administration present simpler backgrounds upon which to evaluate the
effect of the WBC count. In both cases, complications occurred with the
development of marked WBC count elevations a few days after
initiating the cytokine treatment in clinically well individuals. These
cases suggest that an acute elevation in the polymorphonuclear leuko-
cyte count can promote acute sickle cell complications. Alternatively or
additionally, G-CSF–induced changes in granulocyte function, such as
increased adhesiveness, might have played a major pathogenic role in
the above cases since leukocyte adhesion appears to contribute to the
pathophysiology of sickle cell vaso-occlusion. Thus, in the absence of
infection, dehydration, or other clinically important conditions, a large
number of adherent polymorphonuclear leukocytes might have precipi-
tated the fatal vaso-occlusive event described above.

The present case supports the concept that granulocytes play,
or can play, an important role in acute complications of sickle
cell disease. The importance of granulocyte number, versus
functional characteristics, remains unknown, but understanding the
role of granulocytes in acute sickle cell events might provide
insights for new therapeutic intervention in this disease. Pendi-
ging a better understanding of the pathophysiology of vaso-
occlusion, patients with sickle cell disease should receive
G-CSF with great caution.

To the editor:

Acquired and inherited risk factors for splanchic venous thrombosis

We read with great interest the paper of Janssen et al. They
reported an increased risk for Budd-Chiari syndrome (BCS) or
portal vein thrombosis (PVT) among carriers of factor V Leiden or
inherited protein C deficiency. Overall, in 58% of their patients a
possible inherited or acquired cause of thrombophilia was found; in
14% of cases there was the coexistence of inherited or acquired risk
factors. In particular, there was an associated overt chronic
myeloproliferative disease (CMD) in 28 (21%) of 135 patients. The
authors did not consider the patients as affected by a CMD who did
not meet all the diagnostic criteria but in whom the presence of
spontaneous endogenous erythroid colonies (EECs) was detected.
Indeed, such approach has repeatedly been reported as a useful
diagnostic tool for identifying a CMD at very early stages.

The association of unusual or latent forms of CMD diagnosed by
means of the EECs assay has been reported in a large number of patients
with BCS or PVT. Review of 51 published cases with BCS and 69
cases with portal and/or mesenteric vein thrombosis showed the
presence of an overt CMD in 49% of the patients with BCS and 23% of
the patients with portal/mesenteric vein thrombosis; the inclusion of
patients with latent CMD as defined by the presence of EECs increased
the diagnostic yield to 78% among patients with BCS and 48% among
patients with portal/mesenteric vein thrombosis. Therefore, we suggest
that the exclusion of latent CMD as possible underlying cause of
splanchic vein thrombosis could have overstated the role of
inherited thrombophilia as a single risk factor for BCS or PVT. In
our series of 11 patients with BCS and 45 patients with portal/mesenteric
vein thrombosis, 14 (25%) of 56 had inherited thrombophilia (1 had
antithrombin III deficiency; 2, protein C deficiency; 8, factor V Leiden
mutation; and 3, prothrombin G20210A), in good agreement with the
23% reported by Janssen et al. Among the 31 patients assayed for the
presence of EECs, 18 (58%) were considered to be affected by CMD, in
4 cases in association with inherited thrombophilia. An overt polycythe-
mia vera or primary thrombocythemia was present in 7 (22%) of 31
such patients, in 4 cases at the time of thrombosis. Three of the patients
with EECs as the only sign of CMD at the time of thrombosis later
developed an overt thrombocythemia. Thus, in 14 patients the presence
of a CMD even at early stages should have been missed not applying the
EECs assay at the time of thrombosis. Among the 13 patients with no
detectable EECs, 4 had inherited thrombophilia (3, factor V Leiden
mutation; 1, prothrombin G20210A) and 4 had an acquired cause of
thrombosis (1 case each of antiphospholipid antibodies, puerperium,
trauma, and surgery). Therefore among the 31 patients exhaustively
investigated, 26 (84%) had an inherited or acquired cause of thrombo-
ophilia or both. This percentage is higher than that reported by Janssen et
al. and reflects the improvement in detection of CMD as underlying
cause of thrombosis, confirming that a thorough search for CMD is
mandatory in evaluating patients with splanchic venous thrombosis.
Diagnostic yield of atypical or precocious forms of CMD can be
substantially increased by the use of the EECs assay or novel additional
assays such as the megakaryocyte expression of the thrombopoietin
receptor (c-mpl), whose decrease has been recently reported as a
hallmark of polycythemia vera.

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Response:

Acquired and inherited risk factors for Budd-Chiari syndrome and portal vein thrombosis

De Stefano et al describe the role of diagnosing latent myeloproliferative disorder in Budd-Chiari syndrome (BCS) and mesenteric or portal vein thrombosis (PVT). Latent myeloproliferative disorder is diagnosed by growth of erythroid cells in the absence of erythropoietin, also referred to as spontaneous endogenous erythroid colonies (EECs). The association between the presence of EECs and BCS or PVT is well known.³⁴ We agree with De Stefano et al that excluding EECs may lead to an underestimation of the number of patients with an acquired risk factor for thrombosis and, consequently, to an underestimation of those with a combination of acquired and inherited risk factors for thrombosis. EEC assays are technically demanding and not amenable to external quality assurance. As stated in our article, not all of the participating centers tested for the presence of EECs. Thus our data did not allow us to evaluate the relation between EECs and BCS or PVT. It should be emphasized that our study focused on the role of prothrombotic coagulation disorders rather than on myeloproliferative disorders. Risk estimates for coagulation abnormalities are not affected by the underrepresentation of EEC diagnoses.

In our opinion, several of the results presented by De Stefano et al necessitate a balanced interpretation. First, the presence of EECs alone is, using the current criteria, not sufﬁcient to diagnose myeloproliferative disease.⁵⁻⁶ Their presence is used merely as a conﬁrmational criterion for this diagnosis. The prognostic signiﬁcance of the presence of EECs as an indication for latent myeloproliferative disorder has not yet been elucidated. De Stefano et al reported that 3 of 14 patients with EEC developed an overt myeloproliferative disorder. Others have reported a lower incidence of manifest myeloproliferative disorders after long-term follow-up of patients with PVT.⁶ Second, De Stefano et al describe the combined prevalence of myeloproliferative disorders in patients with different diseases (BCS, PVT, and mesenteric vein thrombosis). We did not study patients with isolated mesenteric vein thrombosis. Third, the presented review in which 78% of BCS patients and 48% of PVT patients exhibit a latent or overt myeloproliferative disorder results from data pooling of small-scale studies and early anecdotal reports of highly selected cases.⁷ The expected publication bias of the reports collected in this review paper is exempliﬁed by successive studies from the group of Valla who initially reported latent or overt myeloproliferative disorders in 75% of BCS patients but, after 15 years of follow-up, in 31% of their recently diagnosed patients.¹⁻³ Fourth, it is likely that the 31 patients exhaustively investigated by De Stefano et al are selected patients who were referred to a specialized hematology unit. It would be interesting to know the prevalence of, for example, liver cirrhosis and pancreatitis in the PVT population studied. In our opinion, the population studied by De Stefano et al is incomparable to our wider recruited population, for which we attempted to minimize patient selection.⁹ Therefore, comparison of rates of acquired and/or inherited prothrombotic risk factors between their and our population does not seem appropriate.

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Acquired and inherited risk factors for splanchnic venous thrombosis

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