No potential conflict of interest relevant to this letter was reported.

1. Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. N Engl J Med 2015;373:1835-44.
2. Budde LE, Guthrie KA, Till BG, et al. Mantle cell lymphoma international prognostic index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation. J Clin Oncol 2011;29:3023-9.
3. Dreyling M, Geisler C, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25:Suppl 3:iii83-iii92.
4. Robinson S, Dreger P, Caballero D, et al. The EBMT/EMCL consensus project on the role of autologous and allogeneic stem cell transplantation in mantle cell lymphoma. Leukemia 2015; 29:464-73.
5. Kumar S, Giralt S, Stadtmauer EA, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. Blood 2009;114:1729-35.

DOI: 10.1056/NEJMc1515465

THE AUTHORS REPLY: In our multicenter, phase 2 study, the combination of lenalidomide and rituximab as initial treatment for mantle-cell lymphoma was proposed as an alternative to more intensive approaches such as high-dose chemotherapy and autologous stem-cell transplantation. Patients who participated in the study either were not candidates for transplantation because of coexisting conditions or wished to avoid combination chemotherapy. The ongoing intergroup E1411 study (ClinicalTrials.gov number, NCT01415752) is evaluating a similar approach of induction therapy with rituximab, bendamustine, and bortezomib followed by maintenance therapy with rituximab and lenalidomide in older patients with previously untreated mantle-cell lymphoma.

Studies of the potential effect of lenalidomide treatment on subsequent stem-cell collection in patients with lymphoma are lacking, and this effect was not relevant to our study design. However, this interesting question can be addressed by future studies incorporating lenalidomide-containing regimens.

Jia Ruan, M.D., Ph.D.
John P. Leonard, M.D.
Weill Cornell Medical College
New York, NY
jruan@med.cornell.edu

Since publication of their article, the authors report no further potential conflict of interest.

DOI: 10.1056/NEJMc1515465

Invasive Candidiasis

TO THE EDITOR: In their review on invasive candidiasis, Kullberg and Arendrup (Oct. 8 issue)[1] raise the question of what is the most appropriate initial antifungal therapy for patients who have previously been exposed to echinocandins for prolonged periods. The authors state that triazoles may be the preferred agent in such cases. Recent epidemiologic data show a shift in the distribution of candida species, with a significant increase in *Candida glabrata*, a species that is more likely to be resistant to azoles and the most common species resistant to fluconazole.[2] Furthermore, prior exposure to echinocandins has also been shown to promote not only resistance to these agents but also multidrug resistance, defined as candida resistant to fluconazole and one or more echinocandins.[3] Thus, for patients with previous antifungal selection pressure, triazoles may not be the most appropriate first-line treatment. Liposomal amphotericin B, which has a broad spectrum of activity, may be a better choice as an empirical therapy in this clinical setting.

Frederic M. Jacobs, M.D.
Hôpital Antoine-Béclère
Clamart, France
frederic.jacobs@abc.aphp.fr

No potential conflict of interest relevant to this letter was reported.

1. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med 2015;373:1445-56.
2. Cleveland AA, Harrison LH, Farley MM, et al. Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008-2013: results from population-based surveillance. PLoS One 2015;10(3): e0120452.
3. Lewis JS II, Wiederhold NP, Wickes BL, Patterson TF, Jorgensen JH. Rapid emergence of echinocandin resistance in Candida glabrata resulting in clinical and microbiologic failure. Antimicrob Agents Chemother 2013;57:4559-61.

DOI: 10.1056/NEJMc1514201

TO THE EDITOR: Kullberg and Arendrup have updated the current scenario of invasive candidiasis. Multispecies invasive candidiasis requires attention because it can emerge as a threat.[1] In our recently conducted prospective observational study

that involved 200 critically ill patients who did not have neutropenia, growth of candida species was observed in blood samples from 17 patients (unpublished data). Of these 17 patients, 3 had multispecies candidemia, with growth of more than one species in the same blood-culture bottle or in samples obtained during a 72-hour period. *C. albicans* and *C. auris* were found in 1 patient, and *C. glabrata* and *C. tropicalis* were found in 2 patients. Two patients had severe acute pancreatitis, and 1 patient had multiple coexisting conditions with acute or chronic heart failure; all 3 of these patients died. Polymicrobial bacterial bloodstream infections are generally nosocomial, more common in patients in whom the source of infection is intraabdominal, and associated with a higher mortality than monomicrobial bacterial bloodstream infections.[2] This area remains unexplored in the field of invasive candidiasis. The identification of multispecies invasive candidiasis is important because it may require an aggressive treatment approach.

Afzal Azim, M.D.
Armin Ahmed, M.D.
Rungmei S.K. Marak, M.D.
Sanjay Gandhi Institute of Postgraduate Medicine
Lucknow, India
drarminahmed@gmail.com

No potential conflict of interest relevant to this letter was reported.

1. Nace HL, Horn D, Neofytos D. Epidemiology and outcome of multiple-species candidemia at a tertiary care center between 2004 and 2007. Diagn Microbiol Infect Dis 2009;64:289-94.
2. Lin JN, Lai CH, Chen YH, et al. Characteristics and outcomes of polymicrobial bloodstream infections in the emergency department: a matched case-control study. Acad Emerg Med 2010;17:1072-9.

DOI: 10.1056/NEJMc1514201

TO THE EDITOR: In their scholarly review, Kullberg and Arendrup correctly suggest that germline genetic variations should be considered in selected patients with invasive candidiasis. The authors refer to common variants that have been associated with disease in genomewide association studies. However, these polymorphisms are very weakly associated with candidiasis. Given the fact that the relative risks of candidemia associated with some of these polymorphisms are lower than 2, identification of these genetic variations cannot help physicians at the bedside. Surprisingly, Kullberg and Arendrup did not discuss the role of single-gene inborn errors of immunity, which are caused by rare variants that have been increasingly documented in otherwise healthy children, adolescents, and adults with invasive fungal diseases. In particular, biallelic mutations in caspase recruitment domain-containing protein 9 (CARD9) were reported in patients with hitherto unexplained invasive candidiasis.[1-3] An intriguing aspect of this disorder is that it has complete clinical penetrance for invasive fungal disease but variable expressivity: although invasive candidiasis develops in most patients, invasive dermatophytosis develops in others.[4] Consideration of an underlying monogenic primary immunodeficiency, such as CARD9 deficiency, is therefore warranted in patients who have invasive candidiasis without any clear risk factor. Understanding the human genetic determinism of invasive candidiasis is useful for clinical care and genetic counseling.

Barbara Bosch, M.D.
Isabelle Meyts, M.D., Ph.D.
University Hospitals Leuven
Leuven, Belgium
isabelle.meyts@uzleuven.be
Anne Puel, Ph.D.
INSERM Unité 1163
Paris, France

Dr. Bosch reports receiving support from a Research Foundation–Flanders grant; Dr. Meyts, receiving grants from the Katholieke Universiteit Leuven and the Jeffrey Modell Foundation; and Dr. Puel, receiving grants from the Jeffrey Modell Foundation and the French National Research Agency (project HGDIFD [Human genetic determinism of invasive fungal diseases], ANR-14-CE15-0006). No other potential conflict of interest relevant to this letter was reported.

1. Glocker E-O, Hennigs A, Nabavi M, et al. A homozygous *CARD9* mutation in a family with susceptibility to fungal infections. N Engl J Med 2009;361:1727-35.
2. Lanternier F, Mahdaviani SA, Barbati E, et al. Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species-induced meningoencephalitis, colitis, or both. J Allergy Clin Immunol 2015;135:1558-68.
3. Herbst M, Gazendam R, Reimnitz D, et al. Chronic Candida albicans meningitis in a 4-year-old girl with a homozygous mutation in the CARD9 gene (Q295X). Pediatr Infect Dis J 2015;34:999-1002.
4. Lanternier F, Pathan S, Vincent QB, et al. Deep dermatophytosis and inherited CARD9 deficiency. N Engl J Med 2013;369:1704-14.

DOI: 10.1056/NEJMc1514201

THE AUTHORS REPLY: We agree with Jacobs that azoles are not the preferred drug class for invasive candidiasis due to *C. glabrata* and that changes in species distribution may drive treatment recommendations, as we stated in our review. In epidemiologic studies, an increasing incidence of *C. parapsilosis* infections is the major observation among patients with prior exposure to echinocandins, for which fluconazole is the preferred therapeutic choice. In clinical settings with a notable

incidence of multiresistant *C. glabrata*, *C. krusei*, or other candida species resistant to azoles, liposomal amphotericin B may be an appropriate choice.

Azim et al. describe 3 patients infected by multiple candida species. In seven prospective clinical trials of invasive candidiasis that involved a total of 2342 patients (summarized in Table 3 of our review), 3 to 10% of the patients had been infected by multiple candida species. We are not aware of any of the studies showing higher mortality or treatment-failure rates among those patients.

Bosch et al. correctly point to the rare single-gene inborn errors of immunity that have led to increased susceptibility to fungal infections, of which the *CARD9* mutation is among the most relevant.[1-3] These mutations occur sporadically and may be considered in patients with uncommon manifestations of invasive candidiasis. However, in our review, we specifically focused on polymorphisms that are prevalent in the intensive care unit (ICU) patient population that is seen in daily practice in such units. The identification of subgroups of patients in the ICU who have a risk of candidemia that is 2 to 19 times the risk among other patients in the ICU may considerably steer clinical management in terms of surveillance, prophylaxis, or empirical therapy in the future.[4]

Bart Jan Kullberg, M.D., Ph.D.
Radboud University Medical Center
Nijmegen, the Netherlands
bj.kullberg@radboudumc.nl

Maiken C. Arendrup, M.D., Ph.D.
Statens Serum Institute
Copenhagen, Denmark

Since publication of their article, the authors report no further potential conflict of interest.

1. Glocker E-O, Hennigs A, Nabavi M, et al. A homozygous *CARD9* mutation in a family with susceptibility to fungal infections. N Engl J Med 2009;361:1727-35.
2. Lanternier F, Mahdaviani SA, Barbati E, et al. Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species-induced meningoencephalitis, colitis, or both. J Allergy Clin Immunol 2015;135:1558-68.
3. van de Veerdonk FL, Plantinga TS, Hoischen A, et al. *STAT1* mutations in autosomal dominant chronic mucocutaneous candidiasis. N Engl J Med 2011;365:54-61.
4. Kumar V, Cheng S-C, Johnson MD, et al. Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia. Nat Commun 2014;5:4675.
DOI: 10.1056/NEJMc1514201

SLC25A32 Mutations and Riboflavin-Responsive Exercise Intolerance

TO THE EDITOR: Multiple acyl–coenzyme A dehydrogenation deficiency is an inborn error of metabolism with frequent muscle involvement. This deficiency is due to defects in the electron-transfer flavoprotein genes *ETFA* and *ETFB*[1] or in the electron-transfer flavoprotein ubiquinone oxidoreductase gene *ETFDH*.[2] In patients with this deficiency, all the mitochondrial flavoprotein dehydrogenases are defective with a specific biochemical phenotype for multiple acyl–coenzyme A dehydrogenation deficiency. Yet, in a few patients who have a deficiency that is similar to multiple acyl–coenzyme A dehydrogenation deficiency, no mutations are identified in *ETFA*, *ETFB*, or *ETFDH*.[3]

We report on a 14-year-old girl who presented with recurrent exercise intolerance. She had biochemical features of multiple acyl–coenzyme A dehydrogenation deficiency, but she did not have mutations in *ETFA*, *ETFB*, or *ETFDH*. Oral supplementation with riboflavin led to dramatic improvement in the clinical and biologic abnormalities.

Riboflavin is the precursor of flavin adenine dinucleotide (FAD), the cofactor for electron-transfer flavoprotein and electron-transfer flavoprotein ubiquinone oxidoreductase. We thus suspected a defect in FAD biosynthesis or transport and studied genes involved in riboflavin metabolism.

Two heterozygous mutations, c.425G→A (p.Trp142*) and c.440G→A (p.Arg147His), were identified in solute carrier family 25, member 32 (*SLC25A32*). *SLC25A32* encodes the mitochondrial FAD transporter, an inner mitochondrial membrane carrier that imports FAD from the cytosol into the mitochondria.[3,4] Allelic segregation confirmed autosomal recessive transmission. At the complementary DNA level, the missense mutation appeared homozygous, but the substitution responsible for the nonsense mutation was not identified. Consequently, we speculate that the messenger RNA (mRNA) harboring the nonsense mutation is degraded by the nonsense-mediated mRNA decay machinery.

We performed studies in yeast that showed that the missense mutation introduced in *FLX1*, the homologue of human *SLC25A32* in *Saccharomyces cerevisiae*, resulted in a severe growth defect that was rescued by exogenous expression of wild-type *FLX1* and also by *SLC25A32*. These findings show the deleterious effect of this mutation