

# HOSPITAL PHYSICIAN®

## HEMATOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

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## Acute Myeloid Leukemia

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# Acute Myeloid Leukemia

Brian T. Hill, MD, PhD, and Mikkael A. Sekeres, MD, MS

## INTRODUCTION

Acute myeloid leukemia (AML), also known as acute nonlymphocytic leukemia, represents a group of clonal hematopoietic stem cell disorders in which both failure to differentiate into mature cells and excessive proliferation in the bone marrow stem cell compartment result in the accumulation of myeloblasts.<sup>1</sup> For over 3 decades, the French-American-British (FAB) classification system has been used to describe the different categories of AML. In 2001, the World Health Organization (WHO) published a new classification system for AML incorporating morphologic, genetic, immunophenotypic, biologic, and clinical features.<sup>2</sup> This system was established in an attempt to more accurately predict the prognosis and biologic properties of the subcategories of AML. Intensive treatment entails remission induction followed by post-remission chemotherapy. For patients who have poor-risk disease or who relapse, this treatment approach may be followed by hematopoietic stem cell transplantation. However, treatment recommendations vary, and factors such as patient age, cytogenetics, performance status, and prognosis must be considered when choosing treatment options. This review will discuss epidemiology, pathogenesis, evaluation, and treatment of patients with AML.

## EPIDEMIOLOGY AND PATHOGENESIS

Contrary to the popular impression that AML is a disease of children and young adults, the median age at diagnosis of AML is approximately 67 years in the United States.<sup>3,4</sup> Prognostic and therapeutic information is determined by whether a patient is considered younger (< 60 yr) or older (≥ 60 yr). AML is the most common leukemia, with approximately 12,000 new diagnoses each year in the United States, and its incidence has increased from 1992 through 1998.<sup>5</sup> It represents 1.2% of all new cancer diagnoses and 1.3% of estimated cancer deaths.<sup>6</sup>

Similar to other malignancies, the pathogenesis of

AML involves a combination of environmental insults and genetic predisposition leading to DNA damage or epigenetic changes in affected cells. In AML, the normal process of myeloid stem cell differentiation is interrupted, with a maturation block occurring at a granulocytic cell precursor stage. This transformation can occur either as a *de novo* event or be associated with previous therapy or an antecedent hematologic disorder. This transformation results in the clonal expansion of an immature precursor blast of myeloid lineage. The malignant myeloblasts are unable to differentiate into mature cells and disrupt normal bone marrow function, leading to impaired hematopoiesis.<sup>7</sup>

### • What are the known risk factors for AML?

Several risk factors for AML have been identified. Germline mutations in the *AML1* gene, chromosomal instability in certain autosomal dominant conditions (eg, Fanconi's anemia, ataxia telangiectasia, neurofibromatosis, and Bloom syndrome) as well as congenital immunodeficiency disorders (including infantile X-linked agammaglobulinemia and Down syndrome) have been associated with an increased incidence of AML.<sup>8</sup> Environmental exposures have also been implicated. Ionizing radiation<sup>9</sup> and organic solvents such as benzene and other petroleum products have been associated with a higher risk of developing AML.<sup>10,11</sup> Both *RAS* mutations and polymorphisms resulting in inactivation of NAD(P)H:quinone oxidoreductase have been found in patients with these exposures.<sup>12</sup>

Other risk factors for AML may involve treatment of hematologic malignancies. Therapy-related AML typically develops following alkylating agent-induced damage at a median of 5 to 7 years following therapy for the primary malignancy. It usually is associated with an antecedent myelodysplastic disorder and abnormalities of chromosomes 5 and 7.<sup>13</sup> DNA-topoisomerase II agents have also been shown to produce gene rearrangements leading to AML, typically involving an 11q23 abnormality (the *MLL* gene), with a short latency of 12 to 18 months following treatment.<sup>14</sup> Secondary AML may also develop in patients with various hematologic disorders, including aplastic anemia, myelodysplastic