

Cover Figure

Molecular structure of human synthetic hepcidin-25. This illustration is taken from the review article entitled "Hepcidin: from discovery to differential diagnosis" by Kemna et al., page 90

Editorials and Perspectives

1 Hemolysis-associated hypercoagulability in sickle cell disease: the plot (and blood) thickens!

Mark T. Gladwin and Gregory J. Kato

Thrombophilia and hemostatic activation common to most hemolytic conditions are likely explained by the very feature they all share, intravascular hemolysis. See related article on page 20.

4 Myelodysplastic/myeloproliferative disorders

Luca Malcovati and Mario Cazzola

Myelodysplastic/myeloproliferative disorders are defined as myeloid disorders that have both dysplastic and proliferative features at the time of initial presentation. Mutations of JAK2 and MPL have been reported with the prototype of these disorders, refractory anemia with ringed sideroblasts associated with marked thrombocytosis. See related article on page 34

6 How we diagnose and treat WHO-defined systemic mastocytosis in adults

Ayalew Tefferi, Srdan Verstovsek, and Animesh Pardanani

Current diagnosis and treatment of systemic mastocytosis are challenging for clinicians. This perspective summarizes the diagnostic approach and the treatment strategy adopted at the Mayo Clinic, Rochester, MN, and the M.D. Anderson Cancer Center, Houston, TX. See related article on page 49.

9 Tumor lysis syndrome: current perspective

Jessica Hochberg and Mitchell S. Cairo

Tumor lysis syndrome is characterized by a group of metabolic derangements caused by the rapid lysis of malignant cells. This condition can lead to acute renal failure and even death. The early recognition and treatment of metabolic abnormalities usually prevents the life threatening complications associated with tumor lysis syndrome. See related article on page 67.

14 Impact of cytogenetic and molecular prognostic markers on the clinical management of chronic lymphocytic leukemia

Alexander W. Hauswirth and Ulrich Jäger

Genetic markers have contributed important insights into the biology of chronic lymphocytic leukemia. The available evidence suggests that these markers will increasingly influence treatment decisions for tailored therapy. See related article on page 75.

Original Articles

Red Cell Disorders

20 Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension

Kenneth I. Ataga, Charity G. Moore, Cheryl A. Hillery, Susan Jones, Herbert C. Whinna, Dell Strayhorn, Cathy Sohler, Alan Hinderliter, Leslie V. Parise, and Eugene P. Orringer

Patients with sickle cell disease-associated pulmonary hypertension have increased endothelial dysfunction, coagulation activation and inflammation compared with patients without pulmonary hypertension. Endothelial dysfunction and coagulation activation appear to be the result of chronic hemolysis. See related perspective on page 1.

Bone Marrow Failure

27 Long-term response and outcome following immunosuppressive therapy in thymoma-associated pure red cell aplasia: a nationwide cohort study in Japan for the PRCA collaborative study group

Makoto Hirokawa, Ken-ichi Sawada, Naohito Fujishima, Shinji Nakao, Akio Urabe, Kazuo Dan, Shin Fujisawa, Yuji Yonemura, Fumio Kawano, Mitsuhiro Omine, and Kei-ya Ozawa, for the PRCA Collaborative Study Group

This nationwide survey in Japan indicates that thymoma-associated pure red cell aplasia responds in most instances to cyclosporine A, and that this treatment is also effective in preventing relapse of anemia.

34 JAK2^{V617F} mutation status identifies subtypes of refractory anemia with ringed sideroblasts associated with marked thrombocytosis

Annette H. Schmitt-Graeff, Soon-Siong Teo, Manfred Olschewski, Franz Schaub, Sabine Haxelmans, Andreas Kirn, Petra Reinecke, Ulrich Germing, and Radek C. Skoda

Refractory anemia with ringed sideroblasts and marked thrombocytosis is a condition with both myelodysplastic and myeloproliferative features. This study indicates that a considerable proportion of patients with this condition carry the unique V617F mutation of JAK2, and that the mutant allele burden increases over time. See related perspective on page 4.

Myeloproliferative Disorders

41 Influence of JAK2^{V617F} allele burden on phenotype in essential thrombocythemia

Elisabetta Antonioli, Paola Guglielmelli, Giada Poli, Costanza Bogani, Alessandro Pancrazzi, Giovanni Longo, Vanessa Ponziani, Lorenzo Tozzi, Lisa Pieri, Valeria Santini, Alberto Bosi, and Alessandro M. Vannucchi, for the Myeloproliferative Disorders Research Consortium (MPD-RC)

Variable proportions of mutant alleles are found in patients with JAK2 (V617F)-positive myeloproliferative disorders. This study shows that this variable mutant allele burden influences the clinical phenotype of JAK2 (V617F)-positive essential thrombocythemia.

- 49 Myeloproliferative Disorders**
Activity of imatinib in systemic mastocytosis with chronic basophilic leukemia and a PRKG2-PDGFRB fusion

Idoya Lahortiga, Cem Akin, Jan Cools, Todd M. Wilson, Nicole Mentens, Diane C. Arthur, Irina Maric, Pierre Noel, Can Kocabas, Peter Marynen, Lawrence S. Lessin, Iwona Wlodarska, Jamie Robyn, and Dean D. Metcalfe

Systemic mastocytosis with an associated hematologic non-mast cell lineage disease is a rare subtype of systemic mastocytosis. This study describes a patient with systemic mastocytosis associated with chronic basophilic leukemia and a PRKG2-PDGFRB fusion gene. This patient had a complete response to imatinib mesylate. See related perspective on page 6.

- 57 Acute Myeloid Leukemia**
The effect of the proteasome inhibitor on acute myeloid leukemia cells and drug resistance associated with the CD34⁺ immature phenotype

Enrique Colado, Stela Álvarez-Fernández, Patricia Maiso, Jesús Martín-Sánchez, María Belén Vidriales, Mercedes Garayoa, Enrique M. Ocio, Juan Carlos Montero, Atanasio Pandiella, Jesús F. San Miguel

This study shows that bortezomib induces apoptosis of acute myeloid leukemia cells in vitro. Ad hoc clinical trials might investigate the efficacy of this drug in patients with acute myeloid leukemia.

- 67 Acute Myeloid Leukemia**
Tumor lysis syndrome in patients with acute myeloid leukemia: identification of risk factors and development of a predictive model

Pau Montesinos, Ignacio Lorenzo, Guillermo Martín, Jaime Sanz, Mariluz Pérez-Sirvent, David Martínez, Guillermo Ortí, Lorenzo Algarra, Jesus Martínez, Federico Moscardó, Javier de la Rubia, Isidro Jarque, Guillermo Sanz, and Miguel A. Sanz

Tumor lysis syndrome may represent a life-threatening complication during induction chemotherapy of acute myeloid leukemia. This study shows that pretreatment elevated serum lactate dehydrogenase, increased serum creatinine, high uric acid, and markedly elevated white blood cell counts represent independent risk factors for this complication. See related perspective on page 9.

- 75 Chronic Lymphocytic Leukemia**
Induction of histone H1.2 cytosolic release in chronic lymphocytic leukemia cells after genotoxic and non-genotoxic treatment

Eva Giné, Marta Crespo, Ana Muntaniola, Eva Calpe, Maria Joao Gomes, Neus Villamor, Emili Montserrat, and Francesc Bosch

Nuclear histone H1.2 plays an important role in transmitting apoptotic signals from the nucleus to the mitochondria following DNA double-strand breaks. This study shows that histone H1.2 is released to the cytoplasm of primary neoplastic cells from patients with chronic lymphocytic leukemia following different treatment modalities. See related perspective on page 14.

- 83 Hemostasis**
Factor VIII bypasses CD91/LRP for endocytosis by dendritic cells leading to T-cell activation

Suryasarathi Dasgupta, Ana Maria Navarrete, Sebastien André, Bharath Wootla, Sandrine Delignat, Yohann Repessé, Jagadeesh Bayry, Antonino Nicoletti, Evguni L. Saenko, Roseline d'Oron, Marc Jacquemin, Jean-Marie Saint-Remy, Srinivasa V. Kaveri, and Sebastien Lacroix-Desmazes

Alloimmunization against exogenous factor VIII represents the major hurdle of hemophilia A treatment. This study shows that CD91 and other members of the LDL receptor family are not involved in factor VIII internalization by monocyte-derived dendritic cells.

Progress in Hematology

- 90 Disorders of Iron Metabolism**
Hepcidin: from discovery to differential diagnosis

Erwin H.J.M. Kemna, Harold Tjalsma, Hans L. Willems, and Dorine W. Swinkels

Hepcidin was discovered in 2000. This cysteine-rich peptide was named hepcidin because of its origin in the liver and its antimicrobial properties. Subsequent studies showed that hepcidin is the principal regulator of body iron homeostasis. This review article examines our current knowledge of the pathophysiology of hepcidin.

Decision Making and Problem Solving

- 98 Platelet Disorders**
Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature

Marco Ruggeri, Stefania Fortuna, and Francesco Rodeghiero

This systematic review of the literature shows that confusing terminology and an unacceptable heterogeneity of clinical definitions are used for management decisions in adult patients with idiopathic thrombocytopenic purpura. Standardization of terminology and definitions is needed.

- 104 Infectious Complications**
Scedosporiosis in patients with acute leukemia: a retrospective multicenter report

Morena Caira, Corrado Girmenia, Caterina Giovanna Valentini, Maurizio Sanguinetti, Alessandro Bonini, Giovanni Rossi, Luana Fianchi, Giuseppe Leone, and Livio Pagano

Scedosporiosis is a rare infectious complication in patients with acute myeloid leukemia. This report confirms that scedosporiosis is mainly a complication of acute myeloid leukemia, and that its outcome is very poor.

Brief Reports

- 111 Red Cell Disorders**
Anemia in β -thalassemia patients targets hepatic hepcidin transcript levels independently of iron metabolism genes controlling hepcidin expression
Emilie Camberlein, Giuliana Zanninelli, Lénaïck Detivaud, Anna Rita Lizzi, Francesco Sorrentino, Stefania Vacquer, Marie-Bérengère Troadec, Emanuele Angelucci, Emmanuelle Abgueuen, Olivier Loreal, Paolo Cianciulli, Maria Eliana Lai, and Pierre Brissot

In thalassemia patients, hepcidin mRNA expression was inversely related to erythroid activity, indicating that erythroid marrow expansion inhibits hepatic production of this peptide.

- 116 Red Cell Disorders**
A T2* magnetic resonance imaging study of pancreatic iron overload in thalassemia major
Wing-Yan Au, Wynniew Wai-Man Lam, Winnie Chu, Sidney Tam, Wai-Keng Wong, Raymond Liang, and Shau-Yin Ha

This study shows that pancreatic iron overload cannot be adequately predicted by serum ferritin concentration, and that it correlates with cardiac iron overload.

- 120 Myeloproliferative Disorders**
Biochemical markers predictive for bone marrow involvement in systemic mastocytosis
Marjolein L. Donker, Jasper J. van Doormaal, Frederiek F. van Doormaal, Philip M. Kluin, Eveline van der Veer, Jan G.R. de Monchy, Ido P. Kema, and Hanneke C. Kluin-Nelemans

Serum tryptase and urinary histamine metabolites are useful predictive markers for bone marrow involvement in indolent systemic mastocytosis. See related perspective on page 6.

- 124 Multiple Myeloma**
Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma
Henk M. Lokhorst, Ingo Schmidt-Wolf, Pieter Sonneveld, Bronno van der Holt, Hans Martin, Rene Barge, Uta Bertsch, Jana Schlenzka, Gerard M.J. Bos, Sandra Croockewit, Sonja Zweegman, Iris Breütkreuz, Peter Joosten, Christof Scheid, Marinus van Marwijk-Kooy, Hans-Juergen Salwender, Marinus H.J. van Oers, Ron Schaafsma, Ralph Naumann, Harm Sinnige, Igor Blau, Gregor Verhoef, Okke de Weerd, Pierre Wijermans, Shulamiet Wittebol, Ulrich Duersen, Edo Vellenga, and Hartmut Goldschmidt, for Dutch-Belgian HOVON and German GMMG

Thalidomide as part of initial treatment of multiple myeloma improves pre- and post-transplant response by increasing the proportion of patients achieving a very good partial response.

- 128 Malignant Lymphomas**
18-F FDG-PET in the staging of lymphocyte-predominant Hodgkin's disease
Catherine Ansquer, Thomas Hervouët, Anne Devillers, Sophie de Guibert, Thomas Gastinne, Steven Le Guill, Etienne Garin, Anne Moreau, Françoise Kraeber-Bodéré, and Thierry Lamy

In this retrospective study, FDG-PET proved to be useful in the staging of lymphocyte-predominant Hodgkin's disease.

- 132 Chronic Lymphocytic Leukemia**
Gene expression profile and genomic changes in disease progression of early-stage chronic lymphocytic leukemia
Verónica Fernández, Pedro Jares, Itziar Salaverria, Eva Giné, Silvia Beà, Marta Aymerich, Dolors Colomer, Neus Villamor, Francesc Bosch, Emili Montserrat, and Elias Campo

Clinical progression of early-stage chronic lymphocytic leukemia was associated with karyotype evolution and modulation of the expression of genes involved in cell adhesion and motility. See related perspective on page 14.

- 137 Hemostasis**
Inflammation-associated ADAMTS13 deficiency promotes formation of ultra-large von Willebrand factor
Clemens L. Bockmeyer, Ralf A. Claus, Ulrich Budde, Karim Kentouche, Reinhard Schneppenheim, Wolfgang Lösche, Konrad Reinhart, and Frank M. Brunkhorst

The findings of this study suggest that systemic inflammation results in ADAMTS13 deficiency, and thereby activates hemostasis.

Letters to the Editor

- 141 Red Cell Disorders**
Hb Foggia or $\alpha 117$ (GH5)Phe \rightarrow Ser: a new $\alpha 2$ globin allele affecting the α Hb-AHSP interaction
Giuseppina Lacerra, Clelia Scarano, Gennaro Musollino, Angela Flagiello, Piero Pucci, and Clementina Carestia

- 143 Red Cell Disorders**
Assessment of malaria in pregnancy using rapid diagnostic tests and its association with HIV infection and hematologic parameters in South-Eastern Nigeria
Chigozie J. Uneke, Festus E. Iyare, Patrick Oke, and Dochka D. Duhlinska

- 145 Malignant Lymphomas**
Chromosomal translocations involving BCL6 in MALT lymphoma
Hongtao Ye, Ellen D. Remstein, Chris M. Bacon, Andrew G. Nicholson, Ahmet Dogan, and Ming-Qing Du

- Malignant Lymphomas**
- 147 **High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system**
Gerald Illerhaus, Fabian Müller, Friedrich Feuerhake, Arnd-Oliver Schäfer, Christoph Ostertag, and Jürgen Finke
- Malignant Lymphomas**
- 149 **Decrease in the frequency of meningeal involvement in AIDS-related systemic lymphoma in patients receiving HAART**
José-Tomás Navarro, Ferran Vall-Llovera, José-Luis Mate, Mireia Morgades, Evarist Feliu, and Josep-Maria Ribera
- Chronic Lymphocytic Leukemia**
- 151 **A high rate of chronic lymphocytic leukemia phenotype lymphocytes in autoimmune hemolytic anemia and immune thrombocytopenic purpura**
Sajjan Mittal, Morgan G. Blaylock, Dominic J. Culligan, Robert N. Barker, and Mark A. Vickers
- Monoclonal Gammopathies**
- 153 **Prognostic factors in monoclonal gammopathy of undetermined significance**
Federico Sackmann, Miguel Arturo Pavlovsky, Claudia Corrado, Marco Pizzolato, Mariel Alejandre, and Santiago Pavlovsky
- Platelet Disorders**
- 155 **A novel RUNX1 mutation in familial platelet disorder with propensity to develop myeloid malignancies**
Keita Kirito, Kumi Sakoe, Daisuke Shinoda, Yoshihisa Takiyama, Kenneth Kaushansky, and Norio Komatsu
- Infectious Disorders**
- 157 **Human herpesvirus-6 DNAemia in immunosuppressed adult patients with leukemia at risk for mold infection**
Roy F. Chemaly, Harrys A. Torres, Ray Hachem, Dimitrios P. Kontoyiannis, Amar Safdar, and Issam I. Raad
- Infectious Disorders**
- 159 **Improving outcomes of acute invasive Aspergillus rhinosinusitis in patients with hematological malignancies or aplastic anemia: the role of voriconazole**
Corrado Girmenia, Giampaolo Pizzarelli, Emanuela Pozzi, Giuseppe Cimino, Giuseppe Gentile, and Pietro Martino

Online Only Articles

- e1 **Hypocupremia and bone marrow failure**
A.S. Haddad, V. Subbiah, A.E. Lichtin, K.S. Theil, J.P. Maciejewski
- e6 **Sequential development of large B cell lymphoma in a patient with peripheral T-cell lymphoma**
A. Furlan, F. Pietrogrande, F. Marino, C. Menin, G. Polato, F. Vianello
- e9 **Development of lens opacities with peculiar characteristics in patients affected by thalassemia major on chelating treatment with deferasirox at the Pediatric Clinic in Monza, Italy**
N. Maserà, C. Rescaldani, M. Azzolini, C. Vimercati, L. Tavecchia, G. Maserà, V. De Molfetta, P. Arpa
- e11 **Reduced intensity conditioning haematopoietic stem cell transplantation with mesenchymal stromal cells infusion for the treatment of metachromatic leukodystrophy: a case report**
N. Meuleman, G. Vanhaelen, T. Tondreau, P. Lewalle, J. Kwan, J. Bennani, P. Martiat, L. Lagneaux, D. Bron
- e14 **An unusual hotspot in a young woman with Hodgkin's lymphoma**
C.H. ten Hove, J.M. Zijlstra-Baalbergen, E.F.I. Comans, R.M. van Elburg
- e16 **Laboratory tumor lysis syndrome complicating LBH589 therapy in a patient with acute myeloid leukaemia**
A. Kalff, J. Shortt, J. Farr, R. McLennan, A. Lui, J. Scott, A. Spencer
- e18 **Reply. Kastiris E. et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone containing regimens and the impact of novel agents**
Haematologica 2007; 92:546-9
R. Bergner, M. Hoffmann, M. Uppenkamp
- e20 **Comprehensive care for patients with sickle cell disease in Cuba**
J.D. Fernández Aguila, M. Cabrera Zamora, O. Álvarez Fernández, L. Prieto Jiménez, O. Mediaceja Vicente, I. Villares Álvarez
- e21 **Human Herpes virus 8-negative primary effusion lymphoma with BCL6 rearrangement in a patient with idiopathic CD4 positive T-lymphocytopenia**
D. Niino, K. Tsukasaki, K. Torii, D. Imanishi, T. Tsuchiya, Y. Onimaru, H. Tsushima, S. Yoshida, Y. Yamada, S. Kamihira, M. Tomonaga