.1464-410X.2003.04129.x]
46 **Innerhofer P**, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. *Transfusion* 2005; **45**: 103-110 [PMID: 15647025 DOI: 10.1111/j.1537-2995.2005.04149.x]
47 **Surgenor SD**, DeFoe GR, Fillinger MP, Likosky DS, Groom RC, Clark C, Helm RE, Kramer RS, Leavitt BJ, Klemperer JD, Krumholz CF, Westbrook BM, Galatis DJ, Frumiento C, Ross CS, Olmstead EM, O'Connor GT. Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. *Circulation* 2006; **114**: I43-I48 [PMID: 16820613 DOI: 10.1161/CIRCULATIONAHA.105.001271]
48 **Buetens O**, Shirey RS, Goble-Lee M, Houp J, Zachary A, King KE, Ness PM. Prevalence of HLA antibodies in transfused patients with and without red cell antibodies. *Transfusion* 2006; **46**: 754-756 [PMID: 16686842 DOI: 10.1111/j.1537-2995.2006.00793.x]
49 **Massicotte L**, Lenis S, Thibeault L, Sassine MP, Seal RF, Roy A. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantations. *Liver Transpl* 2006; **12**: 117-123 [PMID: 16382461 DOI: 10.1007/BF03016538]
50 **Massicotte L**, Beaulieu D, Thibeault L. Con: low central venous pressure during liver transplantation. *J Cardiothorac Vasc Anesth* 2008; **22**: 315-317 [PMID: 18375342 DOI:

10.1053/j.jvca.2008.01.001]
51 **Schroeder RA**, Collins BH, Tuttle-Newhall E, Robertson K, Plotkin J, Johnson LB, Kuo PC. Intraoperative fluid management during orthotopic liver transplantation. *J Cardiothorac Vasc Anesth* 2004; **18**: 438-441 [PMID: 15365923]
52 **Schroeder RA**, Kuo PC. Pro: low central venous pressure during liver transplantation--not too low. *J Cardiothorac Vasc Anesth* 2008; **22**: 311-314 [PMID: 18375341 DOI: 10.1053/j.jvca.2007.12.009]
53 **Ferrara A**, MacArthur JD, Wright HK, Modlin IM, McMillen MA. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *Am J Surg* 1990; **160**: 515-518 [PMID: 2240386]
54 **Afshari A**, Wikkelsø A, Brok J, Møller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database Syst Rev* 2011; (3): CD007871 [PMID: 21412912 DOI: 10.1002/14651858.CD007871.pub2]
55 **Wang SC**, Shieh JF, Chang KY, Chu YC, Liu CS, Loong CC, Chan KH, Mandell S, Tsou MY. Thromboelastography-guided transfusion decreases intraoperative blood transfusion during orthotopic liver transplantation: randomized clinical trial. *Transplant Proc* 2010; **42**: 2590-2593 [PMID: 20832550 DOI: 10.1016/j.transproceed.2010.05.144]
56 **Harper PL**, Edgar PF, Luddington RJ, Seaman MJ, Carrell RW, Salt AT, Barnes N, Rolles K, Calne RY. Protein C deficiency and portal thrombosis in liver transplantation in children. *Lancet* 1988; **2**: 924-927 [PMID: 2902380 DOI: 10.1016/S0140-6736(88)92597-4]
57 **Wegner J**, Popovsky MA. Clinical utility of thromboelastography: one size does not fit all. *Semin Thromb Hemost* 2010; **36**: 699-706 [PMID: 20978990 DOI: 10.1055/s-0030-1265286]
58 **Roullet S**, Pillot J, Freyburger G, Biais M, Quinart A, Rault A, Revel P, Sztark F. Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. *Br J Anaesth* 2010; **104**: 422-428 [PMID: 20185519 DOI: 10.1093/bja/aeq022]
59 **Cheema SP**, Hughes A, Webster NR, Bellamy MC. Cardiac function during orthotopic liver transplantation with venovenous bypass. *Anaesthesia* 1995; **50**: 776-778 [PMID: 7573866]
60 **Fan ST**, Yong BH, Lo CM, Liu CL, Wong J. Right lobe living donor liver transplantation with or without venovenous bypass. *Br J Surg* 2003; **90**: 48-56 [PMID: 12520574 DOI: 10.1002/bjs.4026]
61 **Scholz T**, Solberg R, Okkenhaug C, Videm V, Gallimore MJ, Mathisen O, Pedersen T, Mollnes TE, Bergan A, Søreide O, Klintmalm GB, Aasen AO. Veno-venous bypass in liver transplantation: heparin-coated perfusion circuits reduce the activation of humoral defense systems in an in vitro model. *Perfusion* 2001; **16**: 285-292 [PMID: 11486847]
62 **van der Hulst VP**, Henny CP, Moulijn AC, Engbers G, ten Cate H, Gründeman PF, Klopper PJ. Veno-venous bypass without systemic heparinization using a centrifugal pump: a blind comparison of a heparin bonded circuit versus a non heparin bonded circuit. *J Cardiovasc Surg* (Torino) 1989; **30**: 118-123 [PMID: 2925769]
63 **Miyamoto S**, Polak WG, Geuken E, Peeters PM, de Jong KP, Porte RJ, van den Berg AP, Hendriks HG, Slooff MJ. Liver transplantation with preservation of the inferior vena cava. A comparison of conventional and piggyback techniques in adults. *Clin Transplant* 2004; **18**: 686-693 [PMID: 15516245 DOI: 10.1111/j.1399-0012.2004.00278.x]
64 **Gurusamy KS**, Pamecha V, Davidson BR. Piggy-back graft for liver transplantation. *Cochrane Database Syst Rev* 2011; (1): CD008258 [PMID: 21249703 DOI: 10.1002/14651858.CD008258.pub2]
65 **Makwana J**, Paranjape S, Goswami J. Antifibrinolytics in liver surgery. *Indian J Anaesth* 2010; **54**: 489-495 [PMID: 21224964 DOI: 10.4103/0019-5049.72636]
66 **Sun Z**, Chen YH, Wang P, Zhang J, Gurewich V, Zhang P, Liu JN. The blockage of the high-affinity lysine binding sites of plasminogen by EACA significantly inhibits prourokinase-induced plasminogen activation. *Biochim Biophys Acta* 2002; **1596**: 182-192 [PMID: 12007600]
67 **Dalmau A**, Sabaté A, Acosta F, Garcia-Huete L, Koo M, Sansano T, Rafecas A, Figueras J, Jaurrieta E, Parrilla P. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg* 2000; **91**: 29-34 [PMID: 10866882]
68 **Ker K**, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344**: e3054 [PMID: 22611164 DOI: 10.1136/bmj.e3054]
69 **Boylan JF**, Klinck JR, Sandler AN, Arellano R, Greig PD, Nierenberg H, Roger SL, Glynn MF. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. *Anesthesiology* 1996; **85**: 1043-1048; discussion 30A-31A [PMID: 8916821]
70 **Dalmau A**, Sabaté A, Koo M, Bartolomé C, Rafecas A, Figueras J, Jaurrieta E. The prophylactic use of tranexamic acid and aprotinin in orthotopic liver transplantation: a comparative study. *Liver Transpl* 2004; **10**: 279-284 [PMID: 14762867 DOI: 10.1002/lt.20075]
71 **Massicotte L**, Denault AY, Beaulieu D, Thibeault L, Hevesi Z, Roy A. Aprotinin versus tranexamic acid during liver transplantation: impact on blood product requirements and survival. *Transplantation* 2011; **91**: 1273-1278 [PMID: 21617589 DOI: 10.1097/TP.0b013e31821ab9f8]
72 **Gurusamy KS**, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. *Cochrane Database Syst Rev* 2011; (12): CD009052 [PMID: 22161443 DOI: 10.1002/14651858.CD009052.pub2]
73 **Fergusson DA**, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; **358**: 2319-2331 [PMID: 18480196 DOI: 10.1056/NEJMoa0802395]
74 **Landis RC**, Asimakopoulos G, Poullis M, Haskard DO, Taylor KM. The antithrombotic and antiinflammatory mechanisms of action of aprotinin. *Ann Thorac Surg* 2001; **72**: 2169-2175 [PMID: 11789829]
75 **Porte RJ**, Molenaar IQ, Begliomini B, Groenland TH, Januszkiewicz A, Lindgren L, Palareti G, Hermans J, Terpstra OT. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. EMSALT Study Group. *Lancet* 2000; **355**: 1303-1309 [PMID: 10776742]
76 **Molenaar IQ**, Begliomini B, Martinelli G, Putter H, Terpstra OT, Porte RJ. Reduced need for vasopressors in patients receiving aprotinin during orthotopic liver transplantation. *Anesthesiology* 2001; **94**: 433-438 [PMID: 11374602]
77 **Findlay JY**, Rettke SR, Ereth MH, Plevak DJ, Krom RA, Kufner RP. Aprotinin reduces red blood cell transfusion in orthotopic liver transplantation: a prospective, randomized, double-blind study. *Liver Transpl* 2001; **7**: 802-807 [PMID: 11552215 DOI: 10.1053/jlts.2001.27086]
78 **Lentschener C**, Roche K, Ozier Y. A review of aprotinin in orthotopic liver transplantation: can its harmful effects offset its beneficial effects? *Anesth Analg* 2005; **100**: 1248-1255 [PMID: 15845662 DOI: 10.1213/01.ANE.0000148125.12008.9A]
79 **Molenaar IQ**, Warnaar N, Groen H, Tenvergert EM, Slooff MJ, Porte RJ. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant* 2007; **7**: 185-194 [PMID: 17227567 DOI:

10.1111/j.1600-6143.2006.01591.x]
80 **Liu CM**, Chen J, Wang XH. Requirements for transfusion and postoperative outcomes in orthotopic liver transplantation: a meta-analysis on aprotinin. *World J Gastroenterol* 2008; **14**: 1425-1429 [PMID: 18322960 DOI: 10.3748/wjg.14.1425]
81 **Henry DA**, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011; (3): CD001886 [PMID: 21412876]
82 **Roberts HR**, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004; **104**: 3858-3864 [PMID: 15328151 DOI: 10.1182/blood-2004-06-2223]
83 **Niemann CU**, Behrends M, Quan D, Eilers H, Gropper MA, Roberts JP, Hirose R. Recombinant factor VIIa reduces transfusion requirements in liver transplant patients with high MELD scores. *Transfus Med* 2006; **16**: 93-100 [PMID: 16623915 DOI: 10.1111/j.1365-3148.2006.00653.x]
84 **Lodge JP**, Jonas S, Jones RM, Olausson M, Mir-Pallardo J, Soefelt S, Garcia-Valdecasas JC, McAlister V, Mirza DF. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl* 2005; **11**: 973-979 [PMID: 16035095 DOI: 10.1002/lt.20470]
85 **Planinsic RM**, van der Meer J, Testa G, Grande L, Candela A, Porte RJ, Ghobrial RM, Isoniemi H, Schelde PB, Erhardtsen E, Klintmalm G, Emre S. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl* 2005; **11**: 895-900 [PMID: 16035081 DOI: 10.1002/lt.20458]
86 **Pugliese F**, Ruberto F, Summonti D, Perrella S, Cappannoli A, Tosi A, D'alio A, Bruno K, Martelli S, Celli P, Morabito V, Rossi M, Berloco PB, Pietropaoli P. Activated recombinant factor VII in orthotopic liver transplantation. *Transplant Proc* 2007; **39**: 1883-1885 [PMID: 17692642 DOI: 10.1016/j.transproceed.2007.05.062]
87 **Yank V**, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Olkin I, McDonald KM, Owens DK, Stafford RS. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011; **154**: 529-540 [PMID: 21502651 DOI: 10.1059/0003-4819-154-8-201104190-00004]
88 **Alkozai EM**, Lisman T, Porte RJ. Bleeding in liver surgery: prevention and treatment. *Clin Liver Dis* 2009; **13**: 145-154 [PMID: 19150318 DOI: 10.1016/j.cld.2008.09.012]
89 **Markiewicz M**, Kalicinski P, Kaminski A, Laniewski P, Ismail H, Drewniak T, Szymczak M, Nachulewicz P. Acute coagulopathy after reperfusion of the liver graft in children correction with recombinant activated factor VII. *Transplant Proc* 2003; **35**: 2318-2319 [PMID: 14529927]
90 **Lisman T**, Leebeek FW, Meijer K, Van Der Meer J, Nieuwenhuis HK, De Groot PG. Recombinant factor VIIa improves clot formation but not fibrolytic potential in patients with cirrhosis and during liver transplantation. *Hepatology* 2002; **35**: 616-621 [PMID: 11870375 DOI: 10.1053/jhep.2002.31771]
91 **Liumbruno GM**, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Recommendations for the transfusion management of patients in the peri-operative period. II. The intra-operative period. *Blood Transfus* 2011; **9**: 189-217 [PMID: 21527082 DOI: 10.2450/2011.0075-10]
92 **Ashworth A**, Klein AA. Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth* 2010; **105**: 401-416 [PMID: 20802228 DOI: 10.1093/bja/aeq244]
93 **Jabbour N**, Gagandeep S, Shah H, Mateo R, Stapfer M, Genyk Y, Sher L, Zwierzchoniewska M, Selby R, Zeger G. Impact of a transfusion-free program on non-Jehovah's Witness patients undergoing liver transplantation. *Arch Surg* 2006; **141**: 913-917 [PMID: 17001788 DOI: 10.1001/archsurg.141.9.913]
94 **Cardone D**, Klein AA. Perioperative blood conservation. *Eur J Anaesthesiol* 2009; **26**: 722-729 [PMID: 19448549 DOI: 10.1097/EJA.0b013e32832c5280]
95 **Massicotte L**, Thibeault L, Beaulieu D, Roy JD, Roy A. Evaluation of cell salvage autotransfusion utility during liver transplantation. *HPB* (Oxford) 2007; **9**: 52-57 [PMID: 18333113 DOI: 10.1080/13651820601090596]
96 **Lutz JT**, Valentín-Gamazo C, Görlinger K, Malagó M, Peters J. Blood-transfusion requirements and blood salvage in donors undergoing right hepatectomy for living related liver transplantation. *Anesth Analg* 2003; **96**: 351-355, table of contents [PMID: 12538176 DOI: 10.1213/01.ANE.0000041595.94354.48]
97 **Kemper RR**, Menitove JE, Hanto DW. Cost analysis of intraoperative blood salvage during orthotopic liver transplantation. *Liver Transpl Surg* 1997; **3**: 513-517 [PMID: 9346794]
98 **Hendriks HG**, van der Meer J, Klompmaker IJ, Choudhury N, Hagenaars JA, Porte RJ, de Kam PJ, Slooff MJ, de Wolf JT. Blood loss in orthotopic liver transplantation: a retrospective analysis of transfusion requirements and the effects of autotransfusion of cell saver blood in 164 consecutive patients. *Blood Coagul Fibrinolysis* 2000; **11** Suppl 1: S87-S93 [PMID: 10850571]
99 **Brajtbord D**, Paulsen AW, Ramsay MA, Swygert TH, Valek TR, Ramon VJ, Johnson DD, Parks RI, Pyron JT, Walling PT. Potential problems with autotransfusion during hepatic transplantation. *Transplant Proc* 1989; **21**: 2347-2348 [PMID: 2652762]
100 **Van Voorst SJ**, Peters TG, Williams JW, Vera SR, Britt LG. Autotransfusion in hepatic transplantation. *Am Surg* 1985; **51**: 623-626 [PMID: 3904551]
101 **Carless PA**, Henry DA, Moxey AJ, O'connell DL, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2006; (4): CD001888 [PMID: 17054147 DOI: 10.1002/14651858.CD001888.pub2]
102 **Waters JR**, Meier HH, Waters JH. An economic analysis of costs associated with development of a cell salvage program. *Anesth Analg* 2007; **104**: 869-875 [PMID: 17377098 DOI: 10.1213/01.ane.0000258039.79028.7c]
103 **Williamson KR**, Taswell HF, Rettke SR, Krom RA. Intraoperative autologous transfusion: its role in orthotopic liver transplantation. *Mayo Clin Proc* 1989; **64**: 340-345 [PMID: 2495389]
104 **Phillips SD**, Maguire D, Deshpande R, Muiesan P, Bowles MJ, Rela M, Heaton ND. A prospective study investigating the cost effectiveness of intraoperative blood salvage during liver transplantation. *Transplantation* 2006; **81**: 536-540 [PMID: 16495800 DOI: 10.1097/01.tp.0000199318.17013.c5]
105 **Sankarankutty AK**, Teixeira AC, Souza FF, Mente ED, Oliveira GR, Almeida RC, Andrade CM, Origuella EA, Silva Ode C. Impact of blood salvage during liver transplantation on reduction in transfusion requirements. *Acta Cir Bras* 2006; **21** Suppl 1: 44-47 [PMID: 17013513]
106 **Waters JH**. Indications and contraindications of cell salvage. *Transfusion* 2004; **44**: 40S-44S [PMID: 15585004 DOI: 10.1111/j.0041-1132.2004.04176.x]
107 **Sugai Y**, Sugai K, Fuse A. Current status of bacterial contamination of autologous blood for transfusion. *Transfus Apher Sci* 2001; **24**: 255-259 [PMID: 11791700]
108 **Waters JH**, Tuohy MJ, Hobson DF, Procop G. Bacterial reduction by cell salvage washing and leukocyte depletion filtration. *Anesthesiology* 2003; **99**: 652-655 [PMID: 12960550]
109 **Feltracco P**, Michieletto E, Barbieri S, Serra E, Rizzi S, Salvaterra F, Cillo U, Ori C. Microbiologic contamination of intraoperative blood salvaged during liver transplantation. *Transplant Proc* 2007; **39**: 1889-1891 [PMID: 17692644 DOI: 10.1016/j.transproceed.2007.05.005]
110 **Bowley DM**, Barker P, Boffard KD. Intraoperative blood salvage in penetrating abdominal trauma: a randomised, controlled trial. *World J Surg* 2006; **30**: 1074-1080 [PMID: 16736339 DOI: 10.1007/s00268-005-0466-2]
111 Autologous blood transfusions. Council on Scientific Af-

fairs. *JAMA* 1986; **256**: 2378-2380 [PMID: 3773142]
112 **Nieder AM**, Manoharan M, Yang Y, Soloway MS. Intraoperative cell salvage during radical cystectomy does not affect long-term survival. *Urology* 2007; **69**: 881-884 [PMID: 17482926 DOI: 10.1016/j.urology.2007.01.060]
113 **Connor JP**, Morris PC, Alagoz T, Anderson B, Bottles K, Buller RE. Intraoperative autologous blood collection and autotransfusion in the surgical management of early cancers of the uterine cervix. *Obstet Gynecol* 1995; **86**: 373-378 [PMID: 7651645 DOI: 10.1016/0029-7844(95)00183-R]
114 **Kongsgaard UE**, Wang MY, Kvalheim G. Leucocyte depletion filter removes cancer cells in human blood. *Acta Anaesthesiol Scand* 1996; **40**: 118-120 [PMID: 8904269]
115 **Liang TB**, Li DL, Liang L, Li JJ, Bai XL, Yu W, Wang WL, Shen Y, Zhang M, Zheng SS. Intraoperative blood salvage during liver transplantation in patients with hepatocellular carcinoma: efficiency of leukocyte depletion filters in the removal of tumor cells. *Transplantation* 2008; **85**: 863-869 [PMID: 18360269 DOI: 10.1097/TP.0b013e3181671f2e]
116 **Catling S**, Williams S, Freites O, Rees M, Davies C, Hopkins L. Use of a leucocyte filter to remove tumour cells from intraoperative cell salvage blood. *Anaesthesia* 2008; **63**: 1332-1338 [PMID: 19032302 DOI: 10.1111/j.1365-2044.2008.05637]
117 **Muscari F**, Suc B, Vigouroux D, Duffas JP, Migueres I, Mathieu A, Lavayssiere L, Rostaing L, Fourtanier G. Blood salvage autotransfusion during transplantation for hepatocarcinoma: does it increase the risk of neoplastic recurrence? *Transpl Int* 2005; **18**: 1236-1239 [PMID: 16221153 DOI: 10.1111/j.1432-2277.2005.00207.x]
118 **Hansen E**, Bechmann V, Altmeppen J. [Intraoperative blood salvage with irradiation of blood in cancer surgery -- answers to current queries]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 2002; **37**: 740-744 [PMID: 12469288 DOI: 10.1055/s-2002-35917]
119 **Waters JH**, Williams B, Yazer MH, Kameneva MV. Modification of suction-induced hemolysis during cell salvage. *Anesth Analg* 2007; **104**: 684-687 [PMID: 17312230 DOI: 10.1213/01.ane.0000255208.96685.2e]
120 **Sherman LA**, Ramsey G. Solid-organ transplantation. In: Rossi EC, Simon YL, Moss GS, Gould SA, editors. Principles of Transfusion Medicine. 2nd ed. Baltimore: Williams and Wilkins, 1996: 635-637
121 **Feltracco P**, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. *World J Hepatol* 2011; **3**: 61-71 [PMID: 21487537 DOI: 10.4254/wjh.v3.i3.61]

P- Reviewers Boucek C, Eghtesad B **S- Editor** Wen LL
L- Editor A **E- Editor** Li JY

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i1.16

World J Hepatol 2013 January 27; 5(1): 16-25
ISSN 1948-5182 (online)

REVIEW

Diagnosis and management of bacterial infections in decompensated cirrhosis

Maria Pleguezuelo, Jose Manuel Benitez, Juan Jurado, Jose Luis Montero, Manuel De la Mata

Maria Pleguezuelo, Jose Manuel Benitez, Juan Jurado, Jose Luis Montero, Manuel De la Mata, Liver Research Unit, Reina Sofia University Hospital, Avda Menendez Pidal s/n, 14004 Cordoba, Spain
Author contributions: Pleguezuelo M contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be published; Benitez JM contributed to acquisition of data, drafting the article and final approval of the version to be published; Jurado J contributed to acquisition of data, drafting the article and final approval of the version to be published; Montero JL contributed to conception and design, revising it critically for important intellectual content and final approval of the version to be published; De la Mata M contributed to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

Supported by Study under the Scope of CIBERehd and IMIBIC-A02/C05
Correspondence to: Maria Pleguezuelo, MD, PhD, Liver Research Unit, Reina Sofia University Hospital, Avda Menendez Pidal s/n, 14004 Cordoba, Spain. plegue3@hotmail.com
Telephone: +34-95-7010427 Fax: +34-95-7736014
Received: May 22, 2012 Revised: August 29, 2012
Accepted: November 25, 2012
Published online: January 27, 2013

Abstract

Bacterial infections are one of the most frequent complications in cirrhosis and result in high mortality rates. Patients with cirrhosis have altered and impaired immunity, which favours bacterial translocation. Episodes of infections are more frequent in patients with decompensated cirrhosis than those with compensated liver disease. The most common and life-threatening infection in cirrhosis is spontaneous bacterial peritonitis followed by urinary tract infections, pneumonia, endocarditis and skin and soft-tissue infections. Patients with decompensated cirrhosis have increased risk of developing sepsis, multiple organ failure and death. Risk factors associated with the development of infections are severe liver failure, variceal bleeding, low ascitic protein level and prior episodes of spontaneous bacterial peritonitis (SBP). The prognosis of these patients is closely related to a prompt and accurate diagnosis. An appropriate treatment decreases the mortality rates. Preventive strategies are the mainstay of the management of these patients. Empirical antibiotics should be started immediately following the diagnosis of SBP and the first-line antibiotic treatment is third-generation cephalosporins. However, the efficacy of currently recommended empirical antibiotic therapy is very low in nosocomial infections including SBP, compared to community-acquired episodes. This may be associated with the emergence of infections caused by *Enterococcus faecium* and extended-spectrum β-lactamase-producing Enterobacteriaceae, which are resistant to the first line antimicrobial agents used for treatment. The emergence of resistant bacteria, underlines the need to restrict the use of prophylactic antibiotics to patients with the greatest risk of infections. Nosocomial infections should be treated with wide spectrum antibiotics. Further studies of early diagnosis, prevention and treatment are needed to improve the outcomes in patients with decompensated cirrhosis.

Key words: Cirrhosis; Infections; Spontaneous bacterial peritonitis; Ascites; Antibiotics

Pleguezuelo M, Benitez JM, Jurado J, Montero JL, De la Mata M. Diagnosis and management of bacterial infections in decompensated cirrhosis. *World J Hepatol* 2013; 5(1): 16-25 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i1/16.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i1.16

INTRODUCTION

Bacterial infections are one of the most frequent complications in cirrhosis, particularly in decompensated

patients, and account for significant mortality. The current prevalence of this complication ranges between 25% and 30%[1,2] and is responsible for 30%-50% of deaths in these patients[3]. The cumulative mortality after any infection in patients with cirrhosis is 43.5%. It has been suggested that the occurrence of bacterial infection could be considered a further prognosis stage, defining the critically ill cirrhotic[4]. Risk factors associated with the development of infections are high Child-Pugh score, variceal bleeding, low ascitic protein level and prior episodes of spontaneous bacterial peritonitis (SBP).

The most common infections in cirrhosis are SBP[5], followed by urinary tract infections, pneumonia and cellulitis[6]. Sixty percent of bacterial infections are community-acquired and 40% are nosocomial. In hospitalized cirrhotic patients, the most frequent infections are healthcare-associated or hospital-acquired and these infections are frequently resistant to antibiotics. The most frequent causative organisms in community-acquired infections are gram-negative bacilli, mainly *Escherichia coli* (*E. coli*) (60%). The emergence of extended-spectrum beta-lactamase (ESBL)-producing enterobacteria in nosocomial infections has meant that gram-positive cocci are no longer the main bacteria isolated in hospital-acquired infections. Moreover, nosocomial SBP are mainly caused by gram-negative bacteria. However, cultures are positive only in 40%-70% of infections. The treatment of choice for the most common infections occurring in cirrhosis is third-generation cephalosporins since they are active against Enterobacteriaceae and non-enterococcal streptococci as well as being well tolerated[7-9]. However, recent studies have shown that the prevalence of infections caused by multiresistant bacteria is increasing in cirrhosis[10].

Immune defects, mainly acquired but also genetic, and bacterial translocation are the principal mechanism involved in the pathogenesis of infection in cirrhosis[11]. Liver dysfunction is associated with an impaired defense against bacteria, which worsens over time and with disease progression. Both humoral and cell-mediated immunity are depressed. In cirrhosis, decreased bacterial clearance as well as structural and functional alterations in the intestinal mucosa lead to an increase in permeability to bacteria and derived products. This favours bacterial translocation, which increases the susceptibility to infection, particularly SBP. Deficiencies in C3 and C4, impairment of macrophage Fcγ-receptor mediated clearance of antibody-coated bacteria and down-regulation of monocyte human leukocyte antigen-DR expression, may also contribute to this altered defense[12]. In some cases a deregulated immune response produces an important production of inflammatory mediators, which leads to an excessive pro-inflammatory response. This process may contribute to renal impairment, multiple organ failure and high mortality rate[13].

Bacterial infections, regardless of the aetiology, are a severe complication of decompensated cirrhosis, and result in increased mortality and longer hospital stay. The most important predictive factor for mortality after infection is renal failure. The release of inflammatory mediators during infection leads to systemic, renal, and hepatic hemodynamic impairment, which dramatically affects the prognosis even after resolution of infection. The mortality rate after infection in patients with cirrhosis remains high and has not significantly changed over recent decades[4]. The widespread use of quinolones and other antibiotics in cirrhosis has favoured changes in bacterial flora and the development of antibiotic resistance. To improve outcomes, new studies of early diagnosis, prevention and treatment are needed.

DIAGNOSIS OF BACTERIAL INFECTIONS

Early diagnosis and treatment of infections are of paramount importance for the management of patients with decompensated cirrhosis, since bacterial infections are important causes of mortality and morbidity in these patients. Patients with decompensated cirrhosis have increased risk of developing sepsis, multiple organ failure and death[14]. Mortality associated to infections is twenty times higher in patients with cirrhosis than in the general population.

Bacterial infections in patients with cirrhosis can be asymptomatic or pauci-symptomatic, and have to be suspected in any cirrhotic patient with a sudden impairment of liver function[15]. The prognosis of these patients is mainly dependent on a prompt and accurate diagnosis[2]. Identification of the source of infection is the primary concern when deciding on the appropriate antibiotic therapy. The first evaluation must include a detailed physical examination including vital signs (temperature, respiratory and heart rates, mean arterial pressure), abdominal and chest examination, and evaluation of the presence of skin lesions. A complete work-up must include a range of diagnostic tests such as blood cell count and culture, urinary sediment and culture, chest X-ray, sputum culture, ascitic/pleural fluid cultures and abdominal ultrasonography[11].

Diagnosis of spontaneous bacterial peritonitis

SBP is defined as an infection of the ascitic fluid in the absence of a contagious cause of infection (e.g., intestinal perforation or abscess)[7]. SBP is a frequent and severe complication of cirrhosis, with an incidence in hospitalized patients with cirrhosis of 7%-25%. Prospective studies have shown that one-year mortality rates following an episode of SBP, range from 65% to 93%[16]. Risk factors for SBP include impaired liver function, gastrointestinal bleeding, high bilirubin levels, low ascitic fluid protein (< 10-15 g/L), and a prior episode of SBP.

Abdominal pain and fever are the most common symptoms, followed by vomiting, hepatic encephalopathy, gastrointestinal bleeding and renal dysfunction. However, symptoms and signs are sometimes absent[17]. In 40%-60% of cases, the organism responsible for SBP is isolated in ascitic fluid or blood cultures[1-4,6]. Diagnostic paracentesis

should be carried out in all patients with ascites who are admitted to hospital, regardless of symptoms[18].

Diagnosis of SBP is based on the demonstration of an absolute number of polymorphonuclear cells in ascitic fluid equal to or greater than 250/mm^3. Diagnosis of SBP constitutes an indication to initiate an empirical antibiotic therapy and must not be delayed until the ascites bacteriological culture results are available[7,8]. The best specificity for diagnosis has been reported[19-22] with a cut-off of 500 PMN/mm^3. It is unclear whether a positive culture in the absence of elevated ascitic fluid PMN count (bacteriascites), requires antibiotic therapy. In these cases, some guidelines recommend antibiotic treatment only if the patient shows signs of infection[8]. Leukocyte reagent strips have been suggested as a rapid screening test for the diagnosis of SBP at the bedside[23-26]. However, sensitivity varying between 45% and 100%, makes this method suboptimal for the diagnosis of SBP. In patients with hemorrhagic ascites (red blood cell count > 10 000/mm^3), subtraction of one PMN per 250 red blood cells should be made. When there is a predominant lymphocytosis in the ascitic fluid, the differential diagnosis must include tuberculous peritonitis, neoplasms, congestive heart failure, pancreatitis and myxedema, but usually not SBP[18]. Other markers that have been suggested for the diagnosis of SBP are lactoferrin, an iron-binding protein contained in PMN, which has a sensitivity of 96% and a specificity of 97% with cut-off value of ⩾ 242 ng/mL in ascitic fluid[27].

The most frequently identified organisms in patients with SBP are gram-negative bacteria (*E. coli*) and gram-positive cocci (streptococcus and enterococcus). Approximately, 30% of isolated gram-negative bacteria are resistant to quinolones and this resistance is higher in patients undergoing norfloxacin therapy[9]. The most frequent causative organisms in community-acquired SBP are gram-negative bacteria, while in nosocomial infections gram-positive organisms are responsible for most infections.

Secondary peritonitis constitutes the main differential diagnosis of SBP, accounting for 5%-10% of all peritonitis in patients with cirrhosis and ascites. This is due to perforation or inflammation of an intra-abdominal organ, and its mortality is much higher than that of SBP (66% *vs* 10%)[28]. Secondary peritonitis must be suspected in patients with inadequate response to therapy or when multiple organisms are identified in the ascitic fluid[29]. A diagnosis of secondary peritonitis is probable when at least two of the Runyon's criteria are present: glucose level < 50 mg/dL; protein concentration > 10 g/L; or lactate dehydrogenase > 225 mU/mL[8]. When secondary peritonitis is suspected, an abdominal computerized tomography should be performed as soon as possible[30].

Other infections in patients with cirrhosis

Urinary tract infections: Urinary tract infections (UTI) in cirrhosis can be asymptomatic or oligosymptomatic, and asymptomatic bacteriuria is frequent[31,32]. The incidence of UTI is higher in cirrhotic patients with indwelling catheters and in women. The most frequent bacteria causing UTI are *E. coli* and *Klebsiella pneumoniae* (*K. pneumonia*). Quinolones are not recommended for the treatment of UTI in areas with a high prevalence of quinolone-resistant enterobacteria, such as Southern Europe. Amoxicillin-clavulanic acid or an oral cephalosporin should be considered in these high-risk patients[33-35].

Pneumonia: Pneumonia is the third most common infection in liver cirrhosis, after SBP and UTI. Community-acquired pneumonia is most frequent, especially in subjects with active alcoholism[36]. Streptococcus pneumonia is the most common causative organism, followed by *anaerobic bacteria* or *Haemophilus influenza*, *K. pneumonia*, *Mycoplasma pneumonia* or *Legionella*[37,38]. The initial treatment of choice should include macrolides combined with one of the following: cefotaxime, ceftriaxone, amoxicillin-clavulanic acid, imipenem or piperacillin-tazobactam. Factors such as tracheal intubation and hepatic encephalopathy may predispose for hospital-acquired pneumonia, mainly caused by gram-negative bacilli and staphylococci. In these cases, the treatment should be adapted to the local epidemiological pattern of resistant bacteria; meropenem or ceftazidime plus ciprofloxacin may be an adequate option. Vancomycin or linezolid should be added in patients with risk factors for methicillin-resistant Staphylococcus aureus (MRSA) (Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage).

Endocarditis: Streptococcus and Staphylococcus aureus are the most common causative organisms.

Skin and soft-tissue infections: Lymphangitis of the lower extremities and abdominal wall are frequent in cirrhotic patients with edema or ascites. The most common etiologic organisms are Staphylococcus aureus and Streptococcus pyogenes, followed by Enterobacteriaceae and anaerobes[39]. Empirical therapy with cloxacillin has been considered the first-choice. Amoxicillin-clavulanic acid or quinolones (i.e., ofloxacin) may be an adequate alternative. Cellulitis is usually treated with a combination of cloxacillin and a third-generation cephalosporin.

TREATMENT OF SBP IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

In practice, third generation cephalosporins have already been established as the standard treatment of SBP[40-42]. However, the efficacy of currently recommended empirical antibiotic therapy is very low in nosocomial infections, including SBP, when compared to community-acquired episodes. Infections caused by multiresistant bacteria have increased nearly 100%, and are associated to a higher incidence of treatment failure, rapid deterioration of liver function and mortality. This change may be associated with the emergence of infections caused by *Enterococcus*

faecium and extended-spectrum β-lactamase-producing Enterobacteriaceae, which are resistant to the current recommended empirical antibiotic therapy. This findings led to the suggestion that nosocomial SBP should be treated with carbapenems or with tigecycline[43].

Appropriate empirical antibiotic therapy is associated with improved survival. In the absence of ascitic fluid cultures, it is important to use broad-spectrum antibiotics, selected according to the type and severity of infection. Epidemiological factors, such as site of acquisition of the infection (nosocomial *vs* community-acquired infections), and previous history of multiresistant infection, must be taken into account[11]. Prevention and treatment of renal failure, sometimes triggered by infection, is of pivotal importance in the treatment of these patients. Therefore, some antibiotics, such as aminoglycosides, should not be used in cirrhosis because of the high risk of renal failure[44].

Treatment of community-acquired SBP

The organisms traditionally associated with community-acquired SBP are gram-negative bacteria, mainly Enterobacteriaceae. This family of bacteria usually shows optimal response to third-generation cephalosporins (e.g. cefotaxime). Amoxicillin-clavulanic acid and ciprofloxacin have shown similar results. Intravenous cefotaxime 2 g/12 h is considered the first-line antibiotic for the empirical treatment of SBP. A 5-d therapy is as effective as a 10 day treatment. Other effective and safe options are *iv* ceftriaxone 1 g/(12-24) h or *iv* amoxicillin-clavulanic acid (1-2) g/(6-8) h[45]. The use of fluoroquinolones (e.g., ciprofloxacin 200 mg/12 h, *iv*) has demonstrated similar efficacy. In patients with uncomplicated SBP (absence of gastrointestinal hemorrhage, severe encephalopathy, septic shock or creatinine > 3 mg/dL), oral ofloxacin (400 mg/12 h) may be an effective alternative. In patients who develop SBP while receiving norfloxacin prophylaxis, quinolones are not recommended and the best alternative is cefotaxime or amoxicillin/clavulanic acid. In SBP it is of crucial importance to assess the response to treatment by performing a follow-up paracentesis two days after initiation of the antibiotic therapy. A reduction in the ascitic fluid PMN count (< 25%), compared with the pretreatment value, is considered treatment failure and indicates the need for modification of the antibiotic treatment according to *in vitro* sensitivity.

Administration of albumin as adjuvant treatment to antibiotics is considered essential in patients with SBP and impaired renal or liver function, in order to prevent worsening of renal function[46-48]. The recommended dose is 1.5 g/kg on day 1 and 1 g/kg on day 3. The concomitant use of albumin decreases the incidence of type 1 hepatorenal syndrome (from 30% to 10%) and reduces mortality (from 29% to 10%), compared with cefotaxime alone. Treatment with albumin is particularly effective in patients with serum bilirubin ⩾ 4 mg/dL or serum creatinine ⩾ 1 mg/dL, while its use in patients without these criteria remains controversial[49]. However, in unselected patients with SBP, even low-dose albumin (10 g/d on day 1 and 3) reduces tumour necrosis factor and interleukin 6 levels in serum and ascites as well as preventing increases in serum nitric oxide induced by SBP[50].

Treatment of nosocomial SBP

Unfortunately, antibiotic therapy fails in 26%-41% of patients with SBP[51]. One of the explanations may be that current guidelines for the treatment of SBP do not distinguish between community-acquired and nosocomial episodes. Recent studies have reported an increasing prevalence of extended-spectrum β-lactamase-producing bacteria and multiresistant gram-positive bacteria such as Enteroccocus faecium or MRSA[52]. In fact, bacteria isolated in nosocomial SBP are frequently resistant to β-lactams (33%-78%), and this is associated with a low success rate in a significant proportion of nosocomial SBP[53-56], which are being treated with third generation cephalosporins, amoxicillin/clavulanic acid or quinolones.

Clinical and research efforts are focused on decreasing rates of mortality, morbidity and healthcare associated costs. The development of bacterial resistance in community-acquired SBP increases the risk of mortality four-fold, since it is usually associated with empirical treatment failure. Therefore, for an optimal treatment of nosocomial infections in patients with cirrhosis, epidemiological factors and patterns of resistance should be considered. Hospitalisation within the previous 3 mo, intensive care treatment, and prior antibiotic treatment, are independent risk factors for the development bacterial multi-resistance[57].

Carbapenems are the most effective option for nosocomial infections in areas with a high prevalence of extended-spectrum β-lactamase-producing Enterobacteriaceae. Tigecycline may be a potential alternative, although recent studies have showed increased mortality related to its low clinical efficacy and it should not, therefore, be recommended as first-line therapy in the general population[58]. Penicillin used in combination with β-lactamase inhibitors (e.g., piperacilin-tazobactam) may be an adequate alternative. However, the most appropriate antibiotic treatment in any particular case should be selected according to the results of the relevant microbiological studies.

PROPHYLAXIS OF SBP IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

In patients with cirrhosis at high risk of SBP (low protein ascites and advanced liver dysfunction or impaired renal function), norfloxacin administration decreases the 1-year probability of developing this infection and hepatorenal syndrome, and moreover increases 3-mo and 1-year survival[29]. However, recent studies suggest that norfloxacin is not now as affective as it was in the past, possibly due to the development of quinolone-resistant bacteria in the fecal flora of patients receiving long-term prophylaxis. Thus, to prevent antibiotic resistance and to make these strategies cost-effective, antibiotic prophy-

laxis must be restricted to those patients at a very high risk of bacterial infections. Since the gut appears to be the main source of bacteria in SBP, a selective intestinal decontamination by elimination of gram-negative bacilli (mostly responsible for infections in cirrhosis) should be performed.

Primary prophylaxis in patients with gastro-intestinal bleeding

Cirrhotic patients with upper gastrointestinal bleeding are at high risk (25%-65%) of bacterial infections, particularly SBP, during the first 7 d after the bleeding episode. Moreover, bacterial infections increase the risk of early re-bleeding[59]. An increase in portal pressure and changes in hemostasis induced by infection have been suggested as possible mechanisms[60,61]. A beneficial effect of antibiotic prophylaxis on control of bleeding and prevention of re-bleeding has been reported[62]. Current guidelines recommend antibiotic prophylaxis in patients with cirrhosis and gastrointestinal bleeding regardless of the presence of ascites[9]. A meta-analysis of five trials comprising 534 cirrhotic patients with variceal haemorrhage, demonstrated that antibiotic prophylaxis for 4 to 10 d significantly reduced the occurrence of SBP and septicaemia, and improved short-term survival[63]. Similar results were seen in a more recent meta-analysis of twelve trials comprising a total of 1241 patients with cirrhosis and gastrointestinal bleeding, in which antibiotic prophylaxis significantly decreased the incidence of bacterial infections, re-bleeding, length of hospitalisation and mortality. Prophylaxis benefits were observed irrespective of the antibiotic used, although they were stronger with cephalosporins, quinolones and quinolones plus beta-lactams[64]. The use of antibiotic prophylaxis as secondary prevention of variceal bleeding may reduce the incidence of early re-bleeding, mainly in the first seven days after the first haemorrhage[65].

Currently, the recommended antibiotics are mainly oral quinolones (norfloxacin 400 mg *bid* for 7 d) or intravenous cephalosporins (ceftriaxone 1 g/d for 7 d). Norfloxacin is a poorly absorbed quinolone with antibacterial activity against gram-negative bacteria, which is simple to administer and has low cost. The main complication of long-term norfloxacin prophylaxis is the occurrence of infections by quinolone-resistant organism, which are usually susceptible to third-generation cephalosporins. This fact and the lack of efficacy of norfloxacin against gram-positive or anaerobic organisms, may explain the superiority shown by intravenous ceftriaxone over oral norfloxacin in a randomized controlled trial on patients with variceal bleeding and advanced cirrhosis (characterized by at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin > 3 mg/dL)[66]. Invasive procedures used in patients with cirrhosis and haemorrhage are a risk factor for infections caused by gram-positive bacteria. Intravenous administration seems to be more appropriate than oral intake in patients with active upper bleeding who have vomits and very rapid intestinal transit. Intravenous ceftriaxone should, therefore, be used in the prophylaxis of bacterial infections in patients with advanced cirrhosis and upper gastrointestinal bleeding, whereas patients with less severe liver disease may be given oral norfloxacin or an alternative oral quinolone.

Therefore, in patients with upper gastrointestinal bleeding, antibiotic prophylaxis is considered essential. In patients with less severe liver disease norfloxacin may be given, whereas in those with severe liver disease ceftriaxone is the prophylactic antibiotic of choice. Timing of antibiotic administration is also important and prophylaxis should be started from admission, ideally before or immediately after endoscopy[67]. Local bacterial resistance profile and treatment costs, are other factors to consider in the selection of antibiotics.

Primary prophylaxis in patients with ascites

Primary prophylaxis in cirrhotic patients with ascites, but without gastrointestinal bleeding, is controversial. A recent meta-analysis including seven trials comparing antibiotic prophylaxis to no intervention or placebo, showed that the relative risk of SBP and mortality was lower in patients treated with antibiotics (RR 0.2; 0.11 to 0.37) than with no treatment or placebo (RR 0.6; 0.43 to 0.87)[16]. However, these findings must be taken with caution because of the low methodology quality of most of the trials and the likely existence of systematic bias in the trials included. Given the increasing emergence of resistant bacteria and the limited validity of these results, antibiotic prophylaxis in all patients with ascites without bleeding should not be recommended until we have more conclusive evidence.

However, it is well known that the risk of SBP in patients with ascites depends on ascitic fluid protein concentration, since it has been shown that low protein concentration (< 10-15 g/L) is a risk factor, and the incidence is greater in those with advanced liver disease. Several independent studies and meta-analysis have assessed this issue[68-71]. In a placebo-controlled trial on patients with protein ascitic levels < 15 g/L and advanced liver failure or impaired renal function, norfloxacin (400 mg/d) reduced the 1-year probability of developing SBP and improved the 3-mo survival, although at 1 year the difference in survival was not significant[29]. Similarly, a placebo-controlled trial on patients with ascites protein < 15 g/L and moderate liver failure, showed that prophylaxis with ciprofloxacin for 12 mo improved the 1-year survival. However, there was no significant difference between groups in the occurrence of SBP or other infections[72]. A recent meta-analysis of these three trials supports the efficacy of quinolones in these settings, since it demonstrates significant preventive power for SBP and mortality[18]. A previous meta-analysis, which aimed to assess the effect of antibiotic prophylaxis in the prevention of SBP and survival, showed similar results. It included eight studies comprising 647 patients with cirrhosis at risk for developing SBP. In seven of the eight studies the

mean ascitic fluid protein level was < 15 g/L. Criteria for defining advanced liver disease included Child-Pugh scores > 9, bilirubin levels > 2.5 mg/dL, and impaired renal function. The analysis showed that prophylaxis improved short-term survival and reduced the incidence of infections, including SBP[73]. These results suggest that primary prophylaxis has a great impact in the clinical course of patients with low ascites protein content and advanced cirrhosis, and may reduce the incidence of SBP and improve survival. Nevertheless, studies in patients with low ascitic fluid protein but without severe liver disease, have failed to show significant effect of norfloxacin on survival or in the occurrence of SBP[74].

To the light of these studies, patients with protein ascitic levels < 15 g/L and severe liver disease or renal impairment should be considered for long-term prophylaxis with norfloxacin (400 mg/d), particularly those patients awaiting liver transplantation, because antibiotic prophylaxis may increase the applicability of this procedure. The optimal duration of primary antibiotic prophylaxis has not been established. Oral ciprofloxacin is a valid alternative to norfloxacin. In patients with low protein concentration in ascitic fluid, but with mild or moderate liver disease, antibiotic prophylaxis is not currently recommended[9].

Secondary prophylaxis in patients with prior SBP

The probability of survival at 1 year after an episode of SBP is about 30%-50%[75], with a cumulative recurrence rate at 1 year of 70%. Therefore, after one episode of SBP, liver transplantation must be considered. In all patients with a prior episode of SBP it is essential to initiate long-term antibiotic prophylaxis. For secondary prophylaxis, the evidence is strongest for norfloxacin (400 mg/d), since its use after an episode of SBP has been shown to reduce the recurrence from 70% to 20%[76]. This prophylactic strategy results in a substantial cost saving by avoiding resource utilization associated with treatment[77]. Intermitting antibiotic therapy schedules have been suggested as secondary prophylaxis, however this strategy may select resistant flora more rapidly and should, therefore, be avoided.

In these settings prophylaxis should be instituted after the completion of treatment for acute SBP and continued until liver transplantation or disappearance of ascites. The development of bacterial resistance is a potentially harmful complication of long-term antibiotic therapy, and it is greater with longer duration of antibiotic administration. In patients who develop resistance to quinolones, trimethoprim/sulfamethoxazole has been suggested as an alternative to norfloxacin[78]. However, there is a high rate of SBP caused by trimethoprimsulfamethoxazole resistant Gram-negative bacteria (44%-72%), suggesting that this antibiotic is not a suitable alternative to norfloxacin[79,80]. Data supporting the use of trimethoprim/sulfamethoxazole are weak, while its side effects are potentially dangerous and probably under-reported[81]. There are no data to support discontinuation of prophylaxis with quinolones in patients who develop infection due to quinolone-resistant bacteria. Antibiotic cycling or combined treatment regimes have been proposed to reduce the risk of emerging resistant bacteria, but there are no data supporting this strategy.

Probiotics, a non-antibiotic and safe therapy, may decrease bacterial translocation, since it has been reported that they can correct bacterial overgrowth, stabilize mucosal barrier function and decrease bacterial translocation in experimental conditions[82-84]. However *Lactobacillus* failed to reduce bacterial translocation and ascitic fluid infection in an animal model[85,86]. Further studies in patients with cirrhosis are needed to define the possible role of probiotics in SBP prophylaxis.

It has been suggested that acid-suppressive therapy with proton pump inhibitors (PPIs), which is widely used in patients with cirrhosis, may increase the risk of bacterial infections, since they cause bacterial overgrowth in the small intestine and increase intestinal permeability[87-92]. Several studies, including a meta-analysis[93] of four studies involving a total of 772 patients[94-98], found significant association between PPI and the development of SBP in patients with cirrhosis (odds ratio 2.77, 95%CI: 1.82-4.23). However, a recent study suggests that even though PPIs may be a contributing factor, the predominant factor determining infection risk is the stage of the liver disease[99]. Bajaj *et al*[100] identified PPI use as a risk factor for Clostridium Difficile Associated Disease (CDAD) in hospitalized patients with cirrhosis, which is associated with higher mortality, length of stay and costs. However, the relation between PPI use and CDAD has not been confirmed in other populations of patients with impaired immunity[101]. Therefore, more studies are needed to verify this association.

CONCLUSION

Bacterial infections in cirrhosis are common, accounting for significant mortality. Patients with decompensated cirrhosis have more frequent episodes of infection than those with compensated liver disease. Spontaneous bacterial peritonitis is the most common infection in these patients. The development of cirrhosis is associated with impairment in the immune system, which worsens over time, and with disease progression. Risk factors associated with development of infections in cirrhosis are severe liver failure, variceal bleeding, low ascitic protein level and prior episodes of SBP.

Identification of risk factors for SBP is important to develop optimally targeted safe and cost-effective strategies for its prevention. Improvements in survival are achieved with early diagnosis and prompt antibiotic treatment. Empirical antibiotics should be started immediately following the diagnosis of SBP and the first line antibiotic treatment is third-generation cephalosporins. The concomitant administration of albumin decreases the frequency of hepatorenal syndrome and improves survival.

Antibiotic prophylaxis should be used in cirrhotic

patients hospitalized with an episode of gastrointestinal haemorrhage, ascites and a prior history of SBP. Patients with protein ascitic levels < 15 g/L and severe liver disease or renal impairment should be considered for long-term antibiotic prophylaxis. Patients who recover from SBP have to be considered for liver transplantation, since they have a poor long-term survival.

REFERENCES

1 **Fernández J**, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; **35**: 140-148 [PMID: 11786970 DOI: 10.1053/jhep.2002.30082]

2 **Borzio M**, Salerno F, Piantoni L, Cazzaniga M, Angeli P, Bissoli F, Boccia S, Colloredo-Mels G, Corigliano P, Fornaciari G, Marenco G, Pistarà R, Salvagnini M, Sangiovanni A. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. *Dig Liver Dis* 2001; **33**: 41-48 [PMID: 11303974 DOI: 10.1016/S1590-8658(01)80134-1]

3 **Wong F**, Bernardi M, Balk R, Christman B, Moreau R, Garcia-Tsao G, Patch D, Soriano G, Hoefs J, Navasa M. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. *Gut* 2005; **54**: 718-725 [PMID: 15831923 DOI: 10.1136/gut.2004.038679]

4 **Arvaniti V**, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010; **139**: 1246-1256, 1256.e1-5 [PMID: 20558165]

5 **Pinzello G**, Simonetti RG, Craxì A, Di Piazza S, Spanò C, Pagliaro L. Spontaneous bacterial peritonitis: a prospective investigation in predominantly nonalcoholic cirrhotic patients. *Hepatology* 1983; **3**: 545-549 [PMID: 6862365]

6 **Taneja SK**, Dhiman RK. Prevention and management of bacterial infections in cirrhosis. *Int J Hepatol* 2011; **2011**: 784540 [PMID: 22229097]

7 **Rimola A**, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 2000; **32**: 142-153 [PMID: 10673079 DOI: 10.1016/S0168-8278(00)80201-9]

8 **Runyon BA**. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009; **49**: 2087-2107 [PMID: 19475696]

9 **European Association for the Study of the Liver**. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946]

10 **Merli M**, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, Ridola L, Attili AF, Venditti M. Cirrhotic patients are at risk for health care-associated bacterial infections. *Clin Gastroenterol Hepatol* 2010; **8**: 979-985 [PMID: 20621200 DOI: 10.1016/j.cgh.2010.06.024]

11 **Fernández J**, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol* 2012; **56** Suppl 1: S1-12 [PMID: 22300459 DOI: 10.1016/S0168-8278(12)60002-6]

12 **Rajkovic IA**, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. *Hepatology* 1986; **6**: 252-262 [PMID: 3007318 DOI: 10.1002/hep.1840060217]

13 **Navasa M**, Follo A, Filella X, Jiménez W, Francitorra A, Planas R, Rimola A, Arroyo V, Rodés J. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998; **27**: 1227-1232 [PMID: 9581675 DOI: 10.1002/hep.510270507]

14 **Foreman MG**, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. *Chest* 2003; **124**: 1016-1020 [PMID: 12970032 DOI: 10.1378/chest.124.3.1016]

15 **Preda CM**, Ghita R, Ghita C, Mindru C, Vlaicu L, Andrei A, Andrei S, Diculescu M. A retrospective study of bacterial infections in cirrhosis. *Maedica* (Buchar) 2011; **6**: 185-192 [PMID: 22368695]

16 **Cohen MJ**, Sahar T, Benenson S, Elinav E, Brezis M, Soares-Weiser K. Antibiotic prophylaxis for spontaneous bacterial peritonitis in cirrhotic patients with ascites, without gastrointestinal bleeding. *Cochrane Database Syst Rev* 2009; (2): CD004791 [PMID: 19370611]

17 **Chinnock B**, Afarian H, Minnigan H, Butler J, Hendey GW. Physician clinical impression does not rule out spontaneous bacterial peritonitis in patients undergoing emergency department paracentesis. *Ann Emerg Med* 2008; **52**: 268-273 [PMID: 18433932 DOI: 10.1016/j.annemergmed.2008.02.016]

18 **Wiest R**, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. *Gut* 2012; **61**: 297-310 [PMID: 22147550 DOI: 10.1136/gutjnl-2011-300779]

19 **Albillos A**, Cuervas-Mons V, Millán I, Cantón T, Montes J, Barrios C, Garrido A, Escartín P. Ascitic fluid polymorphonuclear cell count and serum to ascites albumin gradient in the diagnosis of bacterial peritonitis. *Gastroenterology* 1990; **98**: 134-140 [PMID: 2293572]

20 **Garcia-Tsao G**, Conn HO, Lerner E. The diagnosis of bacterial peritonitis: comparison of pH, lactate concentration and leukocyte count. *Hepatology* 1985; **5**: 91-96 [PMID: 3967868 DOI: 10.1002/hep.1840050119]

21 **Stassen WN**, McCullough AJ, Bacon BR, Gutnik SH, Wadiwala IM, McLaren C, Kalhan SC, Tavill AS. Immediate diagnostic criteria for bacterial infection of ascitic fluid. Evaluation of ascitic fluid polymorphonuclear leukocyte count, pH, and lactate concentration, alone and in combination. *Gastroenterology* 1986; **90**: 1247-1254 [PMID: 3956943]

22 **Yang CY**, Liaw YF, Chu CM, Sheen IS. White count, pH and lactate in ascites in the diagnosis of spontaneous bacterial peritonitis. *Hepatology* 1985; **5**: 85-90 [PMID: 3967867 DOI: 10.1002/hep.1840050118]

23 **Butani RC**, Shaffer RT, Szyjkowski RD, Weeks BE, Speights LG, Kadakia SC. Rapid diagnosis of infected ascitic fluid using leukocyte esterase dipstick testing. *Am J Gastroenterol* 2004; **99**: 532-537 [PMID: 15056098 DOI: 10.1111/j.1572-0241.2004.04084.x]

24 **Castellote J**, López C, Gornals J, Tremosa G, Fariña ER, Baliellas C, Domingo A, Xiol X. Rapid diagnosis of spontaneous bacterial peritonitis by use of reagent strips. *Hepatology* 2003; **37**: 893-896 [PMID: 12668983 DOI: 10.1053/jhep.2003.50120]

25 **Vanbiervliet G**, Rakotoarisoa C, Filippi J, Guérin O, Calle G, Hastier P, Mariné-Barjoan E, Schneider S, Piche T, Broussard JF, Dor JF, Benzaken S, Hébuterne X, Rampal P, Tran A. Diagnostic accuracy of a rapid urine-screening test (Multistix8SG) in cirrhotic patients with spontaneous bacterial peritonitis. *Eur J Gastroenterol Hepatol* 2002; **14**: 1257-1260 [PMID: 12439122 DOI: 10.1097/00042737-200211000-00015]

26 **Nousbaum JB**, Cadranel JF, Nahon P, Khac EN, Moreau R, Thévenot T, Silvain C, Bureau C, Nouel O, Pilette C, Paupard T, Vanbiervliet G, Oberti F, Davion T, Jouannaud V, Roche B, Bernard PH, Beaulieu S, Danne O, Thabut D, Chagneau-Derrode C, de Lédinghen V, Mathurin P, Pauwels A, Bronowicki JP, Habersetzer F, Abergel A, Audigier JC, Sapey T, Grangé JD, Tran A. Diagnostic accuracy of the Multistix 8 SG reagent strip in diagnosis of spontaneous bacterial peritonitis. *Hepatology* 2007; **45**: 1275-1281 [PMID: 17464969 DOI: 10.1002/hep.21588]

27 **Parsi MA**, Saadeh SN, Zein NN, Davis GL, Lopez R, Boone J, Lepe MR, Guo L, Ashfaq M, Klintmalm G, McCullough AJ.

Ascitic fluid lactoferrin for diagnosis of spontaneous bacterial peritonitis. *Gastroenterology* 2008; **135**: 803-807 [PMID: 18590731]
28 **Soriano G**, Castellote J, Alvarez C, Girbau A, Gordillo J, Baliellas C, Casas M, Pons C, Román EM, Maisterra S, Xiol X, Guarner C. Secondary bacterial peritonitis in cirrhosis: a retrospective study of clinical and analytical characteristics, diagnosis and management. *J Hepatol* 2010; **52**: 39-44 [PMID: 19897273 DOI: 10.1016/j.jhep.2009.10.012]
29 **Fernández J**, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, Vila C, Pardo A, Quintero E, Vargas V, Such J, Ginès P, Arroyo V. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007; **133**: 818-824 [PMID: 17854593 DOI: 10.1053/j.gastro.2007.06.065]
30 **Wiest R**, Schoelmerich J. Secondary peritonitis in cirrhosis: "oil in fire". *J Hepatol* 2010; **52**: 7-9 [PMID: 19910073 DOI: 10.1016/j.jhep.2009.10.022]
31 **Yang YY**, Lin HC. Bacterial infections in patients with cirrhosis. *J Chin Med Assoc* 2005; **68**: 447-451 [PMID: 16265857 DOI: 10.1016/S1726-4901(09)70072-3]
32 **Lipsky BA**. Urinary tract infections in men. Epidemiology, pathophysiology, diagnosis, and treatment. *Ann Intern Med* 1989; **110**: 138-150 [PMID: 2462391]
33 **Caly WR**, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol* 1993; **18**: 353-358 [PMID: 8228129 DOI: 10.1016/S0168-8278(05)80280-6]
34 **Guarner C**, Runyon BA. Macrophage function in cirrhosis and the risk of bacterial infection. *Hepatology* 1995; **22**: 367-369 [PMID: 7601431 DOI: 10.1002/hep.1840220149]
35 **Westphal JF**, Jehl F, Vetter D. Pharmacological, toxicologic, and microbiological considerations in the choice of initial antibiotic therapy for serious infections in patients with cirrhosis of the liver. *Clin Infect Dis* 1994; **18**: 324-335 [PMID: 7741830 DOI: 10.1093/clinids/18.3.324]
36 **Adams HG**, Jordan C. Infections in the alcoholic. *Med Clin North Am* 1984; **68**: 179-200 [PMID: 6361412]
37 **Bradsher RW**. Overwhelming pneumonia. *Med Clin North Am* 1983; **67**: 1233-1250 [PMID: 6355684]
38 **Lévy M**, Dromer F, Brion N, Leturdu F, Carbon C. Community-acquired pneumonia. Importance of initial noninvasive bacteriologic and radiographic investigations. *Chest* 1988; **93**: 43-48 [PMID: 3275531 DOI: 10.1378/chest.93.1.43]
39 **Swartz ML**, Pasternack MS. Cellulitis and superficial infections. *Prin Pract Inf Dis* 1999; **88**: 34-37
40 **Felisart J**, Rimola A, Arroyo V, Perez-Ayuso RM, Quintero E, Gines P, Rodes J. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology* 1985; **5**: 457-462 [PMID: 3888810 DOI: 10.1002/hep.1840050319]
41 **Mercader J**, Gomez J, Ruiz J, Garre MC, Valdes M. Use of ceftriaxone in the treatment of bacterial infections in cirrhotic patients. *Chemotherapy* 1989; **35** Suppl 2: 23-26 [PMID: 2612236 DOI: 10.1159/000238735]
42 **Gómez-Jiménez J**, Ribera E, Gasser I, Artaza MA, Del Valle O, Pahissa A, Martínez-Vázquez JM. Randomized trial comparing ceftriaxone with cefonicid for treatment of spontaneous bacterial peritonitis in cirrhotic patients. *Antimicrob Agents Chemother* 1993; **37**: 1587-1592 [PMID: 8215267 DOI: 10.1128/AAC.37.8.1587]
43 **Fernández J**, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, Pavesi M, Sola E, Moreira L, Silva A, Seva-Pereira T, Corradi F, Mensa J, Ginès P, Arroyo V. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012; **55**: 1551-1561 [PMID: 22183941 DOI: 10.1002/hep.25532]
44 **Cabrera J**, Arroyo V, Ballesta AM, Rimola A, Gual J, Elena M, Rodes J. Aminoglycoside nephrotoxicity in cirrhosis. Value of urinary beta 2-microglobulin to discriminate functional renal failure from acute tubular damage. *Gastroenterology* 1982; **82**: 97-105 [PMID: 6171479]
45 **Ricart E**, Soriano G, Novella MT, Ortiz J, Sàbat M, Kolle L, Sola-Vera J, Miñana J, Dedéu JM, Gómez C, Barrio JL, Guarner C. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. *J Hepatol* 2000; **32**: 596-602 [PMID: 10782908 DOI: 10.1016/S0168-8278(00)80221-4]
46 **Follo A**, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodés J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994; **20**: 1495-1501 [PMID: 7982650 DOI: 10.1002/hep.1840200619]
47 **Hoefs JC**, Canawati HN, Sapico FL, Hopkins RR, Weiner J, Montgomerie JZ. Spontaneous bacterial peritonitis. *Hepatology* 1982; **2**: 399-407 [PMID: 7095741 DOI: 10.1002/hep.1840020402]
48 **Singh N**, Wagener MM, Gayowski T. Changing epidemiology and predictors of mortality in patients with spontaneous bacterial peritonitis at a liver transplant unit. *Clin Microbiol Infect* 2003; **9**: 531-537 [PMID: 12848729 DOI: 10.1046/j.1469-0691.2003.00691.x]
49 **Sort P**, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409 [PMID: 10432325 DOI: 10.1056/NEJM199908053410603]
50 **Heo J**, Seo YS, Yim HJ, Hahn T, Park SH, Ahn SH, Park JY, Park JY, Kim MY, Park SK, Cho M, Um SH, Han KH, Kim HS, Baik SK, Kim BI, Cho SH. Clinical features and prognosis of spontaneous bacterial peritonitis in korean patients with liver cirrhosis: a multicenter retrospective study. *Gut Liver* 2009; **3**: 197-204 [PMID: 20431746 DOI: 10.5009/gnl.2009.3.3.197]
51 **Angeloni S**, Leboffe C, Parente A, Venditti M, Giordano A, Merli M, Riggio O. Efficacy of current guidelines for the treatment of spontaneous bacterial peritonitis in the clinical practice. *World J Gastroenterol* 2008; **14**: 2757-2762 [PMID: 18461661 DOI: 10.3748/wjg.14.2757]
52 **Piroth L**, Pechinot A, Minello A, Jaulhac B, Patry I, Hadou T, Hansmann Y, Rabaud C, Chavanet P, Neuwirth C. Bacterial epidemiology and antimicrobial resistance in ascitic fluid: a 2-year retrospective study. *Scand J Infect Dis* 2009; **41**: 847-851 [PMID: 19922067 DOI: 10.3109/00365540903244535]
53 **Cheong HS**, Kang CI, Lee JA, Moon SY, Joung MK, Chung DR, Koh KC, Lee NY, Song JH, Peck KR. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clin Infect Dis* 2009; **48**: 1230-1236 [PMID: 19302016 DOI: 10.1086/597585]
54 **Campillo B**, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. *Clin Infect Dis* 2002; **35**: 1-10 [PMID: 12060868 DOI: 10.1086/340617]
55 **Bert F**, Andreu M, Durand F, Degos F, Galdbart JO, Moreau R, Branger C, Lambert-Zechovsky N, Valla D. Nosocomial and community-acquired spontaneous bacterial peritonitis: comparative microbiology and therapeutic implications. *Eur J Clin Microbiol Infect Dis* 2003; **22**: 10-15 [PMID: 12582738]
56 **Song JY**, Jung SJ, Park CW, Sohn JW, Kim WJ, Kim MJ, Cheong HJ. Prognostic significance of infection acquisition sites in spontaneous bacterial peritonitis: nosocomial versus community acquired. *J Korean Med Sci* 2006; **21**: 666-671 [PMID: 16891810 DOI: 10.3346/jkms.2006.21.4.666]
57 **Umgelter A**, Reindl W, Miedaner M, Schmid RM, Huber W. Failure of current antibiotic first-line regimens and mortality in hospitalized patients with spontaneous bacterial peritonitis. *Infection* 2009; **37**: 2-8 [PMID: 19169633 DOI:

10.1007/s15010-008-8060-9]
58 **Yahav D**, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother* 2011; **66**: 1963-1971 [PMID: 21685488 DOI: 10.1093/jac/dkr242]
59 **Bernard B**, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. *Gastroenterology* 1995; **108**: 1828-1834 [PMID: 7768389 DOI: 10.1016/0016-5085(95)90146-9]
60 **Goulis J**, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998; **27**: 1207-1212 [PMID: 9581672 DOI: 10.1002/hep.510270504]
61 **Goulis J**, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* 1999; **353**: 139-142 [PMID: 10023916 DOI: 10.1016/S0140-6736(98)06020-6]
62 **Chavez-Tapia NC**, Barrientos-Gutierrez T, Tellez-Avila FI, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010; (9): CD002907 [PMID: 20824832]
63 **Bernard B**, Grangé JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999; **29**: 1655-1661 [PMID: 10347104 DOI: 10.1002/hep.510290608]
64 **Chavez-Tapia NC**, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, Uribe M. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. *Aliment Pharmacol Ther* 2011; **34**: 509-518 [PMID: 21707680 DOI: 10.1111/j.1365-2036.2011.04746]
65 **Hou MC**, Lin HC, Liu TT, Kuo BI, Lee FY, Chang FY, Lee SD. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology* 2004; **39**: 746-753 [PMID: 14999693 DOI: 10.1002/hep.20126]
66 **Fernández J**, Ruiz del Arbol L, Gómez C, Durandez R, Serradilla R, Guarner C, Planas R, Arroyo V, Navasa M. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006; **131**: 1049-1056; quiz 1285 [PMID: 17030175 DOI: 10.1053/j.gastro.2006.07.010]
67 **de Franchis R**. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; **53**: 762-768 [PMID: 20638742 DOI: 10.1016/j.jhep.2010.06.004]
68 **Segarra-Newnham M**, Henneman A. Antibiotic prophylaxis for prevention of spontaneous bacterial peritonitis in patients without gastrointestinal bleeding. *Ann Pharmacother* 2010; **44**: 1946-1954 [PMID: 21098755 DOI: 10.1345/aph.1P317]
69 **Loomba R**, Wesley R, Bain A, Csako G, Pucino F. Role of fluoroquinolones in the primary prophylaxis of spontaneous bacterial peritonitis: meta-analysis. *Clin Gastroenterol Hepatol* 2009; **7**: 487-493 [PMID: 19250986 DOI: 10.1016/j.cgh.2008.12.018]
70 **Alvarez RF**, Mattos AA, Corrêa EB, Cotrim HP, Nascimento TV. Trimethoprim-sulfamethoxazole versus norfloxacin in the prophylaxis of spontaneous bacterial peritonitis in cirrhosis. *Arq Gastroenterol* 2005; **42**: 256-262 [PMID: 16444382]
71 **Rolachon A**, Cordier L, Bacq Y, Nousbaum JB, Franza A, Paris JC, Fratte S, Bohn B, Kitmacher P, Stahl JP. Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. *Hepatology* 1995; **22**: 1171-1174 [PMID: 7557868]
72 **Terg R**, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, Landeira C, Romero G, Dominguez N, Muñoz A, Levi D, Miguez C, Abecasis R. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. *J Hepatol* 2008; **48**: 774-779 [PMID: 18316137 DOI: 10.1016/j.jhep.2008.01.024]
73 **Saab S**, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 993-1001; quiz 1002 [PMID: 19277033 DOI: 10.1038/ajg.2009.3]
74 **Grangé JD**, Roulot D, Pelletier G, Pariente EA, Denis J, Ink O, Blanc P, Richardet JP, Vinel JP, Delisle F, Fischer D, Flahault A, Amiot X. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. *J Hepatol* 1998; **29**: 430-436 [PMID: 9764990]
75 **Rimola A**, Navasa M. Infections in liver disease. 2nd ed. Oxford Textbook of Clinical Hepatology, 1999: 1861-1876
76 **Ginés P**, Rimola A, Planas R, Vargas V, Marco F, Almela M, Forné M, Miranda ML, Llach J, Salmerón JM. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990; **12**: 716-724 [PMID: 2210673 DOI: 10.1002/hep.1840120416]
77 **Inadomi J**, Sonnenberg A. Cost-analysis of prophylactic antibiotics in spontaneous bacterial peritonitis. *Gastroenterology* 1997; **113**: 1289-1294 [PMID: 9322524 DOI: 10.1053/gast.1997.v113.pm9322524]
78 **Singh N**, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. *Ann Intern Med* 1995; **122**: 595-598 [PMID: 7887554]
79 **Cereto F**, Herranz X, Moreno E, Andreu A, Vergara M, Fontanals D, Roget M, Simó M, González A, Prats G, Genescà J. Role of host and bacterial virulence factors in Escherichia coli spontaneous bacterial peritonitis. *Eur J Gastroenterol Hepatol* 2008; **20**: 924-929 [PMID: 18794608 DOI: 10.1097/MEG.0b013e3282fc7390]
80 **Cereto F**, Molina I, González A, Del Valle O, Esteban R, Guardia J, Genescà J. Role of immunosuppression in the development of quinolone-resistant Escherichia coli spontaneous bacterial peritonitis and in the mortality of E. coli spontaneous bacterial peritonitis. *Aliment Pharmacol Ther* 2003; **17**: 695-701 [PMID: 12641519 DOI: 10.1046/j.1365-2036.2003.01491.x]
81 **Nunnari G**, Celesia BM, Bellissimo F, Tosto S, La Rocca M, Giarratana F, Benanti F, Caltabiano E, Russo R, Cacopardo B. Trimethoprim-sulfamethoxazole-associated severe hypoglycaemia: a sulfonylurea-like effect. *Eur Rev Med Pharmacol Sci* 2010; **14**: 1015-1018 [PMID: 21375132]
82 **Adawi D**, Kasravi FB, Molin G, Jeppsson B. Effect of Lactobacillus supplementation with and without arginine on liver damage and bacterial translocation in an acute liver injury model in the rat. *Hepatology* 1997; **25**: 642-647 [PMID: 9049212 DOI: 10.1002/hep.510250325]
83 **Loguercio C**, Federico A, Tuccillo C, Terracciano F, D'Auria MV, De Simone C, Del Vecchio Blanco C. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. *J Clin Gastroenterol* 2005; **39**: 540-543 [PMID: 15942443 DOI: 10.1097/01.mcg.0000165671.25272.0f]
84 **Stadlbauer V**, Mookerjee RP, Hodges S, Wright GA, Davies NA, Jalan R. Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. *J Hepatol* 2008; **48**: 945-951 [PMID: 18433921 DOI: 10.1016/j.jhep.2008.02.015]
85 **Bauer TM**, Fernández J, Navasa M, Vila J, Rodés J. Failure of Lactobacillus spp. to prevent bacterial translocation in a rat model of experimental cirrhosis. *J Hepatol* 2002; **36**: 501-506 [PMID: 11943421 DOI: 10.1016/S0168-8278(02)00003-X]
86 **Wiest R**, Chen F, Cadelina G, Groszmann RJ, Garcia-Tsao G. Effect of Lactobacillus-fermented diets on bacterial trans-

location and intestinal flora in experimental prehepatic portal hypertension. *Dig Dis Sci* 2003; **48**: 1136-1141 [PMID: 12822876 DOI: 10.1023/A: 1023729115659]

87 **Bauer TM**, Steinbrückner B, Brinkmann FE, Ditzen AK, Schwacha H, Aponte JJ, Pelz K, Kist M, Blum HE. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *Am J Gastroenterol* 2001; **96**: 2962-2967 [PMID: 11693333 DOI: 10.1111/j.1572-0241.2001.04668.x]

88 **Wiest R**, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology* 2005; **41**: 422-433 [PMID: 15723320 DOI: 10.1002/hep.20632]

89 **Ersöz G**, Aydin A, Erdem S, Yüksel D, Akarca U, Kumanlioglu K. Intestinal permeability in liver cirrhosis. *Eur J Gastroenterol Hepatol* 1999; **11**: 409-412 [PMID: 10321758 DOI: 10.1097/00042737-199904000-00009]

90 **Scarpellini E**, Valenza V, Gabrielli M, Lauritano EC, Perotti G, Merra G, Dal Lago A, Ojetti V, Ainora ME, Santoro M, Ghirlanda G, Gasbarrini A. Intestinal permeability in cirrhotic patients with and without spontaneous bacterial peritonitis: is the ring closed? *Am J Gastroenterol* 2010; **105**: 323-327 [PMID: 19844200 DOI: 10.1038/ajg.2009.558]

91 **Cariello R**, Federico A, Sapone A, Tuccillo C, Scialdone VR, Tiso A, Miranda A, Portincasa P, Carbonara V, Palasciano G, Martorelli L, Esposito P, Cartenì M, Del Vecchio Blanco C, Loguercio C. Intestinal permeability in patients with chronic liver diseases: Its relationship with the aetiology and the entity of liver damage. *Dig Liver Dis* 2010; **42**: 200-204 [PMID: 19502117 DOI: 10.1016/j.dld.2009.05.001]

92 **Lodato F**, Azzaroli F, Di Girolamo M, Feletti V, Cecinato P, Lisotti A, Festi D, Roda E, Mazzella G. Proton pump inhibitors in cirrhosis: tradition or evidence based practice? *World J Gastroenterol* 2008; **14**: 2980-2985 [PMID: 18494046 DOI: 10.3748/wjg.14.2980]

93 **Trikudanathan G**, Israel J, Cappa J, O'Sullivan DM. Association between proton pump inhibitors and spontaneous bacterial peritonitis in cirrhotic patients - a systematic review and meta-analysis. *Int J Clin Pract* 2011; **65**: 674-678 [PMID: 21564440 DOI: 10.1111/j.1742-1241.2011.02650]

94 **Bajaj JS**, Zadvornova Y, Heuman DM, Hafeezullah M, Hoffmann RG, Sanyal AJ, Saeian K. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Am J Gastroenterol* 2009; **104**: 1130-1134 [PMID: 19337238 DOI: 10.1038/ajg.2009.80]

95 **Bulsiewicz WJ**, Scherer JR, Feinglass JM, Howden CW, Flamm SL. Proton pump inhibitor (PPI) use is independently associated with spontaneous bacterial peritonitis (SBP) in cirrhotics with ascites. *Gastroenterology* 2009; **136**: A-11 [DOI: 10.1016/S0016-5085(09)60053-6]

96 **Goel GA**, Deshpande A, Lopez R, Hall GS, van Duin D, Carey WD. Proton pump inhibitor (PPI) use is associated with spontaneous bacterial peritonitis (SBP) in cirrhosis. *Gastroenterology* 2010; **138**: S-816 [DOI: 10.1016/S0016-5085(10)63761-4]

97 **Campbell MS**, Obstein K, Reddy KR, Yang YX. Association between proton pump inhibitor use and spontaneous bacterial peritonitis. *Dig Dis Sci* 2008; **53**: 394-398 [PMID: 17616817 DOI: 10.1007/s10620-007-9899-9]

98 **Choi EJ**, Lee HJ, Kim KO, Lee SH, Eun JR, Jang BI, Kim TN. Association between acid suppressive therapy and spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Scand J Gastroenterol* 2011; **46**: 616-620 [PMID: 21275825 DOI: 10.3109/00365521.2011.551891]

99 **van Vlerken LG**, Huisman EJ, van Hoek B, Renooij W, de Rooij FW, Siersema PD, van Erpecum KJ. Bacterial infections in cirrhosis: role of proton pump inhibitors and intestinal permeability. *Eur J Clin Invest* 2012; **42**: 760-767 [PMID: 22288900 DOI: 10.1111/j.1365-2362.2011.02643]

100 **Bajaj JS**, Ananthakrishnan AN, Hafeezullah M, Zadvornova Y, Dye A, McGinley EL, Saeian K, Heuman D, Sanyal AJ, Hoffmann RG. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: A national and tertiary center perspective. *Am J Gastroenterol* 2010; **105**: 106-113 [PMID: 19844204 DOI: 10.1038/ajg.2009.615]

101 **Pohl JF**, Patel R, Zobell JT, Lin E, Korgenski EK, Crowell K, Mackay MW, Richman A, Larsen C, Chatfield BA. Clostridium difficile Infection and Proton Pump Inhibitor Use in Hospitalized Pediatric Cystic Fibrosis Patients. *Gastroenterol Res Pract* 2011; **2011**: 345012 [PMID: 22144994]

P- Reviewers Lonardo A, Huang GC **S- Editor** Song XX
L- Editor Hughes D **E- Editor** Li JY

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i1.26

World J Hepatol 2013 January 27; 5(1): 26-32
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Outcomes following liver transplantation in intensive care unit patients

Lena Sibulesky, Michael G Heckman, C Burcin Taner, Juan M Canabal, Nancy N Diehl, Dana K Perry, Darren L Willingham, Surakit Pungpapong, Barry G Rosser, David J Kramer, Justin H Nguyen

Lena Sibulesky, C Burcin Taner, Juan M Canabal, Dana K Perry, Darren L Willingham, Surakit Pungpapong, Barry G Rosser, David J Kramer, Justin H Nguyen, Department of Transplantation, Mayo Clinic, Jacksonville, FL 32225, United States
Michael G Heckman, Nancy N Diehl, Biostatistics Unit, Mayo Clinic, Jacksonville, FL 32225, United States
Michael G Heckman, Departments of Transplantation and Critical Care Medicine, Mayo Clinic, Jacksonville, FL 32225, United States
Darren L Willingham, Department of Critical Care Medicine and Internal Medicine, Aurora Health Care, Milwaukee, WI 53204, United States
Author contributions: Sibulesky L, Canabal JM and Kramer DJ contributed to direct participation in the study, including substantial contributions to conception and design of study, or acquisition of data, or analysis and interpretation of data; Sibulesky L, Heckman MG, Taner CB, Canabal JM, Perry DK, Willingham DL, Pungpapong S, Rosser BG, Kramer DJ and Nguyen JH contributed to manuscript writing, including drafting the article, or revising it critically for important intellectual content; Heckman MG and Diehl NN contributed to supportive work, including statistical analysis of data, or acquisition of funding, or administration, technology and materials support, or supervision, or supportive contributions.
Correspondence to: Lena Sibulesky, MD, Department of Transplantation, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, United States. sibulesky.lena@mayo.edu
Telephone: +1-904-9563261 Fax: +1-904-9563359
Received: July 10, 2012 Revised: September 8, 2012
Accepted: November 14, 2012
Published online: January 27, 2013

Abstract

AIM: To determine feasibility of liver transplantation in patients from the intensive care unit (ICU) by estimating graft and patient survival.

METHODS: This single center retrospective study included 39 patients who had their first liver transplant directly from the intensive care unit and 927 non-ICU patients who were transplanted from hospital ward or home between January 2005 and December 2010.

RESULTS: In comparison to non-ICU patients, ICU patients had a higher model for end-stage liver disease (MELD) at transplant (median: 37 *vs* 20, $P < 0.001$). Fourteen out of 39 patients (36%) required vasopressor support immediately prior to liver transplantation (LT) with 6 patients (15%) requiring both vasopressin and norepinephrine. Sixteen ICU patients (41%) were ventilator dependent immediately prior to LT with 9 patients undergoing percutaneous tracheostomy prior to transplantation. Twenty-five ICU patients (64%) required dialysis preoperatively. At 1, 3 and 5 years after LT, graft survival was 76%, 68% and 62% in ICU patients *vs* 90%, 81% and 75% in non-ICU patients. Patient survival at 1, 3 and 5 years after LT was 78%, 70% and 65% in ICU patients *vs* 94%, 85% and 79% in non-ICU patients. When formally comparing graft survival and patient survival between ICU and non-ICU patients using Cox proportional hazards regression models, both graft survival [relative risk (RR): 1.94, 95%CI: 1.09-3.48, $P = 0.026$] and patient survival (RR: 2.32, 95%CI: 1.26-4.27, $P = 0.007$) were lower in ICU patients *vs* non-ICU patients in single variable analysis. These findings were consistent in multivariable analysis. Although not statistically significant, graft survival was worse in both patients with cryptogenic cirrhosis (RR: 3.29, $P = 0.056$) and patients who received donor after cardiac death (DCD) grafts (RR: 3.38, $P = 0.060$). These findings reached statistical significance when considering patient survival, which was worse for patients with cryptogenic cirrhosis (RR: 3.97, P = 0.031) and patients who were transplanted with DCD livers (RR: 4.19, $P = 0.033$). Graft survival and patient survival were not significantly worse for patients on mechanical ventilation (RR: 0.91, $P = 0.88$ in graft loss; RR: 0.69, $P = 0.56$ in death) or patients on vasopressors (RR: 1.06, $P = 0.93$ in graft loss; RR: 1.24, $P = 0.74$ in death) immediately prior to LT. Trends toward lower graft survival and patient survival were observed for patients on

dialysis immediately before LT, however these findings did not approach statistical significance (RR: 1.70, P = 0.43 in graft loss; RR: 1.46, P = 0.58 in death).

CONCLUSION: Although ICU patients when compared to non-ICU patients have lower survivals, outcomes are still acceptable. Pre-transplant ventilation, hemodialysis, and vasopressors were not associated with adverse outcomes.

Key words: Donor pool; Donor outcomes; Onor after cardiac death grafts; Liver graft survival; Patient survival

Sibulesky L, Heckman MG, Taner CB, Canabal JM, Diehl NN, Perry DK, Willingham DL, Pungpapong S, Rosser BG, Kramer DJ, Nguyen JH. Outcomes following liver transplantation in intensive care unit patients. *World J Hepatol* 2013; 5(1): 26-32 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i1/26.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i1.26

INTRODUCTION

Liver transplantation (LT) is a life-saving procedure for patients with a wide range of end-stage liver diseases (ESLD). Significant improvement in surgical technique, medical management, and advances in immunosuppression therapy have all contributed to the success of LT. Recent studies have demonstrated that the overall outcome of LT depends on a combination of factors including recipient condition, donor organ quality, as well as the transplant center volume[1-4].

Liver disease is progressive in nature and the care for such patients is complex and challenging. As a result, transplant candidates may require intensive care unit admission while awaiting transplantation[5,6]. It is not uncommon for some patients to have multiorgan system failure (MOSF) requiring ventilatory support, hemodynamic support, and renal replacement therapy (RRT) in the course of their disease. Transplantation of such patients could lead to poor post-transplant outcomes[7,8]. Given the scarcity of organ donors, LT is currently offered to patients with the expected survival of at least 50% in 5 years after the transplantation[9]. As a result, controversy arises: from an individual stand point there is always a benefit to LT because the outcome of deteriorating ESLD is uniformly fatal. From a societal perspective futile outcomes are not acceptable in the time of donor organ shortage.

The current established absolute contraindications for LT include advanced cardiopulmonary disease, extrahepatic malignancy with metastasis, active substance abuse, sepsis, and inability to comply with medical treatment[10]. Despite multiple efforts, there is currently no agreed upon definition of "too sick to transplant", nor there are standardized guidelines for when a critically ill patient should be removed from a transplant waiting list[11,12]. Criteria that are used to delist a sick patient are transplant program dependent. Many regard ventilatory support and vasopressor therapy in a cirrhotic patient as contraindications to proceeding with transplantation[6].

The aim of our study was to determine the feasibility of LT in patients from the ICU by estimating graft and patient survival in this patient group and also compare these outcomes with non-ICU patients. We also evaluated associations of pre-transplant donor and recipient characteristics with outcomes in ICU patients.

MATERIALS AND METHODS

Study patients and data collection

This single center retrospective study included 39 patients who underwent first LT directly from the ICU between January, 2005 and December, 2010 and 927 non-ICU patients, who underwent first LT over the same time period. Non-ICU patients were defined as patients transplanted from the hospital ward or home. This study was exempt from IRB review. Patients who underwent re-transplantation, multiple organ transplant, patients who underwent transplant for fulminant liver failure were excluded. For both ICU and non-ICU patients, information was collected regarding patient characteristics (age, gender, body mass index, etiology of ESLD, model for end-stage liver disease (MELD) score at transplant, previous abdominal operations), operative characteristics (operative time, blood transfusion), donor characteristics [age, gender, recipient-donor gender incompatibility, donation after cardiac death (DCD), donor risk index, cold ischemia time, warm ischemia time], and outcomes (date of graft loss, date of death, date of last follow-up). The following additional information was collected for ICU patients: pre-LT information (length of time from hospital admission to ICU admission, length of time from ICU admission to transplant, MELD at ICU admission, pre-transplant ambulatory status, mechanical ventilation, dialysis, vasopressor use and dose, tracheostomy, positive end-expiratory pressure (PEEP), FiO_2, mean airway pressure, PaO_2) at the time of transplant and post-LT information (tracheostomy, length of hospital stay, length of ICU stay, discharge status, readmission within 3 mo after LT).

Statistical analysis

Patient, operative, and donor characteristics were compared between ICU and non-ICU patients using a Wilcoxon rank sum test or Fisher's exact test. The Kaplan-Meier method was used to estimate graft survival and patient survival after LT, censoring on the date of last follow-up for patients who did not experience graft loss or death (graft survival) or death (patient survival). Cox proportional hazards regression models were used to compare graft survival and patient survival between ICU and non-ICU patients. Single variable models (i.e., models with no adjustment for other variables) were utilized, as well as multivariable models adjusted for variables that differed between ICU and non-ICU patients with a P value of 0.10 or less, excluding variables that are known

Table 1 Patient, operative and donor characteristics in intensive care unit and non-intensive care unit patients

Variable	ICU patients (n = 39)	Non-ICU patients (n = 927)	P value
Patient characteristics			
Age at transplant	57 (33-74)	57 (16-77)	0.91
Gender (male)	21 (54%)	653 (70%)	0.033
BMI	25.7 (18.0-38.0)	28.4 (16.4-61.1)	0.091
Diagnosis			
Hepatitis C	18 (46%)	364 (41%)	0.41
ETOH	10 (26%)	138 (15%)	0.11
Cryptogenic cirrhosis	8 (21%)	147 (16%)	0.5
NASH	0 (0%)	76 (8%)	0.066
PSC	0 (0%)	61 (7%)	0.17
Other	3 (8%)	141 (15%)	0.25
MELD at transplant	37 (24-50)	20 (6-45)	< 0.001
Previous operation	13 (34%)	402 (47%)	0.13
Operative characteristics			
Operative time (min)	230 (129-596)	231 (100-745)	0.69
Blood transfusion (mL)	3850 (1400-15 400)	2800 (0-44 100)	0.002
Cold ischemia time (h)	6.3 (3.4-10.4)	6.3 (2.0-14.0)	0.71
Warm ischemia time (min)	30 (18-84)	31 (10-141)	0.59
Donor characteristics			
Age	42 (8-78)	48 (7-88)	0.016
Gender (male)	17 (46%)	551 (59%)	0.12
Recipient-donor gender incompatibility	15 (41%)	348 (38%)	0.73
Donation after cardiac death	6 (16%)	146 (16%)	1.00
Donor risk index	1.53 (0.88-2.60)	1.66 (0.85-4.30)	0.085

The sample median (minimum-maximum) is given for numerical variables. P values result from Fisher's exact test or a Wilcoxon rank sum test. Information was unavailable regarding previous operations (ICU: n = 1; non-ICU: n = 80), operative time (ICU: n = 2; non-ICU: n = 1), blood transfusion (ICU: n = 3; non-ICU: n = 13), cold ischemia time (ICU: n = 2), warm ischemia time (ICU: n = 2), and all donor characteristics (ICU: n = 2). ICU: Intensive care unit; BMI: Body mass index; ETOH: Ethanol; NASH: Nonalcoholic steatohepatitis; PSC: Primary sclerosing cholangitis; MELD: Model for end-stage liver disease.

Table 2 Additional information for intensive care unit patients only

Variable	Summary (n = 39)
Patient characteristics	
Vasopressors	14 (36%)
Vasopressin	12 (31%)
Dose (units/min)	0.04 (0.01-0.04)
Norepinephrine	8 (21%)
Dose (mcg/kg per min)	0.07 (0.01-0.18)
Vasopressin and norepinephrine	6 (15%)
Length of time from hospital admission to ICU admission (d)	3 (1-32)
Length of time from ICU admission to liver transplant (d)	12 (1-65)
MELD at ICU admission	32 (15-52)
MELD at transplant	37 (24-50)
Pre-transplant ambulation	14 (42%)
Dialysis	25 (64%)
Tracheostomy	9 (23%)
Mechanical ventilation	16 (41%)
Positive end-expiratory pressure (cm H_20)	7 (7-12)
FiO_2 (%)	40 (28-60)
Mean airway pressure (cm H_20)	12 (9-18)
PaO_2 (mmHg)	103 (60-147)
Post-operative characteristics	
Post-operatively placed tracheostomy	4 (10%)
Length of hospital stay	42 (15-516)
Length of ICU stay	27 (7-327)
Discharged status	
Home	19 (49%)
Rehab	14 (36%)
Death	6 (15%)
3-mo readmission	16 (41%)

The sample median (minimum-maximum) is given for numerical variables. Information regarding positive end-expiratory pressure, FiO_2, mean airway pressure, and PaO_2 were only available for patients with mechanical ventilation. Information was unavailable regarding ambulation (n = 5), mean airway pressure (n = 2), and PaO_2 (n = 1). ICU: Intensive care unit; MELD: Model for end-stage liver disease.

to differ between the two groups due to the nature of ICU patients (MELD at transplant), variables that are potentially on the causal pathway between ICU status and graft loss or death (operative time, blood transfusion), variables that did not occur in ICU patients (NASH diagnosis), or variables with any missing data in ICU patients. Relative risks (RRs) and 95%CIs were estimated. In ICU patients, associations of patient and donor characteristics with graft survival and patient survival were evaluated using Cox proportional hazards regression models. Only single variable analysis was performed; multivariable analysis was not attempted owing to the small number of ICU patients who experienced the endpoints of interest[13]. $P \leqslant 0.05$ was considered as statistically significant. All statistical analyses were performed using SAS (Version 9.2; SAS Institute, Inc., Cary, North Carolina) and R Statistical Software (Version 2.11.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A comparison of patient, operative, and donor characteristics between ICU patients and non-ICU patients is displayed in Table 1. In comparison to non-ICU patients, ICU patients were less often male (54% *vs* 70%, P = 0.033), had a lower body mass index (BMI) (median: 25.7 *vs* 28.4, P = 0.091), and had a higher MELD at transplant (median: 37 *vs* 20, P < 0.001). Intraoperatively, ICU patients had a greater packed red blood cell transfusion requirement (median: 3850 mL *vs* 2800 mL, P = 0.002). When compared to non-ICU patients, the ICU patients received liver grafts from the younger median: 1.53 *vs* 1.66, P = 0.085).

A summary of additional patient and post-operative characteristics for the 39 ICU patients is shown in Table 2. Fourteen out of 39 patients (36%) required vasopressor support immediately prior to LT with 6 patients (15%) requiring both vasopressin and norepinephrine. The range of the dose of vasopressin was 0.01 to 0.04 units/min, while norepinephrine dose ranged from 0.01 to 0.18 mcg/kg per minute. Sixteen ICU patients (41%) were ventilator dependent immediately prior to LT with 9 patients undergoing percutaneous tracheostomy prior to transplantation. The range of PEEP was 7 cm to 12

Table 3 Graft survival and patient survival in intensive care unit patients and non- intensive care unit patients

Outcome/time since transplant	Estimate (95%CI) ICU patients (n = 39)	Non-ICU patients (n = 927)
Graft survival		
1 yr	76% (62%-91%)	90% (88%-92%)
2 yr	72% (58%-89%)	84% (82%-87%)
3 yr	68% (52%-86%)	81% (78%-83%)
4 yr	62% (44%-83%)	78% (75%-81%)
5 yr	62% (41%-83%)	75% (72%-78%)
Patient survival		
1 yr	78% (65%-93%)	94% (92%-95%)
2 yr	75% (61%-91%)	89% (87%-91%)
3 yr	70% (55%-88%)	85% (83%-87%)
4 yr	65% (47%-86%)	82% (79%-84%)
5 yr	65% (43%-86%)	79% (76%-82%)

ICU: Intensive care unit.

cm H_2O and FiO_2 ranged from 28% to 60%. Twenty-five ICU patients (64%) required dialysis preoperatively. 32 out of 39 patients (82%) required at least one out of three types of therapy. Median length of time from hospital admission to ICU admission was 3 d (range: 1-32 d). Median length of time from ICU admission to transplant was 12 d (range: 1-65 d). Median MELD at ICU admission was 32 (range: 15-52). Median length of hospital stay was 42 d (range: 15-516 d) and median length of ICU stay was 27 d (range: 7-327 d). Nineteen patients (49%) were discharged home, 14 patients (36%) were discharged to rehab. Six patients (15%) died on the same hospitalization, 2 of which died in the operating room.

The median length of follow up in the overall cohort of 966 patients was 3.5 years (range: 0 d-6.8 years). In the 39 ICU patients, median length of follow up was 1.8 years (range: 0 d-5.6 years). Graft survival and patient survival after LT in ICU patients and non-ICU patients are displayed (Figure 1 and Table 3). At 1, 3 and 5 years after LT, graft survival was 76%, 68% and 62% in ICU patients and 90%, 81% and 75% in non-ICU patients. Patient survival at 1, 3 and 5 years after LT was 78%, 70% and 65% in ICU patients compared to 94%, 85% and 79% in non-ICU patients. When formally comparing graft survival and patient survival between ICU and non-ICU patients using Cox proportional hazards regression models, both graft survival (RR: 1.94, 95%CI: 1.09-3.48, P = 0.026) and patient survival (RR: 2.32, 95%CI: 1.26-4.27, P = 0.007) were lower in ICU patients compared to non-ICU patients in single variable analysis. These findings were consistent in multivariable analysis, adjusting for the potentially confounding variables of patient gender and BMI, graft survival was significantly worse in ICU patients (RR: 2.03, 95%CI: 1.13-3.65, P = 0.018), as was patient survival (RR: 2.44, 95%CI: 1.32-4.50, P = 0.004).

An evaluation of associations of patient and donor characteristics with graft survival and patient survival in ICU patients is provided in Table 4; a total of 12 ICU patients experienced graft loss or death, while 11 patients died. Although not statistically significant, graft

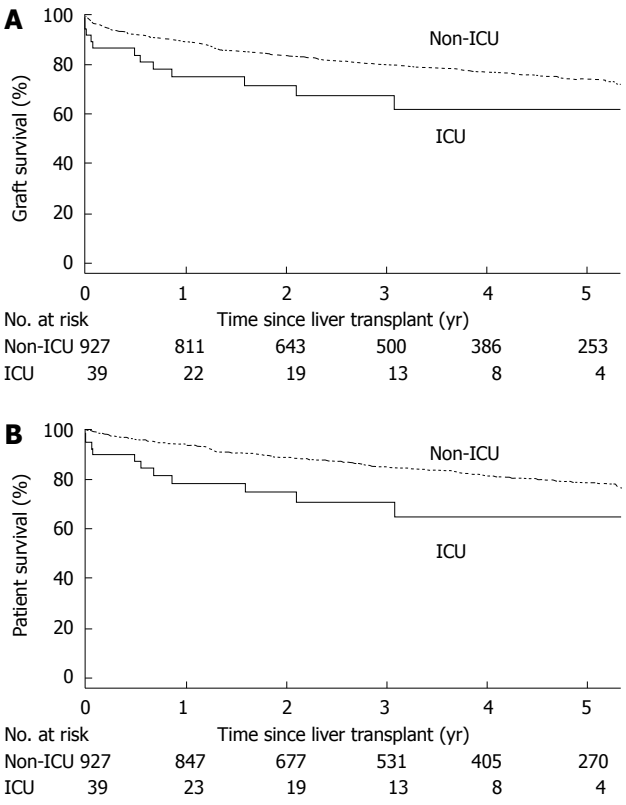

Figure 1 Graft survival (A) and patient survival (B) in intensive care unit patients and non- intensive care unit patients. ICU: Intensive care unit.

survival was worse in both patients with cryptogenic cirrhosis (RR: 3.29, P = 0.056) and patients who received DCD grafts (RR: 3.38, P = 0.060). These findings reached statistical significance when considering patient survival, which was worse for patients with cryptogenic cirrhosis (RR: 3.97, P = 0.031) and patients who were transplanted with DCD livers (RR: 4.19, P = 0.033). The findings regarding DCD liver grafts and the outcomes of their recipients are further illustrated in Figure 2.

Given the aforementioned finding regarding DCD grafts and the consistently documented poorer outcomes of DCD grafts in the literature, we re-calculated graft survival and patient survival excluding 6 ICU patients with DCD donors. When excluding these 6 DCD patients from the ICU group, graft survival in the remaining 31 ICU patients at 1, 3 and 5 years was 78%, 73% and 73%, while patient survival at these time points was 81%, 76% and 76%. When comparing outcomes between this ICU patient subgroup with the overall cohort of 927 non-ICU patients in multivariable analysis, graft survival (RR: 1.59, 95%CI: 0.78-3.23, P = 0.20) and patient survival (RR: 1.80, 95%CI: 0.84-3.85, P = 0.13) were still lower in ICU patients, but these findings are no longer statistically significant.

Graft survival and patient survival were not significantly worse for patients on mechanical ventilation (RR: 0.91, P = 0.88 in graft loss; RR: 0.69, P = 0.56 in death) or patients on vasopressors (RR: 1.06, P = 0.93 in graft loss; RR: 1.24, P = 0.74 in death) immediately prior to LT. Trends toward lower graft survival and patient survival were observed for patients on dialysis immediately

Table 4 Associations of patient and donor characteristics with graft survival (graft loss or death endpoint) and patient survival (death endpoint) in intensive care unit patients

	Association with graft survival (graft loss or death endpoint)		Association with patient survival (death endpoint)	
Variable	**Relative risk (95%CI)**	***P* value**	**Relative risk (95%CI)**	***P* value**
Patient characteristics				
Age at transplant (10 yr increase)	0.98 (0.49-1.99)	0.96	1.00 (0.47-2.11)	0.99
Gender (male)	1.33 (0.42-4.19)	0.63	1.10 (0.34-3.61)	0.88
BMI (10 unit increase)	0.63 (0.24-1.66)	0.35	0.57 (0.20-1.59)	0.28
Diagnosis				
Hepatitis C	0.99 (0.32-3.08)	0.99	0.79 (0.24-2.59)	0.69
ETOH	0.57 (0.12-2.59)	0.46	0.65 (0.14-3.02)	0.58
Cryptogenic cirrhosis	3.29 (0.97-11.15)	0.056	3.97 (1.14-13.87)	0.031
MELD at transplant (5 unit increase)	0.99 (0.63-1.57)	0.97	1.09 (0.68-1.75)	0.72
MELD at ICU admission (5 unit increase)	0.85 (0.56-1.30)	0.47	1.03 (0.66-1.61)	0.89
Previous operation	1.07 (0.31-3.67)	0.91	0.76 (0.20-2.95)	0.69
Vasopressors	1.06 (0.32-3.51)	0.93	1.24 (0.36-4.23)	0.74
Vasopressin	0.78 (0.23-2.59)	0.68	0.91 (0.27-3.11)	0.88
Norepinephrine	0.29 (0.04-2.22)	0.23	0.32 (0.04-2.51)	0.28
Vasopressin and norepinephrine	0.44 (0.06-3.44)	0.44	0.50 (0.06-3.90)	0.51
Length of time from hospital admission to ICU admission (doubling)	0.91 (0.64-1.28)	0.57	0.88 (0.61-1.27)	0.49
Ambulation	1.30 (0.36-4.72)	0.69	1.30 (0.36-4.72)	0.69
Dialysis	1.70 (0.46-6.32)	0.43	1.46 (0.38-5.54)	0.58
Tracheostomy	1.00 (0.27-3.71)	1.00	0.61 (0.13-2.83)	0.53
Mechanical ventilation	0.91 (0.29-2.88)	0.88	0.69 (0.20-2.37)	0.56
Donor characteristics				
Age (10 yr increase)	0.97 (0.67-1.41)	0.88	0.91 (0.61-1.36)	0.65
Gender (male)	0.74 (0.21-2.63)	0.64	0.52 (0.13-2.09)	0.36
Recipient-donor gender incompatibility	1.33 (0.36-4.91)	0.67	1.76 (0.45-6.87)	0.41
Donation after cardiac death	3.38 (0.95-12.05)	0.060	4.19 (1.12-15.70)	0.033
Donor risk index (1 unit increase)	2.15 (0.54-8.62)	0.28	1.61 (0.36-7.15)	0.53

Relative risks and *P* values result from single variables Cox proportional hazards regression models. Relative risks correspond to presence of the given characteristic (categorical variables) or the increase given in parenthesis (numerical variables). A higher relative risk indicates an increased likelihood of experiencing the given endpoint. ICU: Intensive care unit; BMI: Body mass index; ETOH: Ethanol; MELD: Model for end-stage liver disease..

before LT, however these findings did not approach statistical significance (RR: 1.70, $P = 0.43$ in graft loss; RR: 1.46, $P = 0.58$, in death).

DISCUSSION

LT has evolved from an experimental procedure to a life-saving therapy for patients with end-stage liver disease. The complicated pathophysiology of end-stage liver disease, sophisticated surgery and challenging post-operative care requires center expertise and collaborative team of skilled, innovative clinicians, including surgeons, hepatologists, anesthesiologists, and transplant intensivists in order to achieve the best possible outcome.

Advanced liver disease frequently mandates ICU admission. The admission to ICU is associated with high mortality and LT becomes the only definitive therapeutic option for a decompensated cirrhotic patient. At this time, one of the most complex decisions the clinicians face is when an extremely ill candidate no longer becomes suitable for this procedure. Currently, there are no specific recommendations to define the individuals who are too sick to transplant and thus avoid futile therapy. It is left up to the center's experience and subjective "eyeball test" to define criteria for delisting[12].

In our study, over a period of 6 years, critically ill patients who underwent LT directly from the ICU had an average MELD score of 37 at the time of transplantation, which was significantly higher than the average MELD of 20 in non-ICU patients. Post LT overall patient and graft survival rates in patients transplanted directly from the ICU were lower than in patients transplanted either from home or from the hospital ward. However, despite these poorer outcomes in ICU patients compared to non-ICU patients, they are still higher than what is considered acceptable by the transplant community[9].

One of the possible reasons for better outcomes in our patients is likely due to the high volume of LT operations at our center. Ozhathil *et al*[3] reported decreased risk of allograft failure and recipient death after LT in high volume centers defined as centers performing 78-215 cases per year. This has been demonstrated in retransplantation as well by Reese *et al*[14].

Further investigation of outcomes in ICU patients revealed that patients who received a DCD liver graft had more than 3-fold increased risk of losing a graft and more than a 4-fold increased risk of dying compared to the ICU patients who received a non-DCD graft. In fact, graft and patient survival between non-ICU patients and ICU patients excluding the patients who received DCD grafts were reasonably comparable, particularly at 5-year after LT where graft and patient survival were 73% and

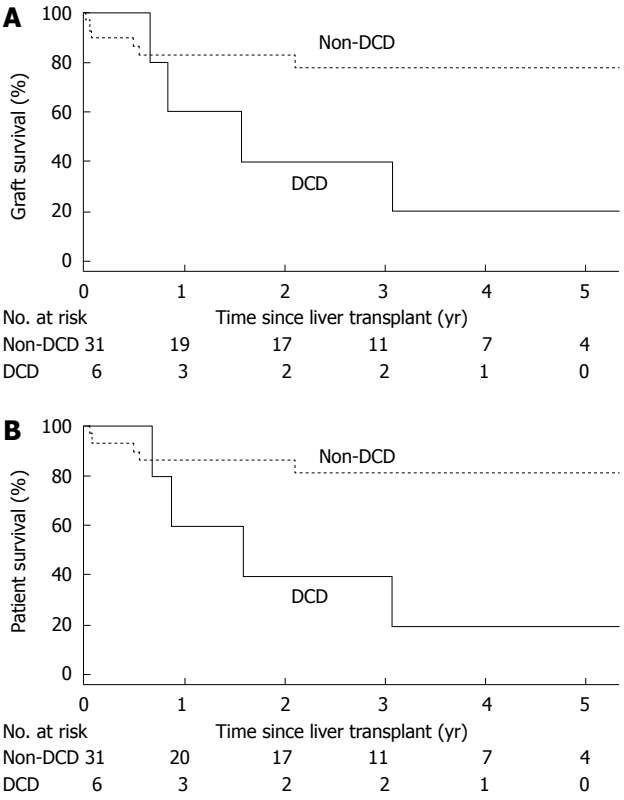

Figure 2 Graft survival (A) and patient survival (B) in intensive care unit patients according to donor after cardiac death. DCD: Donation after cardiac death.

76% in ICU patients and 75% and 79% in non-ICU patients. Our findings are consistent with the results reported previously in the literature[15]. DCD donors have recently been used to increase the number of deceased donors and bridge the gap between the number of available organs and the number of candidates on the waiting list. These organs are considered marginal because this type of graft is thought to be of inferior quality when compared to the liver grafts from DBD donors[16]. Analyzing the UNOS database, Mateo *et al*[15] have demonstrated that with DCD livers the graft survival at 1 year and 3 years was 71% and 60% respectively, which was significantly lower than 80% and 72% in patients who received DBD grafts. The graft survival significantly improved to 81% and 67% at 1 and 3 years respectively, if these organs were placed in low risk patients (i.e., patients without previous history of LT, non-ICU patients, patients not requiring life support, and patients not on dialysis), and became similar to that of DBD donors.

In our analysis of risk factors for graft loss and death in ICU patients, in addition to aforementioned DCD finding, we also observed that patients with cryptogenic cirrhosis had poorer patient and graft survival than patients with liver disease from other causes. However, this finding is of uncertain significance and should be further evaluated in larger series.

In the ICU, deteriorating patients with ESLD awaiting LT develop MOSF requiring mechanical ventilatory support, intermittent or continuous RRT, and pharmacologic hemodynamic support. Vasopressor requirement and intubation have been considered to be contraindications to transplantation and regarded as criteria for delisting[6]. We sought to investigate whether any of the above factors which have been traditionally linked to worse outcomes would be prognosticators of poor outcomes in our experience.

Mechanical ventilation is required for airway protection in a setting of hepatic encephalopathy, for respiratory failure due to ARDS, pulmonary edema, and infections. In previous reports it has been demonstrated that preoperative mechanical ventilation played a role in prolonged postoperative intubation[17]. Preoperative mechanical intubation has been identified as one of the independent risk factors for decreased patient and graft survival[4,18]. In our study 46% of patients transplanted from the ICU were on a ventilator at the time of LT. More than half of the intubated patients underwent percutaneous tracheostomy placement prior to LT. All the patients who were ventilator dependent prior to LT had PEEP of $\leqslant$ 12 mmHg and $FiO_2 \leqslant 60\%$. In contrast to previous publications, in our sample of 39 patients transplanted from the ICU, ventilatory support prior to LT did not have a negative effect on patient or graft survival.

Patients with ESLD are in hyperdynamic state with low systemic arterial pressure sometimes requiring vasopressor support[6]. In our analysis, 36% of patients were on vasopressors with 15% of patients being on a combination of vasopressin and norepinephrine. The patients with active sepsis were not transplanted. Based on our analysis, the patients who required pharmacologic hemodynamic support at the time of LT did not experience inferior graft or patient survival as evidenced by RR of approximately one or less in magnitude.

Due to disturbances in renal function, renal failure develops in many patients with cirrhosis[19]. In most instances continuous RRT is the modality of choice due to patient hemodynamic instability. Multiple investigations have linked preoperative hemodialysis to poorer outcomes after LT[18,20-22]. In our cohort, 65% of patients were on dialysis, and while we did not observe a statistically significant association between dialysis and either graft or patient survival, the RR that we observed of 1.70 and 1.45, respectively, suggest a trend to lower outcomes. Our study has several limitations. It has a retrospective design and a relatively small number of ICU patients who underwent LT. Related to the limited number of ICU patients, power to detect associations of recipient and donor characteristics with outcomes in ICU patient is limited, and the possibility of Type II error (i.e., a false-negative association) is important to consider. In addition, our results reflect the experience of a single high-volume center and thus might not be applicable to other centers. The criteria for ICU admission might vary from center to center.

In conclusion, to our knowledge, this is the largest study that directly examined the outcomes of the patients who have undergone LT directly from the ICU. We have demonstrated that patients who require mechanical ventilatory support, pharmacologic hemodynamic support, and RRT can have acceptable patient and graft outcomes after

LT. A much larger group of ICU patients, likely from a multi-center study, is needed to better define criteria for a successful liver transplant.

COMMENTS

Background

Liver transplantation (LT) is a life-saving procedure for patients with end-stage liver diseases. Improvements in surgical technique, medical management, and advances in immunosuppression therapy have all contributed to the success of LT.

Research frontiers

It is not uncommon for patients with significantly decompensated liver disease to require intensive care unit (ICU) admission for multiorgan system failure requiring ventilatory support, hemodynamic support, and renal replacement therapy (RRT) in the course of their disease. Transplantation of such patients could lead to poor post-transplant outcomes. Given the scarcity of organ donors transplantation of such patients could be futile and thus acceptable in the time of donor organ shortage.

Innovations and breakthroughs

This is the largest study that investigated the feasibility of LT in patients from the ICU, patients who require mechanical ventilatory support, pharmacologic hemodynamic support, and RRT by estimating graft and patient survival in this patient population. The authors have demonstrated that this group of patients can have acceptable patient and graft outcomes after LT.

Applications

The data can contribute to the widening of recipient criteria in LT.

Peer review

The authors reported the outcomes following LT in ICU patients. The clinical result was very good for the new insight and encouragement of physicians dealing with this challenging filed.

REFERENCES

1 **Rana A**, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, Guarrera JV, Brown RS, Emond JC. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant* 2008; **8**: 2537-2546 [PMID: 18945283 DOI: 10.1111/j.1600-6143.2008.02400.x]

2 **Schaubel DE**, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. *Am J Transplant* 2008; **8**: 419-425 [PMID: 18190658 DOI: 10.1111/j.1600-6143.2007.02086.x]

3 **Ozhathil DK**, Li YF, Smith JK, Tseng JF, Saidi RF, Bozorgzadeh A, Shah SA. Impact of center volume on outcomes of increased-risk liver transplants. *Liver Transpl* 2011; **17**: 1191-1199 [PMID: 21604357 DOI: 10.1002/lt.22343]

4 **Desai NM**, Mange KC, Crawford MD, Abt PL, Frank AM, Markmann JW, Velidedeoglu E, Chapman WC, Markmann JF. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function. *Transplantation* 2004; **77**: 99-106 [PMID: 14724442 DOI: 10.1097/01.TP.0000101009.91516.FC]

5 **Ginès P**, Fernández J, Durand F, Saliba F. Management of critically-ill cirrhotic patients. *J Hepatol* 2012; **56** Suppl 1: S13-S24 [PMID: 22300462 DOI: 10.1016/S0168-8278(12)60003-8]

6 **Findlay JY**, Fix OK, Paugam-Burtz C, Liu L, Sood P, Tomlanovich SJ, Emond J. Critical care of the end-stage liver disease patient awaiting liver transplantation. *Liver Transpl* 2011; **17**: 496-510 [PMID: 21506240 DOI: 10.1002/lt.22269]

7 **Umgelter A**, Lange K, Kornberg A, Büchler P, Friess H, Schmid RM. Orthotopic liver transplantation in critically ill cirrhotic patients with multi-organ failure: a single-center experience. *Transplant Proc* 2011; **43**: 3762-3768 [PMID: 22172843 DOI: 10.1016/j.transproceed.2011.08.110]

8 **Sobhonslidsuk A**, Neff GW, Molina EG, Yamashiki N, Nishida S, Reddy KR, Tzakis AG, Schiff ER. Prediction of survival outcome of ICU patients awaiting orthotopic liver transplantation. *Transplant Proc* 2002; **34**: 1223-1225 [PMID: 12072322 DOI: 10.1016/S0041-1345(02)02814-2]

9 **Brown RS**, Lake JR. The survival impact of liver transplantation in the MELD era, and the future for organ allocation and distribution. *Am J Transplant* 2005; **5**: 203-204 [PMID: 15643978 DOI: 10.1111/j.1600-6143.2005.00769.x]

10 **Varma V**, Mehta N, Kumaran V, Nundy S. Indications and contraindications for liver transplantation. *Int J Hepatol* 2011; **2011**: 121862 [PMID: 22007310]

11 **Merion RM**. When is a patient too well and when is a patient too sick for a liver transplant? *Liver Transpl* 2004; **10**: S69-S73 [PMID: 15382215 DOI: 10.1002/lt.20265]

12 **Charpentier KP**, Mavanur A. Removing patients from the liver transplant wait list: A survey of US liver transplant programs. *Liver Transpl* 2008; **14**: 303-307 [PMID: 18306339 DOI: 10.1002/lt.21353]

13 **Peduzzi P**, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995; **48**: 1503-1510 [PMID: 8543964 DOI: 10.1016/0895-4356(95)00048-8]

14 **Reese PP**, Yeh H, Thomasson AM, Shults J, Markmann JF. Transplant center volume and outcomes after liver retransplantation. *Am J Transplant* 2009; **9**: 309-317 [PMID: 19120081 DOI: 10.1111/j.1600-6143.2008.02488.x]

15 **Mateo R**, Cho Y, Singh G, Stapfer M, Donovan J, Kahn J, Fong TL, Sher L, Jabbour N, Aswad S, Selby RR, Genyk Y. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. *Am J Transplant* 2006; **6**: 791-796 [PMID: 16539637 DOI: 10.1111/j.1600-6143.2006.01243.x]

16 **Mathur AK**, Heimbach J, Steffick DE, Sonnenday CJ, Goodrich NP, Merion RM. Donation after cardiac death liver transplantation: predictors of outcome. *Am J Transplant* 2010; **10**: 2512-2519 [PMID: 20977642 DOI: 10.1111/j.1600-6143.2010.03293.x]

17 **Huang CT**, Lin HC, Chang SC, Lee WC. Pre-operative risk factors predict post-operative respiratory failure after liver transplantation. *PLoS One* 2011; **6**: e22689 [PMID: 21829646 DOI: 10.1371/journal.pone.0022689]

18 **Markmann JF**, Markmann JW, Markmann DA, Bacquerizo A, Singer J, Holt CD, Gornbein J, Yersiz H, Morrissey M, Lerner SM, McDiarmid SV, Busuttil RW. Preoperative factors associated with outcome and their impact on resource use in 1148 consecutive primary liver transplants. *Transplantation* 2001; **72**: 1113-1122 [PMID: 11579310 DOI: 10.1097/00007890-200109270-00023]

19 **Ginès P**, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; **361**: 1279-1290 [PMID: 19776409 DOI: 10.1056/NEJMra0809139]

20 **Li C**, Wen TF, Yan LN, Li B, Yang JY, Wang WT, Xu MQ, Wei YG. Predictors of patient survival following living donor liver transplantation. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 248-253 [PMID: 21669566 DOI: 10.1016/S1499-3872(11)60041-6]

21 **Wong LP**, Blackley MP, Andreoni KA, Chin H, Falk RJ, Klemmer PJ. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. *Kidney Int* 2005; **68**: 362-370 [PMID: 15954928 DOI: 10.1111/j.1523-1755.2005.00408.x]

22 **Gonwa TA**, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, Klintmalm GB. Renal replacement therapy and orthotopic liver transplantation: the role of continuous veno-venous hemodialysis. *Transplantation* 2001; **71**: 1424-1428 [PMID: 11391230 DOI: 10.1097/00007890-200105270-00012]

P- Reviewers Selinger CP, Herceg Z **S- Editor** Xiong L
L- Editor A **E- Editor** Li JY

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i1.33

World J Hepatol 2013 January 27; 5(1): 33-37
ISSN 1948-5182 (online)

BRIEF ARTICLE

Pancreatic fistula: A proposed percutaneous procedure

Silvia Pradella, Ernesto Mazza, Francesco Mondaini, Stefano Colagrande

Silvia Pradella, Stefano Colagrande, Department of Experimental and Clinical Biomedical Sciences, Section of Radiodiagnostics, University of Florence, Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy
Ernesto Mazza, Francesco Mondaini, Department of Diagnostic Imaging, Section of Interventional Radiology, Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy
Author contributions: All the authors have contributed to all the phases of the article.
Correspondence to: Stefano Colagrande, Associate Professor of Radiology, Department of Experimental and Clinical Biomedical Sciences, Section of Radiodiagnostics, University of Florence, Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy. stefano.colagrande@unifi.it
Telephone: +39-55-7946338 Fax: +39-55-431970
Received: June 29, 2012 Revised: December 7, 2012
Accepted: December 23, 2012
Published online: January 27, 2013

Abstract

AIM: To propose a percutaneous treatment for otherwise intractable pancreatic fistula (PF).

METHODS: From 2005 to 2011, 12 patients (9 men and 3 women, mean age 59 years, median 63 years, range 33-78 years) underwent radiological treatment for high-output PF associated with peripancreatic fluid collection. The percutaneous procedures were performed after at least 4 wk of unsuccessful conservative treatments. We chose either a one or two step procedure, depending on the size and characteristics of the fistula and the fluid collection (with an arbitrary cut-off of 2 cm). Initially, 2 to 6 pigtail drainages of variable size from 8.3 (8.3-Pig Duan Cook, Bloomington, Indiana, United States) to 14 Fr (Flexima, Boston Scientific, Natick, United States) were positioned inside the collection using a transgastric approach. In a second procedure, after 7-10 d, two or more endoprostheses (cystogastrostomic 8 Fr double-pigtail, Cook, Bloomington, Indiana, United States in 10 patients; covered Niti-S stent, TaeWoong Medical Co, Seoul, South Korea in 2 patients) were placed between the collection and the gastric lumen. In all cases the metal or plastic prostheses were removed within one year after positioning.

RESULTS: Four out of 12 high-output fistulas fistulas were external while 8/12 were internal. The origin of the fistulous tract was visualised by computer tomography (CT) imaging studies: in 11 patients it was at the body, and in 1 patient at the tail of the pancreas. Single or multiple drainages were positioned under CT guidance. The catheters were left in place for a varying period (0 to 40 d - median 10 and 25th-75th percentile 0-14). In one case external transgastric drainages were left in place for a prolonged time (40 d) due to the presence of vancomycin-resistant bacteria (Staphylococcus) and fluconazole-resistant fungi (Candida) in the drained fluid. In this latter case systemic and local antibiotic therapy was administered. In both single and two-step techniques, when infection was present, we carried out additional washing with antibiotics to improve the likelihood of the procedure's success. In all cases the endoprostheses were left *in situ* for a few weeks and endoscopically removed after remission of collections, as ascertained by CT scan. Procedural success rate was 100% as the resolution of external PF was achieved in all cases. There were no peri-procedural complications in any of the patients. The minimum follow-up was 18 mo. In two cases the procedure was repeated after 1 year, due to the onset of new fluid collections and the development of pseudocysts. Indeed, this type of endoprosthesis is routinely employed for the treatment of pseudocysts. Endoscopy was adopted both for control of the positioning of the endoprosthesis in the stomach, and for its removal after resolution of the fistula and fluid collection. The resolution of the external fistula was assessed clinically and CT scan was employed to demonstrate the resolution of peripancreatic collections for both the internal and external fistulae.

CONCLUSION: The percutaneous placement of cistogastrostomic endoprostheses can be used for the treatment of PF that cannot be treated with other procedures.

Key words: Pancreas; Pancreatic fistula; Interventional radiology; Pancreatic surgery; Complications

Pradella S, Mazza E, Mondaini F, Colagrande S. Pancreatic fistula: A proposed percutaneous procedure. *World J Hepatol* 2013; 5(1): 33-37 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i1/33.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i1.33

INTRODUCTION

Postoperative pancreatic fistula (PF) is a possible complication of acute or chronic pancreatitis, partial pancreatectomy, or trauma to the pancreatic duct during upper abdominal surgery, pancreatic biopsy, or blunt abdominal trauma. PF may lead to prolonged hospitalization, increased costs, and mortality. PFs occur in about 10% to 28% of patients who undergo pancreatic resection[1]. PFs may be internal or external, and therapeutic options for both can be conservative (medical), endoscopic, percutaneous (under radiological guidance), or surgical.

Closure of external PFs is mainly achieved by medical therapy. In selected patients who have failed with less invasive procedures, surgical treatment maybe provided, with good results, but also with significant mortality rates[1]. Improvements in both skill levels and in medical devices, have progressively increased the success rate of endoscopic methods[2,3]. Nonetheless, some patients must be excluded from these procedures, mainly for technical reasons. In such rare cases, for example when the pancreatic duct cannulation is difficult for anatomical reasons or because of the patient's clinical condition, the percutaneous approach is possible and may be favored.

On the basis of twelve personal cases, we propose a percutaneous radiologically guided technique for treatment of PFs, which can be used when other procedures are not indicated or would be ineffective. This method seems to be extremely helpful in achieving a complete resolution.

MATERIALS AND METHODS

Patients

From 2005 to 2011, 12 patients (9 men and 3 women, mean age 59 years, median 63 years, range 33-78 years) received radiological treatment for high-output PF associated with peripancreatic fluid collection. The percutaneous procedures were performed after at least 4 wk of inconclusive conservative treatments (total parenteral nutrition with nasojejunal tube and administration of somatostatin analogues). All patients underwent abdominal computed tomography scans in order to demonstrate the origin of the fistulous tract and to evaluate the fluid collection. In our series of patients the surgeon, in consultation with the endoscopist, considered cannulation of the pancreatic duct to be contraindicated and decided to try a percutaneous radiological approach.

Table 1 Pancreatic fistula: Characteristics of patients

No.	Sex	Age (yr)	Pathology	Drainage	Dimension (fr)	Time (d)	Endo.	Time (mo)	Proc.
1	M	61	Post-surgery PD	2	8.3	8	2	9	2
2	M	77	Post-surgery PD	2	8.3	10	2	5	2
3	M	66	Post-surgery PD	1	14	0	2	4	2
4	F	78	Post-surgery PD	2	8.3	12	2	5	2
5	M	65	Post-surgery PD	2	10	14	2	6	1
6	F	78	Post-surgery pancreatic tail resection	1	14	0	2	6	2
7	M	41	Post-traumatic	2	14	18	2	6	2
8	M	52	Post-traumatic	1	14	0	2	4	1
9	M	33	Post-traumatic	6	8.3	10	6	6	4
10	F	66	Post-pancreatitis	3	14	40	3	5	4
11	F	60	Post-pancreatitis	3	14	14	2	6	3
12	M	35	Post-pancreatitis	2	10	10	2	6	2

M: Male; F: Female; PD: Pancreatico-duodenectomy; Endo.: Endoprosthesis; Proc.: Procedure; Time (d): Period of left *in situ* of drainages; Time (mo): Period of left *in situ* of endoprosthesis.

Procedure technique

In all patients (Table 1) one or more drains (Flexima, Boston Scientific, Natick, United States) were placed under computer tomography (CT) guidance. Where necessary, the catheters were left in place for mean period of 10 d (range 0-40 d). A minimum of two prostheses (cystogastrostomic 8 Fr double-pigtail, Cook, Bloomington, Indiana, United States in 10 patients; covered Niti-S stent, TaeWoong Medical Co, Seoul, South Korea in 2 patients) were then placed under fluoroscopic guidance and endoscopic control.

All procedures were performed by an expert interventional radiologist. Depending on the dimensions of the fluid collection, we adopted two different possible procedures (Figure 1).

In cases of retrogastric pancreatic fluid collections larger than 2 cm (8 patients), a two-step procedure was adopted (Figure 2A). Initially, 2 to 6 pigtail drains of size from 8.3 (8.3-Pig Duan Cook, Bloomington, Indiana, United States) to 14 Fr (Flexima, Boston Scientific, Natick, United States) were positioned inside the collection using a transgastric approach (Figure 2B and C). In a second procedure, 7-10 d later, two or more endoprostheses (cystogastrostomic 8 Fr double-pigtail, Cook, Bloomington, Indiana, United States in 10 patients; covered Niti-S stent, TaeWoong Medical Co, Seoul, South Korea in 2 patients) were placed between the collection and the gastric lumen.

The first step of the procedure was a trans-gastric CT-guided puncture of the collection using a 18 G Chiba needle (Figure 2B). Through this needle a rigid guide (extra stiff Amplaz 0.035 inch Cook, Bloomington, Indiana, United States) was inserted, and a sufficient number of drains introduced. Correct positioning was verified by

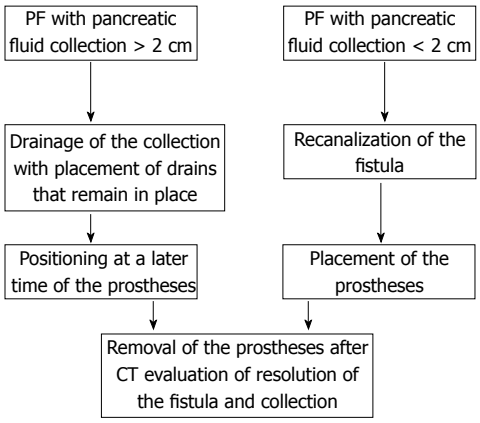

Figure 1 Flow chart of two-step (on the left) and one-step (on the right) procedures. PF: Pancreatic fistula; CT: Computer tomography.

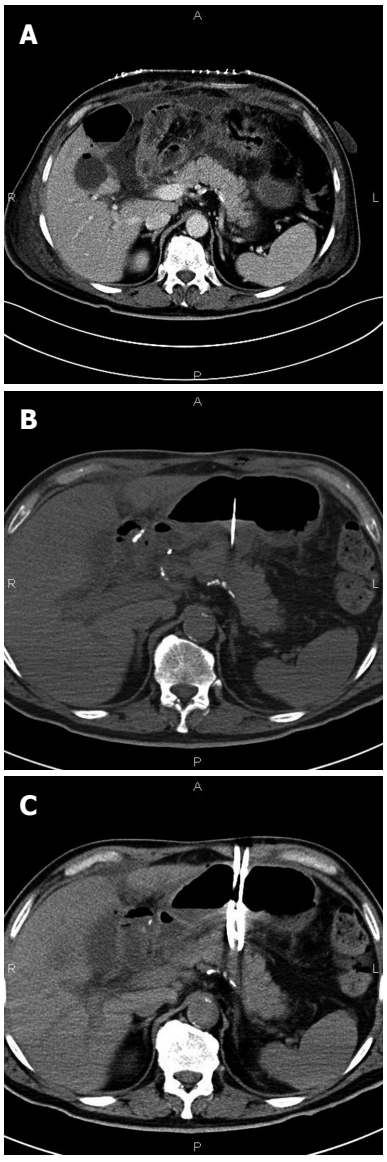

Figure 2 Diagnostic enhanced computer tomography scan (A), and unenhanced computer tomography scan scans (B, C) performed during interventional procedure. A: Patient developed a pancreatic fistula and abdominal fluid collection after surgery for pancreatic neoplasm; B, C: Percutaneous approach, was then adopted: images show trans-gastric puncture (B) and the access and placement of 2 drains in the collection(C).

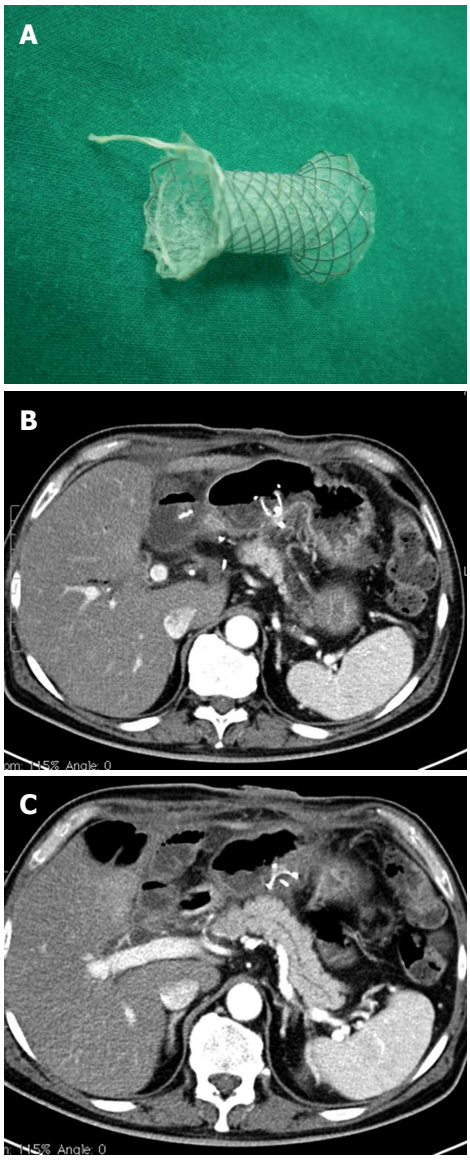

Figure 3 Prosthesis fully extended (Niti-S stent covered, TaeWoong Medical Co., Seoul, South Korea) (A) and enhanced computer tomography scans (B, C) performed after interventional procedure. Images demonstrate prosthesis *in situ* and resolution of peripancreatic collections.

CT scan. Then, the drainage was removed and the prostheses placed under fluoroscopic guidance (Figure 3).

In cases of retrogastric pancreatic fluid collections smaller than 2 cm (4 patients) with external fistulas caused by surgical or percutaneous drainage, a one step procedure was preferred (Figure 4). Through the fistula, an angiographic guide (hydrophilic-curved guidewire 0.035 inch Terumo, Tokyo, Japan) and then an extra-stiff guidewire (Amplatz extra stiff inch 0.035 Boston Scientific, Natick, United States) were inserted. Through this latter guide a TIPSS cannula (transjugular intrahepatic Access set Cook, Bloomington, Indiana, United States) was positioned, the guide removed, and a mandrel inserted.

Then, under fluoroscopic guidance, the cannula was pushed into the gastric lumen, the mandrel removed, and a new guide/s inserted, as described in the literature[4]. Thus, using a prosthesis, a by-pass is created between the

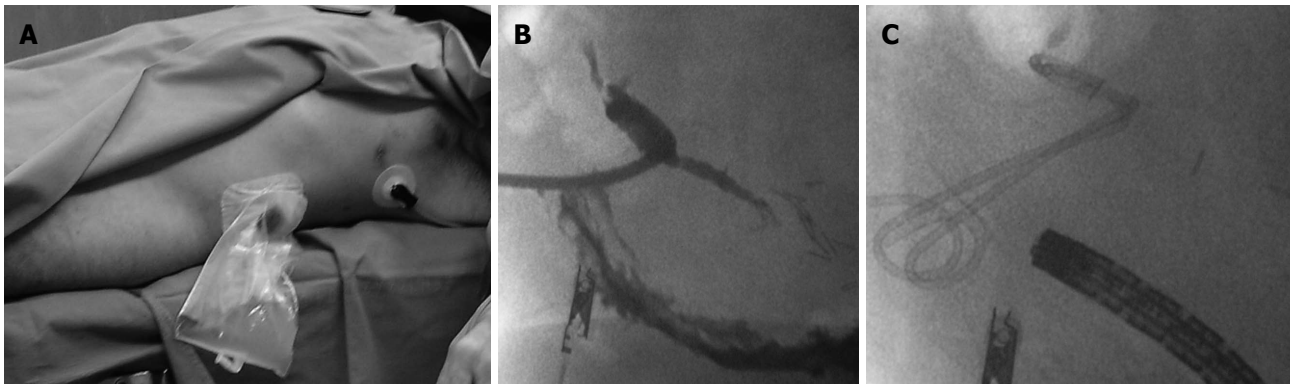

Figure 4 The external fistula opens on the skin surface (A), a catheter has been positioned through the fistula (B) and two prostheses have then been placed through these two guides (C).

origin of the fistula and the lumen of the stomach. The procedure (performed under local anesthesia associated with a mild analgo-sedation Remifentanil and Midazolam based) was carried out under endoscopic surveillance. Prosthesis positioning follow-up was guided by CT (Figure 3B and C). In all cases, the metal or plastic prostheses were removed within one year after positioning. Recently a new device (Niti-S stent covered, TaeWoong Medical Co., Seoul, South Korea) has been introduced into clinical practice consisting of a self-expandable, coated, removable Nitinol metal stent, spool-shaped, 2 cm long, narrower in the central portion (12 mm) and wider at the ends (29 mm) (Figure 3A). This device, positioned between the collection and the gastric lumen, does not clog simply because it is large. We employed this tool in the last two patients. It will probably replace the plastic prostheses in the treatment of pancreatic fistulas.

RESULTS

The patients' characteristics are shown in Table 1. In all patients, one or more drains were positioned under CT guidance (Table 1). Four of the 12 fistulas were external while 8/12 were internal, all were high-output fistulas. External fistulas occurred in 2 patients with pancreatitis, and in 2 other patients post-surgical drainage. In all patients the CT examination showed a discontinuity of the main pancreatic duct, allowing us to localize the origin site of the fistula: this origin was at the body in 11 patients and at the tail of the pancreas in 1 patient. The catheters were left in place for 0 to 40 d (median 10 and 25th-75th percentile 0-14). The longest period was in a case showing the presence of vancomycin-resistant bacteria (*Staphylococcus*) and fluconazole-resistant fungi (*Candida*) in the drained fluid. In this case systemic and local (via catheter) antibiotic therapy was administered. The endoprostheses were left *in situ* for few weeks and endoscopically removed after remission of collections, demonstrated by CT scan.

The resolution of external PF was achieved in all cases, and there were no peri-procedural complications. In two cases the procedure was repeated after 1 year using new external drains, following the onset of pseudocyst and new fluid collections.

DISCUSSION

The percutaneous method we have described, seems to be extremely promising for achieving a complete resolution of PF under radiologic guidance.

Even though PF is a frequent complication of pancreatic resection, its management is still not standardized[3]. PFs may be internal or external and both result from leakage of pancreatic juice from a disrupted pancreatic duct. External PFs extend from the pancreas (or peripancreatic fluid collection) to the skin surface, and a pancreatic fluid collection is frequently associated with a fistula. On the basis of the amount of secretions, PFs are classified into high-output (> 200 mL per 24 h), and low-output (< 200 mL per 24 h) type[1].

The choice of treatment depends on the characteristics the patient and the fistula. The overall success rate of the medical approach is high, 68%-100% of cases[1], and in failed cases, endoscopic treatment has been suggested as a reasonable next step to achieve healing a PF within a few weeks[4]. Surgical treatment is indicated only for patients who have failed the less invasive attempts and has a success rate of about 90%-92%, but with a significant mortality rate of 6%-9%[1]. Endoscopic procedures include various drainage techniques, comprehensive cannulation of the injured pancreatic duct and stent positioning. The case studies reported in the literature, however, involve few patients, and success is dependent on the experience of physicians[2,5].

Some patients are not eligible for the above mentioned treatments, mainly due to technical limitations of endoscopic retrograde cholangio pancreatography, related to duodenal and pancreatic duct stricture or post-surgical anatomy, that make duct cannulation complex or impossible[6].

In these patients radiological treatment can be considered although not all cases are eligible, as with other minimally invasive methods. The interventional radiologist evaluates each case, and when the access is ad-

equate, may decide to use the method described above, a procedure already well established in cases of pancreatic pseudocyst and characterized by low complication and mortality rates. The prostheses are left in position for a few weeks to allow the normal flow or egress of pancreatic juices into the gut, facilitating the closure of the fistula. In our experience, this technique allows the resolution of the fistula without significant complications. Obviously, the cases treated were few because this procedure is rarely necessary. However, we have described this technique because we believe that it can be a feasible option or may be used in addition to other treatments.

COMMENTS

Background

The pancreatic fistula (PF) is a possible complication, especially in pancreatic surgery, still associated with a significant mortality. In almost all cases, medical therapy leads to healing but problems exists in a few cases. These patients have different treatments options. The procedure described here is an additional alternative that does not exclude other therapeutic options.

Research frontiers

Modern surgery of the pancreas is still burdened with complications, such as fistulas, and the challenge is to reduce resulting mortality. The minimally invasive procedures proposed in the literature are all based on only a few cases. The procedure described here fits into the puzzle of customized treatments.

Innovations and breakthroughs

In selected cases, described in the paper, the authors adopted a treatment previously used in pancreatic pseudocysts for the treatment of patients with PFs. They observed a remission of fistula associated with the drainage of pancreatic fluid within the stomach. So, the procedure described is not "new" but is a innovative employment of a method generally used for pancreatic pseudocyst treatment.

Applications

The technique represents a further option within the framework of minimally invasive procedures of intractable fistulas in selected patients. This procedure does not preclude surgery or other treatments.

Peer review

The manuscript proposes a new technique to solve persistent high-output PF.

REFERENCES

1 **Butturini G**, Daskalaki D, Molinari E, Scopelliti F, Casarotto A, Bassi C. Pancreatic fistula: definition and current problems. *J Hepatobiliary Pancreat Surg* 2008; **15**: 247-251 [PMID: 18535760 DOI: 10.1007/s00534-007-1301-y]

2 **Hirota M**, Kanemitsu K, Takamori H, Chikamoto A, Hayashi N, Horino K, Baba H. Percutaneous transfistulous pancreatic duct drainage and interventional pancreatojejunostomy as a treatment option for intractable pancreatic fistula. *Am J Surg* 2008; **196**: 280-284 [PMID: 18639662 DOI: 10.1016/j.amjsurg.2007.05.055]

3 **Cicek B**, Parlak E, Oguz D, Disibeyaz S, Koksal AS, Sahin B. Endoscopic treatment of pancreatic fistulas. *Surg Endosc* 2006; **20**: 1706-1712 [PMID: 16960673 DOI: 10.1007/s00464-005-0764-7]

4 **Seewald S**, Ang TL, Kida M, Teng KY, Soehendra N. EUS 2008 Working Group document: evaluation of EUS-guided drainage of pancreatic-fluid collections (with video). *Gastrointest Endosc* 2009; **69**: S13-S21 [PMID: 19179137 DOI: 10.1016/j.gie.2008.12.035]

5 **Saeed ZA**, Ramirez FC, Hepps KS. Endoscopic stent placement for internal and external pancreatic fistulas. *Gastroenterology* 1993; **105**: 1213-1217 [PMID: 8405869]

6 **Barkay O**, Sherman S, McHenry L, Yoo BM, Fogel EL, Watkins JL, DeWitt J, Al-Haddad MA, Lehman GA. Therapeutic EUS-assisted endoscopic retrograde pancreatography after failed pancreatic duct cannulation at ERCP. *Gastrointest Endosc* 2010; **71**: 1166-1173 [PMID: 20303489 DOI: 10.1016/j.gie.2009.10.048]

P- Reviewer Vigano L **S- Editor** Cheng JX
L- Editor Hughes D **E- Editor** Li JY

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i1.38

World J Hepatol 2013 January 27; 5(1): 38-42
ISSN 1948-5182 (online)

BRIEF ARTICLE

Treatment of Budd-Chiari syndrome with a focus on transjugular intrahepatic portosystemic shunt

Anders Bay Neumann, Stine Degn Andersen, Dennis Tønner Nielsen, Peter Holland-Fischer, Hendrik Vilstrup, Henning Grønbæk

Anders Bay Neumann, Stine Degn Andersen, Peter Holland-Fischer, Hendrik Vilstrup, Henning Grønbæk, Department of Medicine V (Gastroenterology and Hepatology), Aarhus University Hospital, DK-8000 Aarhus C, Denmark
Dennis Tønner Nielsen, Department of Radiology R,Aarhus University Hospital, DK-8000 Aarhus C, Denmark
Author contributions: Neumann AB, Andersen SD and Grønbæk H designed the study; Andersen SD, Nielsen DT and Holland-Fischer P collected the data and later supplemented by Neumann AB; Neumann AB and Grønbæk H analysed the data; Neumann AB, Holland-Fischer P, Vilstrup H and Grønbæk H wrote the paper; and all authors have approved the final version of the manuscript.
Supported by A grant from the NOVO Nordisk Foundation, to Grønbæk H
Correspondence to: Anders Bay Neumann, MD, Department of Medicine V (Gastroenterology and Hepatology), Aarhus University Hospital, Norrebrogade 44, DK-8000 Aarhus C, Denmark. andersbn@dadlnet.dk
Telephone: +45-78462800 Fax: +45-78462860
Received: Febuary 13, 2012 Revised: August 4, 2012
Accepted: December 23, 2012
Published online: January 27, 2013

Abstract

AIM: To evaluate long-term complications and survival in patients with Budd-Chiari syndrome (BCS) referred to a Danish transjugular intrahepatic portosystemic shunt (TIPS) centre.

METHODS: Twenty-one consecutive patients from 1997-2008 were retrospectively included [15 women and 6 men, median age 40 years (range 17-66 years)]. Eighteen Danish patients came from the 1.8 million catchment population of Aarhus University Hospital and three patients were referred from Scandinavian hospitals. Management consisted of tests for underlying haematological, endocrinological, or hypercoagulative disorders parallel to initiation of specific treatment of BCS.

RESULTS: BCS was mainly caused by thrombophilic (33%) or myeloproliferative (19%) disorders. Forty-three percents had symptoms for less than one week with ascites as the most prevalent finding. Fourteen (67%) were treated with TIPS and 7 (33%) were manageable with treatment of the underlying condition and diuretics. The median follow-up time for the TIPS-treated patients was 50 mo (range 15-117 mo), and none required subsequent liver transplantation. Ascites control was achieved in all TIPS patients with a marked reduction in the dose of diuretics. A total of 14 TIPS revisions were needed, mostly of uncovered stents. Two died during follow-up: One non-TIPS patient worsened after 6 mo and died in relation to transplantation, and one TIPS patient died 4 years after the TIPS-procedure, unrelated to BCS.

CONCLUSION: In our BCS cohort TIPS-treated patients have near-complete survival, reduced need for diuretics and compared to historical data a reduced need for liver transplantation.

Key words: Ascites; Budd-Chiari syndrome; Myeloproliferative disorder; Thrombophilia; Thrombosis; Transjugular intrahepatic portosystemic shunt

Neumann AB, Andersen SD, Nielsen DT, Holland-Fischer P, Vilstrup H, Grønbæk H. Treatment of Budd-Chiari syndrome with a focus on transjugular intrahepatic portosystemic shunt. *World J Hepatol* 2013; 5(1): 38-42 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i1/38.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i1.38

INTRODUCTION

Budd-Chiari syndrome (BCS) is caused by an obstruction

of the hepatic venous outflow and presents with a variety of clinical patterns from sub-clinical disease to acute liver failure[1]. The obstruction can occur anywhere from the small hepatic veins to the right atrium of the heart. In western countries, it is most often caused by thrombosis, whereas in Asia and Africa, a membranous obstruction accounts for the majority of cases[1,2]. Register-based studies from Nordic countries report incidences of 0.5-0.8 per million per year[3,4].

The hepatic outflow obstruction results in portal hypertension and sinusoidal congestion with ischaemic hepatocyte dysfunction. This causes the dominant clinical features of abdominal pain, hepato- and splenomegaly, ascites, and oesophageal varices and the development of fulminant hepatic failure. In half of BCS patients, symptom duration is less than one month[5,6].

Due to the rarity of BCS, there are no randomised clinical treatment trials. The usual treatment is a stepwise strategy with anti-coagulants, correction of risk factors, use of diuretics and drugs aiming at the reduction of portal pressure, angioplasty for short-length venous stenoses, transjugular intrahepatic portosystemic shunt (TIPS), and ultimately liver transplantation[7,8]. Rapid TIPS treatment with decompression of the portal hypertension and sinusoidal congestion is reported to dramatically change the overall transplant-free survival of BCS patients[9-13].

The aim of the present study was to present a single-centre long-term clinical experience and outcome of BCS after the establishment of TIPS treatment.

MATERIALS AND METHODS

Twenty-one patients with BCS (ICD-10: I82.0) were referred to our department from January 1997 to December 2008. Two patients came from Norway, one from Latvia, and the 18 Danish patients came from the 1.8 million catchment population of Aarhus University Hospital. All data were retrospectively collected from hospital records and laboratory databases.

The immediate clinical management consisted of anticoagulation, diuretics and treatment of any underlying haematological or endocrinological disease. The patients were tested for haematological and hypercoagulative disorders including the JAK2 tyrosine kinase mutation in the most recent cases.

As of January 1997, we implemented TIPS treatment and offered it to the patients who could not be managed by medical treatment. In the early years, bare stents were inserted [Smartstent (n = 5) (Cordis Corporation - Johnson and Johnson Medical N.V./S.A., Waterloo, Belgium), Luminexx (n = 1), or Memothermstent (n = 1) (Bard Denmark AB, Helsingor, Denmark)] and since 2002 the majority of the stents were covered [polytetrafluoroethylene (PTFE)-covered Viatorr stents (n = 8) (W. L. Gore and Associates GmbH, Putzbrunn, Germany)].

Statistical analysis

Descriptive statistics are presented as median and range. The Kaplan-Meier algorithm was used to describe survival. $P < 0.05$ was considered statistically significant.

Table 1 Aetiology and clinical presentation of Budd-Chiari syndrome patients at baseline

	All patients	Subgroups	
		Medical therapy only	TIPS
	(n = 21)	(n = 7)	(n = 14)
Male/female	6/15	3/4	3/11
Age (yr) at first contact, median (range)	40 (17-66)	41 (17-64)	38 (20-66)
Aetiology, n (%)			
Thrombophilia[1]	7 (33)	2	5
Protein C deficiency	1 (5)	0	1
Protein S deficiency	1 (5)	1	0
Factor V leiden mutation	1 (5)	1	0
Hyperhomocysteinemia	2 (10)	0	2
Paroxysmal nocturnal haemoglobinuria	2 (10)	0	2
Myeloproliferative disorder	4 (19)	2	2
Polycythemia vera	4 (19)	2	2
Other	4 (19)	4	0
Diabetic ketoacidosis	3 (14)	3	0
Angio leiomyosarcoma in caval vena	1 (5)	1	0
Unknown[2]	7 (33)	0	7
More than one predisposing risk factors	1 (5)[3]	1[3]	0
Clinical presentation, n (%)			
Ascites	15 (71)	3	12
Abdominal pain	14 (67)	6	8
Hepatomegaly	11 (52)	4	7
Jaundice	1 (5)	0	1
Hepatic encephalopathy	1 (5)	0	1
Variceal bleeding	0	0	0

[1]13 patients were screened for thrombophilic disorders; [2]6 of 7 with unknown risk factors were screened for thrombophilic disorders with negative result; [3]This patient suffered from polycythemia vera and had a Factor V Leiden mutation. TIPS: Transjugular intrahepatic portosystemic shunt.

RESULTS

The diagnosis of BCS was based on imaging techniques supported by clinical, biochemical, and pathological findings. Ultrasound (US) was the primary imaging technique (n = 18), followed by computer tomography (CT) (n = 11) and magnetic resonance imaging (MRI) (n = 1). One patient had secondary BCS with an angioleiomyosarcoma in the inferior caval vein. Half (54%) of the patients tested had an identifiable hypercoagulable condition.

The dominant clinical presentation was ascites, abdominal pain, and hepatomegaly (Table 1). Seventeen patients (81%) had symptom duration of less than 1 mo, and 9 patients (43%) had symptoms that lasted less than 1 wk.

Fourteen patients (67%) were treated with TIPS and six patients (29%) were controlled with pharmacological therapy. Two patients died during follow-up: One patient was responding well to medical treatment for 6 mo but suddenly developed acute liver failure and died from liver transplantation related complications. The other patient died (71 years old) 4 years after TIPS, from causes unrelated to BCS (multi infarct dementia and lung embolus).

Table 2 Diuretics treatment before and after transjugular intrahepatic portosystemic shunt treatment

	Before TIPS	After TIPS
Any diuretics treatment (*n*/*n*)	13/14	10/14
Furosemide dose [*n*/*n*,	12/14	3/14
median (range), mg/d]	80 (40-240)	200 (40-240)
Spironolactone dose [*n*/*n*,	12/14	9/14
median (range), mg/d]	175 (25-200)	100 (25-200)

TIPS: Transjugular intrahepatic portosystemic shunt.

Twelve of the 14 TIPS patients received anticoagulation therapy, primarily warfarin. The remaining 2 TIPS patients with hyperhomocysteinemia were treated with folic acid supplements and aspirin. In the non-TIPS group, 4 patients with constitutional risk factors were treated with warfarin or aspirin, and the other 3 patients were given anticoagulants for a shorter period (months) or not at all.

TIPS procedure

The 14 patients treated with TIPS experienced no procedure-related complication, and their portocaval pressure gradient was lowered to less than 10 mmHg in all cases (Figure 1). The need for diuretics was substantially reduced or eliminated ($n = 4$) post-TIPS (Table 2).

The TIPS patients were followed up every 6-12 mo with blood tests and ultrasound-Doppler examination to secure TIPS patency. The median follow-up time was 50 mo (range 15-117 mo). The blood tests improved after TIPS and then remained stable (Table 3). The patients' estimated 5-year survival was 88%.

A total of 14 TIPS revisions were needed, 4 of covered stents and 10 of uncovered stents. The revisions were done median 15 mo post-TIPS (range 6-75 mo) and the majority (79%) within the first 24 mo. The patients with covered stents had 0.54 revisions per patient and those with uncovered stents 1.67 per patient. At 24 mo, the stent patency was 63% in the covered stents group *vs* 33% in the bare stents group ($P = 0.47$) (Figure 2).

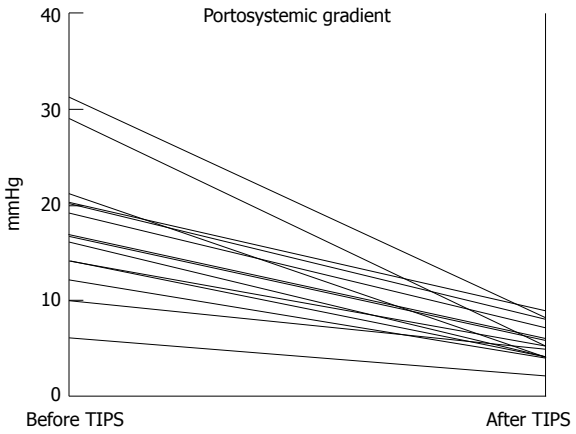

Figure 1 Reductions in portosystemic pressure gradient by transjugular intrahepatic portosystemic shunt insertion (14 patients). TIPS: Transjugular intrahepatic portosystemic shunt.

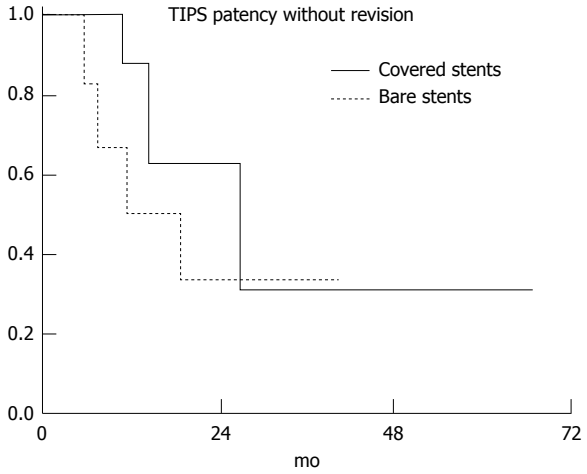

Figure 2 Transjugular intrahepatic portosystemic shunt patency without interventional revision (Kaplan-Meier method). In the bare stents group 3 patients needed 3 revisions each. More than one revision does not affect the calculation of this graph, thus the total need of revisions in the bare stents group is considerably underestimated in this graphic representation ($P = 0.47$). TIPS: Transjugular intrahepatic portosystemic shunt.

DISCUSSION

We have reported results from a cohort of 21 BCS patients of which 14 were treated with TIPS and had a 5-year survival rate of 88%. No TIPS patient required liver transplantation. Seven patients were controlled with medical therapy alone and one of them developed liver failure and died in relation to transplantation. Eight TIPS-treated patients required 14 TIPS revisions, mainly during the first 2 years post-TIPS and primarily in bare stents. Our treatment results are comparable with those reported from other centres[10,13,14].

We estimated an incidence of primary BCS of approximately 0.8 million/year in our region, similar to results noted in register-based Nordic studies[3,4].

During the median 4 years' follow-up of the cohort of 14 TIPS patients, one patient died of causes unrelated to BCS or TIPS treatment. This survival rate is comparable to other studies with 1-year survival rates within the range of 71%-93%[9,13-15]. Two studies reported 4- and 5-year survival rates of 93% and 74%, respectively[10,14], similar to our estimated 5-year survival rate of 88%. These high survival rates notably contrasts the poor historical untreated survival rate of only four years, 40 years ago[16].

Stent patency is an important aspect of TIPS treatment, not at least in the BCS patients. We found that the introduction of the PTFE covered stents doubled the 2-year TIPS patency rate, from 33% to 63%. Another study reported an even larger increase, from 12% to 56%[17]. With the covered stents, the long-term TIPS patency in BCS seems to be the same as in cirrhosis patients[18]. Previous TIPS treatment does not influence patient or graft survival in BCS patients undergoing liver transplantation due to acute liver failure[19]. The introduction of TIPS has markedly reduced the need for donor livers for BCS patients, thus saving these grafts for other patients[11,20].

Table 3 Biochemical changes before transjugular intrahepatic portosystemic shunt and during follow up

	Reference interval	Before TIPS	6 mo	12 mo	24 mo	36 mo
n		14	11	11	11	10
Alanine aminotransaminase (U/L)	(10-70) (M)/(10-45) (F)	73 (15-533)	41 (23-66)	34 (22-62)	42 (19-58)	35 (11-77)
Bilirubin (μmol/L)	5-25	35 (10-86)	28 (10-50)	27 (4-94)	25 (12-152)	21 (14-85)
Alkaline phosphatase (U/L)	35-105	180 (22-1105)	182 (86-391)	186 (94-461)	154 (88-358)	154 (89-349)
Albumin (μmol/L)	542-722	466 (331-711)	595 (439-707)	601 (554-714)	605 (532-684)	622 (497-727)
Creatinine (μmol/L)	(60-105) (M)/(45-90) (F)	76 (19-119)	71 (51-106)	69 (49-98)	71 (47-98)	59 (45-86)

Results are given as median (range). M: Male reference values, F: Female reference values; TIPS: Transjugular intrahepatic portosystemic shunt.

Symptom duration in BCS is often short[21], and the condition may rapidly deteriorate[22]. Therefore, and because of the complexity of correct BCS diagnosis and treatment, we suggest that patients with newly developed tense ascites in a previous liver healthy subject should immediately be referred to a liver transplant centre with TIPS experience.

Non-invasive imaging techniques (US, CT or MRI), and especially US, are excellent tools in most cases for the diagnosis of BCS[23-25]. The diagnostic finding is absence of flow in the hepatic veins and enlargement of the caudate lobe. US and/or CT were the primary diagnostic imaging method used for the majority of patients in the present study. A liver biopsy is not necessary for diagnosis in classic cases but will exhibit centrilobular fibrosis or necrosis, congestion, distended sinusoids, and in long standing cases bridging fibrosis or cirrhosis[7,23]. Invasive procedures with hepatic venography may visualise the extent of hepatic vein obstruction[25,26].

The most common aetiologies to BCS are haematologic or thrombophilic disorders that result in a thrombogenic state. Only 7 of 21 patients (33%) did not present such identified aetiologic features and one patient had more than one aetiology. This supports current recommendations for a full and systematic haematologic and thrombophilic work-up in all patients, even if one primary risk factor is identified[6]. Our proportion of BCS without identified aetiology may partly be due to the limited diagnostic tools available in the beginning of the study period (e.g., no detection of the JAK2 mutation). A complete testing repertoire has reduced the proportion of BCS without aetiology from 30% to 5%-15% and there is often identified more than one risk factor[27,28]. In a large series of 160 patients, at least one thrombophilic disorder was identified in 84%, and 46% presented with 2 or more disorders. Overt myeloproliferative disease or the JAK2 mutation, a marker for latent myeloproliferative disease, was present in 39% of patients. Oral contraceptives and systemic diseases may also be involved[6].

Because of this frequent occurrence of such thrombogenic risk factors, anti-coagulative treatment is currently recommended for all patients in absence of major contraindications[7]. However, there is still little direct evidence to support the efficacy of the treatment. One historical study showed an increase in 5-year-survival rate from 50% to 75% from 1970 to 1985 and attributed the increase to the introduction of oral anticoagulation therapy[29]. In our study, all the 17 patients with constitutional risk factors received permanent anticoagulation therapy.

In conclusion, the rare and life-threatening disease BCS can in most cases be treated with rapid establishment of a TIPS, leading to a very satisfactory survival probability and much reduced need for liver transplantation. Therefore, patients suspected of BCS, including patients with acute tense unexplained ascites, should be referred without delay to a liver centre with a TIPS programme.

COMMENTS

Background

Budd-Chiari syndrome (BCS) typically affects younger to middle aged persons (median age 40 years). BCS is present when the blood drainage from the liver is obstructed, most often caused by thrombosis. The disease is rare (approximately 1 per million per year) but historically has had a grave prognosis with an expected median survival of 1 year after the diagnosis. Over the last decades survival has improved drastically as new medical and interventional treatment options have been introduced.

Research frontiers

Transjugular intrahepatic portosystemic shunt (TIPS) was introduced to treat patients with cirrhosis and portal hypertension. Several studies have reported promising results with the use of TIPS in BCS patients as alternative to shunt surgery or liver transplantation when the disease is not controlled by medical treatment alone.

Innovations and breakthroughs

TIPS has been used since 1990s and reports of long-term results show promising results. In the early days bare metal stents were used but often complicated by stent thrombosis with need for intervention. The introduction of covered stents has improved long-term stent patency and reduced the need for interventions.

Applications

The study support the growing evidence that TIPS in BCS show stable long-term results as qualified by liver function test and ultrasonography. BCS patients must be evaluated by a multidisciplinary team with expertise in vascular liver disorders, including transplant surgeons. No randomized controlled trials exist so data are based on descriptive cohort studies and expert recommendations.

Peer review

It is an important report on the TIPS experience in BCS and is well-written.

REFERENCES

1 **Janssen HL**, Garcia-Pagan JC, Elias E, Mentha G, Hadengue A, Valla DC. Budd-Chiari syndrome: a review by an expert panel. *J Hepatol* 2003; **38**: 364-371 [PMID: 12586305 DOI: 10.1016/S0168-8278(02)00434-8]

2 **Okuda K**, Kage M, Shrestha SM. Proposal of a new nomenclature for Budd-Chiari syndrome: hepatic vein thrombosis versus thrombosis of the inferior vena cava at its hepatic portion. *Hepatology* 1998; **28**: 1191-1198 [PMID: 9794901]

3 **Almdal TP**, Sørensen TI. Incidence of parenchymal liver diseases in Denmark, 1981 to 1985: analysis of hospitalization registry data. The Danish Association for the Study of the Liver. *Hepatology* 1991; **13**: 650-655 [PMID: 2010159 DOI:

10.1002/hep.1840130407]
4 **Rajani R**, Melin T, Björnsson E, Broomé U, Sangfelt P, Danielsson A, Gustavsson A, Grip O, Svensson H, Lööf L, Wallerstedt S, Almer SH. Budd-Chiari syndrome in Sweden: epidemiology, clinical characteristics and survival - an 18-year experience. *Liver Int* 2009; **29**: 253-259 [PMID: 18694401 DOI: 10.1111/j.1478-3231.2008.01838.x]
5 **Valla DC**. Primary Budd-Chiari syndrome. *J Hepatol* 2009; **50**: 195-203 [PMID: 19012988 DOI: 10.1016/j.jhep.2008.10.007]
6 **Darwish Murad S**, Plessier A, Hernandez-Guerra M, Fabris F, Eapen CE, Bahr MJ, Trebicka J, Morard I, Lasser L, Heller J, Hadengue A, Langlet P, Miranda H, Primignani M, Elias E, Leebeek FW, Rosendaal FR, Garcia-Pagan JC, Valla DC, Janssen HL. Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med* 2009; **151**: 167-175 [PMID: 19652186]
7 **de Franchis R**. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; **53**: 762-768 [PMID: 20638742 DOI: 10.1016/j.jhep.2010.06.004]
8 **de Franchis R**. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005; **43**: 167-176 [PMID: 15925423 DOI: 10.1016/j.jhep.2005.07.001]
9 **Garcia-Pagán JC**, Heydtmann M, Raffa S, Plessier A, Murad S, Fabris F, Vizzini G, Gonzales Abraldes J, Olliff S, Nicolini A, Luca A, Primignani M, Janssen HL, Valla D, Elias E, Bosch J. TIPS for Budd-Chiari syndrome: long-term results and prognostics factors in 124 patients. *Gastroenterology* 2008; **135**: 808-815 [PMID: 18621047 DOI: 10.1053/j.gastro.2008.05.051]
10 **Zahn A**, Gotthardt D, Weiss KH, Richter G, Schmidt J, Stremmel W, Sauer P. Budd-Chiari syndrome: long term success via hepatic decompression using transjugular intrahepatic porto-systemic shunt. *BMC Gastroenterol* 2010; **10**: 25 [PMID: 20193077 DOI: 10.1186/1471-230X-10-25]
11 **Plessier A**, Sibert A, Consigny Y, Hakime A, Zappa M, Denninger MH, Condat B, Farges O, Chagneau C, de Ledinghen V, Francoz C, Sauvanet A, Vilgrain V, Belghiti J, Durand F, Valla D. Aiming at minimal invasiveness as a therapeutic strategy for Budd-Chiari syndrome. *Hepatology* 2006; **44**: 1308-1316 [PMID: 17058215 DOI: 10.1002/hep.21354]
12 **Valla DC**. Budd-Chiari syndrome and veno-occlusive disease/sinusoidal obstruction syndrome. *Gut* 2008; **57**: 1469-1478 [PMID: 18583397 DOI: 10.1136/gut.2007.133637]
13 **Mancuso A**, Fung K, Mela M, Tibballs J, Watkinson A, Burroughs AK, Patch D. TIPS for acute and chronic Budd-Chiari syndrome: a single-centre experience. *J Hepatol* 2003; **38**: 751-754 [PMID: 12763367 DOI: 10.1016/S0168-8278(03)00118-1]
14 **Rössle M**, Olschewski M, Siegerstetter V, Berger E, Kurz K, Grandt D. The Budd-Chiari syndrome: outcome after treatment with the transjugular intrahepatic portosystemic shunt. *Surgery* 2004; **135**: 394-403 [PMID: 15041963 DOI: 10.1016/j.surg.2003.09.005]
15 **Corso R**, Intotero M, Solcia M, Castoldi MC, Rampoldi A. Treatment of Budd-Chiari syndrome with transjugular intrahepatic portosystemic shunt (TIPS). *Radiol Med* 2008; **113**: 727-738 [PMID: 18618075 DOI: 10.1007/s11547-008-0288-z]
16 **Tavill AS**, Wood EJ, Kreel L, Jones EA, Gregory M, Sherlock S. The Budd-Chiari syndrome: correlation between hepatic scintigraphy and the clinical, radiological, and pathological findings in nineteen cases of hepatic venous outflow obstruction. *Gastroenterology* 1975; **68**: 509-518 [PMID: 1112452]
17 **Darwish Murad S**, Luong TK, Pattynama PM, Hansen BE, van Buuren HR, Janssen HL. Long-term outcome of a covered vs. uncovered transjugular intrahepatic portosystemic shunt in Budd-Chiari syndrome. *Liver Int* 2008; **28**: 249-256 [PMID: 18251982 DOI: 10.1111/j.1478-3231.2007.01649.x]
18 **Bureau C**, Pagan JC, Layrargues GP, Metivier S, Bellot P, Perreault P, Otal P, Abraldes JG, Peron JM, Rousseau H, Bosch J, Vinel JP. Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study. *Liver Int* 2007; **27**: 742-747 [PMID: 17617116 DOI: 10.1111/j.1478-3231.2007.01522.x]
19 **Segev DL**, Nguyen GC, Locke JE, Simpkins CE, Montgomery RA, Maley WR, Thuluvath PJ. Twenty years of liver transplantation for Budd-Chiari syndrome: a national registry analysis. *Liver Transpl* 2007; **13**: 1285-1294 [PMID: 17763380 DOI: 10.1002/lt.21220]
20 **Olliff SP**. Transjugular intrahepatic portosystemic shunt in the management of Budd Chiari syndrome. *Eur J Gastroenterol Hepatol* 2006; **18**: 1151-1154 [PMID: 17033433 DOI: 10.1097/01.meg.0000236874.75601.a1]
21 **Dilawari JB**, Bambery P, Chawla Y, Kaur U, Bhusnurmath SR, Malhotra HS, Sood GK, Mitra SK, Khanna SK, Walia BS. Hepatic outflow obstruction (Budd-Chiari syndrome). Experience with 177 patients and a review of the literature. *Medicine* (Baltimore) 1994; **73**: 21-36 [PMID: 8309360 DOI: 10.1097/00005792-199401000-00003]
22 **Verma A**, Sharma G, Mohan S, Saraswat VA, Baijal SS. TIPS can be lifesaving in acute liver failure associated with portal vein and inferior vena cava thrombosis in a case of Budd Chiari syndrome due to protein S deficiency. *Cardiovasc Intervent Radiol* 2008; **31** Suppl 2: S197-S199 [PMID: 18046604 DOI: 10.1007/s00270-007-9198-z]
23 **Miller WJ**, Federle MP, Straub WH, Davis PL. Budd-Chiari syndrome: imaging with pathologic correlation. *Abdom Imaging* 1993; **18**: 329-335 [PMID: 8220030 DOI: 10.1007/BF00201775]
24 **Millener P**, Grant EG, Rose S, Duerinckx A, Schiller VL, Tessler FN, Perrella RR, Ragavendra N. Color Doppler imaging findings in patients with Budd-Chiari syndrome: correlation with venographic findings. *AJR Am J Roentgenol* 1993; **161**: 307-312 [PMID: 8333368]
25 **Cura M**, Haskal Z, Lopera J. Diagnostic and interventional radiology for Budd-Chiari syndrome. *Radiographics* 2009; **29**: 669-681 [PMID: 19448109 DOI: 10.1148/rg.293085056]
26 **Holland-Fischer P**, Grønbaek H, Astrup L, Keiding S, Nielsen DT, Vilstrup H. Budd-Chiari and inferior caval vein syndromes due to membranous obstruction of the liver veins: successful treatment with angioplasty and transcaval transjugular intrahepatic porto-systemic shunt. *Scand J Gastroenterol* 2004; **39**: 1025-1028 [PMID: 15513347 DOI: 10.1080/00365520410007935]
27 **Hadengue A**, Poliquin M, Vilgrain V, Belghiti J, Degott C, Erlinger S, Benhamou JP. The changing scene of hepatic vein thrombosis: recognition of asymptomatic cases. *Gastroenterology* 1994; **106**: 1042-1047 [PMID: 8143970]
28 **Denninger MH**, Chaït Y, Casadevall N, Hillaire S, Guillin MC, Bezeaud A, Erlinger S, Briere J, Valla D. Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. *Hepatology* 2000; **31**: 587-591 [PMID: 10706547 DOI: 10.1002/hep.510310307]
29 **Zeitoun G**, Escolano S, Hadengue A, Azar N, El Younsi M, Mallet A, Boudet MJ, Hay JM, Erlinger S, Benhamou JP, Belghiti J, Valla D. Outcome of Budd-Chiari syndrome: a multivariate analysis of factors related to survival including surgical portosystemic shunting. *Hepatology* 1999; **30**: 84-89 [PMID: 10385643 DOI: 10.1002/hep.510300125]

P- Reviewers Genescà J, Kietzmann T **S- Editor** Cheng JX
L- Editor A **E- Editor** Li JY

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i1.43

World J Hepatol 2013 January 27; 5(1): 43-45
ISSN 1948-5182 (online)

CASE REPORT

Hepatitis B reactivation related to everolimus

Sema Sezgin Göksu, Şerife Bilal, Hasan Şenol Coşkun

Sema Sezgin Göksu, Şerife Bilal, Hasan Şenol Coşkun, Faculty of Medicine, Department of Medical Oncology, Akdeniz Univercity, 07058 Antalya, Turkey

Author contributions: Sezgin Göksu S reviewed the literature and wrote, submitted and revised the article; Bilal S collected the data of the patient; and Coşkun HS edited the article.

Correspondence to: Sema Sezgin Göksu, MD, Faculty of Medicine, Department of Medical Oncology, Akdeniz Univercity, 07058 Antalya, Turkey. drsemagoksu@yahoo.com.tr

Telephone: +90-24-22496729 Fax: +90-24-22272412

Received: July 31, 2012 Revised: September 25, 2012
Accepted: November 17, 2012
Published online: January 27, 2013

Abstract

Reactivation of hepatitis B virus (HBV) during chemotherapy is a well known complication in patients with chronic hepatitis B and cancer. The clinical manifestations range from subclinical elevation of liver enzymes to severe, potentially fatal fulminant hepatitis. Reactivation can occur in a patient with previous inactive HBV infection; either an inactive carrier or a patient with resolved hepatitis. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor approved in renal cell carcinoma, neuroendocrine tumours and breast cancer. mTOR inhibitors are a new generation of drugs for targeted treatment; therefore, little about their side effects is known. Here, we report a patient with renal cell carcinoma who experienced a flare of hepatitis B infection during treatment with everolimus. Clinicians should be aware of HBV reactivation in patients who are undergoing treatment with everolimus, and screening for hepatitis B infection and prophylactic antiviral treatment should be considered.

Key words: Hepatitis B; Virus reactivation; Everolimus; Mammalian target of rapamycin inhibitors; Immunosuppressive treatment; Renal cell carcinoma

Sezgin Göksu S, Bilal S, Coşkun HS. Hepatitis B reactivation related to everolimus. *World J Hepatol* 2013; 5(1): 43-45 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i1/43.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i1.43

INTRODUCTION

Reactivation of hepatitis B virus (HBV) during chemotherapy is a well known complication in patients with chronic hepatitis B and cancer. The clinical manifestations range from subclinical elevation of liver enzymes to severe, potentially fatal fulminant hepatitis[1]. Mammalian target of rapamycin (mTOR) inhibitors are a new generation of drugs for targeted treatment; however, little of their side-effects is known. As a result of their immunosuppressive properties, the mTOR inhibitors are associated with treatment-related infections. In Europe, the product information for everolimus warns patients about the risk of HBV reactivation, because this occurred in some patients taking everolimus[2]. Here, we report a case of renal cell carcinoma (RCC) in a patient who experienced a flare of hepatitis B during treatment with everolimus.

CASE REPORT

A 49-year-old man who had undergone partial nephrectomy in 2008 was diagnosed with RCC. He had been diagnosed as an inactive carrier of HBV more than 5 years previously. RCC progressed to lung and axillary lymph node metastasis in December, 2010. He was treated with bevacizumab 10 mg/kg every 2 wk, and interferon α 9 MU three times per week. He had partial remission in March, 2011 and continued treatment. He developed hypertension and did not want to continue bevacizumab and interferon in May, 2011. Computed tomography showed progression of lung metastasis in June 2011, and he started treatment with sunitinib 50 mg/d for 4 wk and 2 wk off. He had further progression in January, 2012 and was treated with everolimus, 10 mg/d. He had no further clinical and radiological progression. His liver enzymes

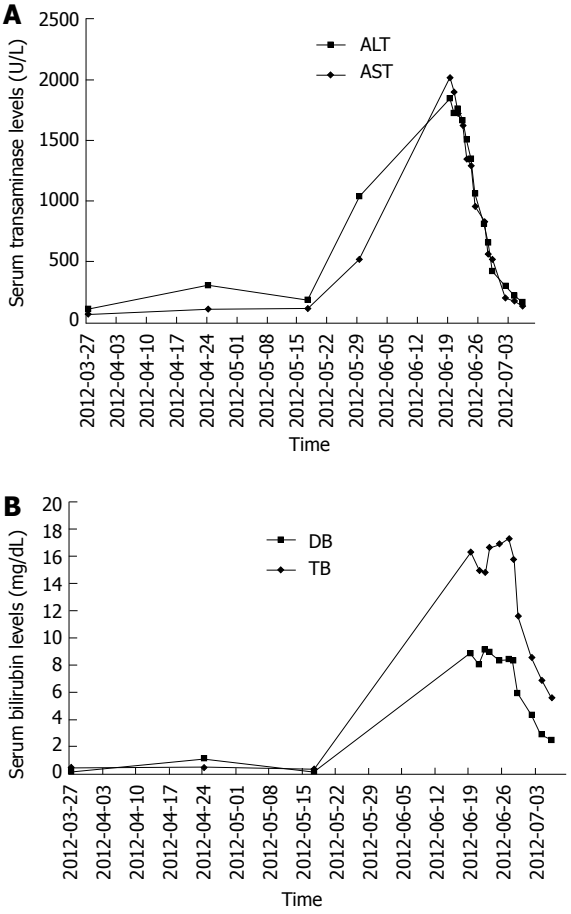

Figure 1 Serum transaminase (A) and bilirubin (B) levels of the hepatitis B virus reactivation patient. Everolimus treatment was initiated in January, 2012. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DB: Direct bilirubin; TB: Total bilirubin.

were elevated in March, 2012 [aspartate aminotransferase (AST) 76 U/L, alanine aminotransferase (ALT) 115 U/L]. He continued everolimus treatment. One month later, liver enzyme levels continued to increase [AST 111 U/L, ALT 306 U/L, total bilirubin (TB)/direct bilirubin 0.39/0.1 mg/dL] and he was offered to continue everolimus with a dose reduction to 5 mg/d. At the end of May 2012, liver enzymes had increased to nearly 25-fold of the upper limits (AST 522 U/L, ALT 1038 U/L). Serological tests showed that the patient was positive for hepatitis B surface antigen. He was not using any other drugs that could have caused hepatitis reactivation. Treatment with everolimus was stopped immediately and he was referred to a gastroenterologist. He started treatment with an oral nucleoside analogue, tenofovir. Ten days later, he was submitted to another hospital with nausea, asthenia, and jaundice. Laboratory findings showed elevated AST (2014 U/L), ALT (1841 U/L), and TB (16.3 mg/dL). Prothrombin time was 14.8 s. HBV DNA level had markedly increased to 1.26×10^9 copies/mL. Hepatitis D virus DNA was negative. He continued treatment with tenofovir. Ultrasound imaging of the liver showed no metastatic disease. The liver enzyme levels decreased after 20 d and he was discharged from hospital.

DISCUSSION

Reactivation of hepatitis B is defined as the recurrence or an abrupt rise in HBV replication by at least an increase in serum HBV DNA levels of 1 $\log_{10}$, often with an increase in serum transaminase levels (at least threefold greater than the baseline, Figure 1). Reactivation can occur in a patient with a previous inactive HBV infection; either an inactive carrier or a patient with resolved hepatitis[3]. A recent annual nationwide survey confirmed that HBV reactivation related to immunosuppressive therapy is increasing in patients with malignant lymphoma, other haematological malignancies, solid tumours or rheumatological disease[1].

Everolimus is one of the newer targeted therapies approved for the management of RCC. Our clinical experience with this agent is limited. Data from clinical trials show that everolimus is associated with treatment-related infections. The European product information for everolimus states that some patients experience hepatitis B reactivation during treatment[2]. To our knowledge, no such case has been reported in the literature. Elevations of liver enzymes have also been reported during everolimus treatment, but grade 3/4 elevations of transaminase and bilirubin occurred in < 1% of patients[4]. Viral hepatitis should be considered in the differential diagnosis of patients with elevated liver enzymes, even if there is no history of viral infection.

Since everolimus and sirolimus (another mTOR inhibitor) are also used as immunosuppressive agents after liver transplantation[5,6], possible reactivation of hepatitis B in patients with chronic hepatitis should be monitored.

Hepatitis B reactivation by chemotherapy is a well-known phenomenon. Use of corticosteroids and certain chemotherapeutic agents, including anthracylines, cyclophosphamide and vinca alkaloids, is associated with HBV reactivation[7]. A similar phenomenon has been reported for temazolamide[8] and gemcitabine[9]. Molecular-targeted agents can also cause HBV reactivation. Rituximab-related HBV reactivation in patients with non-Hodgkin's lymphoma is well-established[10]. HBV reactivation during treatment with imatinib[11] and alemtuzumab[12] has also been reported.

Previous studies have shown that the risk of HBV reactivation can be greatly reduced by the use of prophylactic nucleoside analogues in susceptible patients[13]. Lamivudine has proven efficacy and safety in preventing HBV reactivation related to chemotherapy. However, a major problem with prolonged usage of lamivudine is the possibility of viral breakthrough following the emergence of treatment-resistant HBV variants[14]. New generation oral nucleoside analogues, such as entecavir or tenofovir, exhibit high potency and low rates of resistance. These drugs are thought to be effective for treatment of HBV reactivation[1].

Here, we report a patient with reactivation of hepatitis B related to treatment with everolimus. Clinicians should be aware of HBV reactivation in patients who are undergoing everolimus treatment, and screening for

hepatitis B and prophylactic antiviral treatment should be considered.

REFERENCES

1 **Oketani M**, Ido A, Uto H, Tsubouchi H. Prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy. *Hepatol Res* 2012; **42**: 627-636 [PMID: 22686858 DOI: 10.1111/j.1872-034X.2012.00998.x]

2 EU SmPC Afinitor. Available from: URL: http: //www.Ema.europa.eu/humandocs/Humans/EPAR/afinitor/afinitor.htm. Accessed November 8, 2010

3 **Manzano-Alonso ML**, Castellano-Tortajada G. Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy. *World J Gastroenterol* 2011; **17**: 1531-1537 [PMID: 21472116 DOI: 10.3748/wjg.v17.i12.1531]

4 **Motzer RJ**, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Kay A, Ravaud A. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer* 2010; **116**: 4256-4265 [PMID: 20549832 DOI: 10.1002/cncr.25219]

5 **Casanovas T**, Argudo A, Peña-Cala MC. Everolimus in clinical practice in long-term liver transplantation: an observational study. *Transplant Proc* 2011; **43**: 2216-2219 [PMID: 21839237 DOI: 10.1016/j.transproceed.2011.06.015]

6 **Kawahara T**, Asthana S, Kneteman NM. m-TOR inhibitors: what role in liver transplantation? *J Hepatol* 2011; **55**: 1441-1451 [PMID: 21781947 DOI: 10.1016/j.jhep.2011.06.015]

7 **Torres HA**, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat Rev Clin Oncol* 2012; **9**: 156-166 [PMID: 22271089 DOI: 10.1038/nrclinonc.2012.1]

8 **Ohno M**, Narita Y, Miyakita Y, Ueno H, Kayama T, Shibui S. Reactivation of hepatitis B virus after glioblastoma treatment with temozolomide--case report. *Neurol Med Chir* (Tokyo) 2011; **51**: 728-731 [PMID: 22027252 DOI: 10.2176/nmc.51.728]

9 **Cheong K**, Li J, Karapetis CS. Gemcitabine and reactivation of hepatitis B. *Med Oncol* 2003; **20**: 385-388 [PMID: 14716036 DOI: 10.1385/MO: 20: 4: 385]

10 **Evens AM**, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, Dai MS, Chiu BC, Fintel B, Cheng Y, Chuang SS, Lee MY, Chen TY, Lin SF, Kuo CY. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol* 2011; **22**: 1170-1180 [PMID: 21115603 DOI: 10.1093/annonc/mdq583]

11 **Kang BW**, Lee SJ, Moon JH, Kim SN, Chae YS, Kim JG, Hwang YJ, Sohn SK. Chronic myeloid leukemia patient manifesting fatal hepatitis B virus reactivation during treatment with imatinib rescued by liver transplantation: case report and literature review. *Int J Hematol* 2009; **90**: 383-387 [PMID: 19641858]

12 **Mastroianni CM**, Lichtner M, Citton R, Del Borgo C, Rago A, Martini H, Cimino G, Vullo V. Current trends in management of hepatitis B virus reactivation in the biologic therapy era. *World J Gastroenterol* 2011; **17**: 3881-3887 [PMID: 22025876]

13 **Yeo W**, Chan PK, Ho WM, Zee B, Lam KC, Lei KI, Chan AT, Mok TS, Lee JJ, Leung TW, Zhong S, Johnson PJ. Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 2004; **22**: 927-934 [PMID: 14990649 DOI: 10.1200/JCO.2004.05.161]

14 **Loomba R**, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148**: 519-528 [PMID: 18378948]

P- Reviewer Lu SN **S- Editor** Wen LL **L- Editor** A **E- Editor** Li JY

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
www.wjgnet.com

World J Hepatol 2013 January 27; 5(1): I-V
ISSN 1948-5182 (online)

GENERAL INFORMATION

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

WJH covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

WJH is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 42 OA clinical medical journals, including 41 in English, has a total of 15 471 editorial board members or peer reviewers, and is a world first-class publisher.

Columns

The columns in the issues of *WJH* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers; (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, *etc.*; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-quality clinical case conference; (11) Original Articles: To report innovative and original findings in hepatology; (12) Brief Articles: To briefly report the novel and innovative findings in hepatology; (13) Meta-Analysis: To evaluate the clinical effectiveness in hepatology by using data from two or more randomised control trials; (14) Case Report: To report a rare or typical case; (15) Letters to the Editor: To discuss and make reply to the contributions published in *WJH*, or to introduce and comment on a controversial issue of general interest; (16) Book Reviews: To introduce and comment on quality monographs of hepatology; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

Name of journal

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

Launch date

October 31, 2009

Frequency

Monthly

Editor-in-Chief

Masatoshi Kudo, MD, PhD, Professor, Department of Gas-

troenterology and Hepatology, Kinki University School of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama, 589-8511 Osaka, Japan

Editorial office
Jian-Xia Cheng, Director
Jin-Lei Wang, Vice Director
World Journal of Hepatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjh@wjgnet.com
http://www.wjgnet.com

Publisher
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Telephone: +852-58042046
Fax: +852-31158812
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

Production center
Beijing Baishideng BioMed Scientific Co., Limited
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893

Representative office
USA Office
8226 Regency Drive,
Pleasanton, CA 94588-3144, United States

Instructions to authors
Full instructions are available online at http://www.wjgnet.com/1948-5182/g_info_20100316080002.htm.

Indexed and Abstracted in
PubMed Central, PubMed, Digital Object Identifier, and Directory of Open Access Journals.

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing
Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJH* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the

case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5182/g_info_20100316080002.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjh@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision on acceptance is made only when at least two experts recommend publication of an article. All peer-reviewers are acknowledged on Express Submission and Peer-review System website.

Abstract

There are unstructured abstracts (no less than 200 words) and structured abstracts. The specific requirements for structured abstracts are as follows:

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of P values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-5182/g_info_20100107115140.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

All types of articles' writing style and requirement will be found in the link: http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15

RESUBMISSION OF THE REVISED MANUSCRIPTS

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade A certificate (for non-native speakers of English), should be submitted to the online system via the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/1948-5182/g_info_20100107114726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1948-5182/g_info_20100107114601.htm.

Proof of financial support

For papers supported by a foundation, authors should provide a copy of the approval document and serial number of the foundation.

Links to documents related to the manuscript

WJH will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Publication fee

WJH is an international, peer-reviewed, OA online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium and format, provided the original work is properly cited. The use is non-commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. All invited articles are published free of charge.

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Room 1701, 17/F, Henan Building,
No. 90 Jaffe Road, Wanchai, Hong Kong, China
Telephone: +852-58042046
Fax: +852-31158812
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com