Aplastic anemia is a term describing the common findings of pancytopenia and marrow hypoplasia arising from a variety of disease states, including acquired aplastic anemia and a variety of congenital marrow failure states. The management of children with these disorders has been confounded by difficulties of diagnosis. The availability of molecular testing has assisted in partial resolution of this problem but has raised new issues, such as the potential of genetic predisposition and the management of asymptomatic individuals with molecular markers. Longitudinal data from large cohort studies and disease registries are providing a rational basis for making more informed treatment decisions for children with these disorders. In particular, the ability to subset patients more accurately has improved triage of treatments. Approaches to hematopoietic stem cell transplantation (SCT), using both conventional and alternative donors, are changing rapidly, and the long-term sequelae of newer approaches are not entirely clear. Improved diagnosis and longer survival have fostered an understanding of the multidisciplinary approach necessary to manage both the underlying problems and the significant sequelae of treatment in both acquired and congenital disease.

Bone marrow failure syndromes encompass a number of moderately well described entities, defined largely by clinical presentation rather than results of specific testing, that share the common findings of peripheral blood cytopenia in the setting of marrow hypoplasia. While an increasing number of specific genetic abnormalities have been associated with different congenital marrow failure syndromes over the past few years, only a proportion of patients within each congenital disease category have the mutations described. This suggests both that many other mutations remain to be identified and that many combinations of events, genetic and environmental, can combine to yield similar clinical syndromes. Nonetheless, the availability of such “genetic testing” has revealed increasing numbers of individuals who by clinical criteria appear to have idiopathic aplastic anemia (AA) and appear phenotypically normal yet have molecular hallmarks of congenital marrow failure syndromes. The issues of misdiagnosis and therefore mismanagement have thus become more prominent. Additionally, management of the asymptomatic individual now presents itself as a clinical problem—one that is largely unexplored—and the question of whether mutations confer predisposition versus establish diagnosis, as well as the role of somatic mutation, will need to be considered in devising management strategies. The following sections present some implications of our altered knowledge for management of children with marrow failure. This discussion is not meant to be inclusive. The first section emphasizes examples bearing on how the rapidly evolving array of diagnostic tests and epidemiologic information might best be incorporated into care for individual patients while the second provides a brief summary of general trends in treatment.

**Patient-specific Issues in Evaluation and Management**

In an era of molecular diagnostics and computer assistance for evidence-based practice, the roles of history and physical exam are at risk as the basis for clinical guidance. While determining the onset, duration, and severity of signs and symptoms related to poor marrow function may be of diminished value in discriminating diagnoses, a sophisticated history at diagnosis and thereafter remains critical to guiding management. For example, issues related to pubertal progression appear nowhere on the list of differential diagnoses for marrow failure, are unlikely to appear as part of a “clinical practice guideline,” and may not appear to be salient when faced with new onset marrow failure in a child. However, it is exactly this information that will assist in forming a prospective plan for management of menstruation, either suppression of menses in anemic and thrombocytopenic post-menarchal females or prospective counseling for pre-menarchal but clearly pubertal female patients and their families. To extend this example, the same information about pubertal status will guide thinking regarding potential sperm banking for pubertal male patients who may go on to receive chemotherapy such as cyclophosphamide or undergo hematopoietic stem cell transplantation (SCT) conditioning. As the care plan for aplastic patients with matched siblings may evolve rapidly, prospective recognition of these details and their management are critical. As the patient population is sufficiently rare and each patient sufficiently unique, it is my experience that the re-
sponsibility for thinking early and iteratively about the complex subspecialty issues surrounding the marrow failure patient will rest solely on the shoulders of the hematologist. The above is only one of many examples.

Whereas histories attempting to establish drug/toxin exposure may guide management and counseling, time spent attempting to establish an infectious history is unlikely to be of much use in establishing a specific diagnosis or management plan. In contrast, a history and a physical exam guided by the epidemiologic information from increasingly sizable and well-organized databases having entered patients with various congenital marrow failure syndromes\(^3,4\) are likely to have management significance above and beyond diagnosis. While a description of similar hematologic or physical findings in family members may help to substantiate or debunk a hypothetical inherited disorder, the now aggregated patient data demonstrate that the concordance of clinical phenotype and disease severity within families, including those with the same genetic mutation, may be quite limited.\(^5,7\) The extended family may contain individuals with characteristic physical findings but no known hematologic disease and vice versa. Indeed, the effects of variable penetrance as well as the influence of other non-disease specific genes on the hematologic and nonhematologic expression of these syndromes appear to be significant.

Given the still incomplete tool kit of diagnostics to determine with certainty the patient with idiopathic versus congenital marrow failure as well as the divergence in treatment options, tolerability of treatment, and the open-ended questions relating to management of previously undiagnosed family members, all the potential avenues of ascertainment should be explored. The family history for leukemia should be extended to include a family history of osteogenic sarcoma, squamous cell carcinoma of head and neck and/or genitourinary tract, and breast cancer, excess risks that marrow failure disease-specific registries have helped to define.\(^5,8,10\) In addition to the alteration in breadth of the family history, however, the most critical difference over time has been how it will inform management of the entire kindred, ranging from providing appropriate reassurance for those in whom no “genetic” disorder can currently be established to genetic testing and cancer surveillance for those with congenital marrow failure.

This broad view of the family as a diagnostic and management “continuum” is one salient difference between management of adult and pediatric marrow failure patients. In part this is driven by the prominence of SCT in the management of children with idiopathic marrow failure\(^16\) as well as its role in the management of those with congenital disease.\(^12,13\) An understanding of hematopoietic stem cell donor options is necessary to effectively triage potential therapies for the patient, and thus consideration of the state of health of siblings and other potential family donors should be undertaken earlier than might be the case with adult patients. Early involvement of genetic counseling may be appropriate, particularly because families of pediatric patients are often still establishing their families and there may be ongoing or planned pregnancies that become medically relevant. In an era of pre-implantation genetic diagnosis, this becomes especially important. Parenthetically, the importance of carrier status in donors is incompletely understood for any of the marrow failure states but will doubtless become better appreciated. A recent case report suggests that a carrier for c-MPL mutation in congenital amegakaryocytic thrombocytopenia (CAMT) can successfully serve as a bone marrow donor.\(^14\)

While the importance of meticulously examining the patient for stigmata of a congenital syndrome is obvious, the registry and case compilation data have put the problem of unequivocally identifying and initiating treatment for the patient with idiopathic AA in sharp relief. A significant proportion of patients with the inherited syndromes have normal physical exams.\(^1,3\) Therefore, absence of characteristic findings in the patient or family is insufficient to eliminate consideration of congenital syndromes as a cause of marrow failure and should be viewed with caution as sufficient criteria to initiate therapy for acquired AA. In contrast, the presence, type and severity of somatic abnormalities can provide very useful information for management above and beyond diagnosis. For example, a severe somatic phenotype has been associated with shorter time to onset of hematologic abnormalities and subsequent risk for leukemia in patients with Fanconi anemia (FA).\(^15\) These data are likely to become increasingly robust and useful over time and should be used to assist in decision making about treatment initiation, frequency of surveillance and whether and when to consider SCT or participation in relevant phase I studies.

Blood counts at diagnosis and thereafter significantly impact management, acutely and long term. Since the literature of response and prognosis in AA rests on published diagnostic peripheral blood and bone marrow criteria, strict adherence to these standards is important. Although we tend to think of AA as pancytopenia, it is important to recognize that bilineage failure fulfills these criteria and should be evaluated and managed accordingly. In addition to definition, an appreciation of the importance of severity has evolved over time. Severe AA (SAA) is generally defined by the presence of neutrophil counts less than 500/µL and what is often referred to as very severe AA (VSAA) as the presence of neutrophil counts less than 200/µL.\(^16\) Moderate or non-severe refers to marrow failure with less dramatic findings than those noted above. These values have some prognostic value and have been used to analyze results of various treatment strategies.\(^16,19\) Of course, counts vary over time, sometimes rather broadly, and the implications of these swings on expectations of efficacy for potential therapy remain somewhat indeterminate. While immediate SCT from a matched family donor is the treatment of choice for most children with SAA,\(^11\) these counts may guide the triage of alternative therapies for those for whom such...
SCT is not an option.\textsuperscript{20,21} For example, although good outcomes reported for patients with moderate AA may encourage a minimalist approach to therapy, the combination of antithymocyte globulin (ATG) and cyclosperine has been demonstrated to be better than that of cyclosperine alone, suggesting that less aggressive approaches may not be prudent.\textsuperscript{22} Patients with SAA fare better with combination immunosuppression than with single agents, but the addition of granulocyte colony-stimulating factor (G-CSF) has not further improved overall response or survival in this group.\textsuperscript{17,19,23} The outcome of treatment of young patients with VSAA has variably been worse, equivalent or better than that of children with SAA,\textsuperscript{17,19,24} but certainly results with the use of multi-agent immunosuppression appear favorable enough to encourage use of immunosuppression versus alternative donor SCT.

Use of blood counts in establishing transfusion threshold varies by practitioner. Leukodepletion techniques have decreased rates of allosensitization overall with some consistent findings in AA.\textsuperscript{23} However, transfusion-related problems of sensitization, iron overload and infection persist and confound the supportive care of pancytopenia. Prediction of significant hemorrhage is imprecise, and general guidelines for platelet support, in particular, should be constantly reviewed in view of individual history, exam and infectious status. Iron status should be followed and where iron accumulation appears particularly rapid, evaluation for genetic predisposition to iron retention may be helpful. Chelation should be initiated at a trigger ferritin level that is determined relative to the ability of the patient and family to support this treatment. The efficacy and toxicity of newer oral agents should be revisited as more data become available. Persistent neutropenia poses a risk of bacterial and fungal infection. It is not currently standard practice to use prophylactic antibiotics although individual history of specific infection may support subsequent prophylaxis. There is little evidence to guide these decisions. The frequency of \textit{Pneumocystis carinii} pneumonia (PCP) and significant viral infections in these populations is quite limited. While it seems reasonable to provide PCP prophylaxis for patients receiving multi-agent immunosuppression, neither optimal duration nor efficacy of such therapy is prospectively established.

The bone marrow aspirate provides another readily available guide to management. Subtlest of the various marrow failure states aside, the most important role is in dismissing the presence of malignancy and in establishing the index of suspicion for myelodysplasia (MDS). There is frequently some dyserythropoiesis in patients with marrow failure, regardless of cause, making the always thorny issue of MDS difficult to address. Pediatricians may be less adept than their adult peers in evaluating MDS morphologically because it occurs so infrequently. Even so, patients with clinical idiopathic AA and classic “empty” marrows may have clonal chromosomal findings common to MDS. It is not infrequent for the pancytopenic marrow to yield poor specimens; it is incumbent upon the practitioner to establish whether the laboratory obtained sufficient cells and, within reason, to pursue attempts to get an adequate cytogenetic assessment. The cultural issues of parents and pediatricians around procedures in children are many, but in this case the importance of the information should be the primary driver of practice. Abnormal cytogenetic results will impact on diagnosis and management. SCT is a widely reported therapy for children with MDS; the intensity of conditioning differs for SAA and MDS, depending upon donor selection, with significant consequences regarding potential relapse of MDS. Although some patients with MDS may have hematologic improvement with ATG,\textsuperscript{26,27} I am unaware of an informative experience in children and this would not be a current standard approach to care. The activity of thalidomide in MDS, and the dramatic effect of treatment with the thalidomide derivative lenalidomide in adults with 5q– MDS, suggest that therapeutic choices for MDS patients will increase.\textsuperscript{28,29} The tolerability and suitability of newer agents for children, let alone their efficacy in contrast with chemotheraphy or SCT, will be important to establish and then incorporate into optimal treatment strategies.

Chromosomal findings also influence the management of patients with congenital diseases. For example, development of genetic and partial trisomies and tetrasomies of chromosome 3q in patients with FA have been associated with particularly rapid, fatal complications.\textsuperscript{30} Conversely, the presence of isochromosome 7q in patients with Shwachman-Diamond syndrome (SDS) has been associated with failure to progress to hematologic malignancy.\textsuperscript{31,32} Patients with SAA and 13q– have been reported to have a high response rate to immunosuppression and low risk of progression to MDS, although the youngest patient reported was 19.\textsuperscript{33} While the identification of such specific findings in patients mandates careful reassessment of therapeutic strategies, the implications of other cytogenetic abnormalities are subject to some debate. The observation of “transient” abnormalities has further clouded this area in both acquired and congenital marrow failure management.\textsuperscript{32,34} However, incorporation of more frequent and more effectively analyzed cytogenetic sampling of hematopoietic cells into routine care is wise, and more standard responses to cytogenetic information in longitudinally followed patients will evolve shortly.

Associations of specific mutations with natural history of patients with congenital disease are also impacting management strategies. After cloning of the first FA gene, \textit{FANCC}, the International Fanconi Anemia Registry (IFAR) was used to determine that IVS4 or exon 14 mutations defined a particularly high risk group for early onset disease and bad outcome among \textit{FANCC} patients.\textsuperscript{35} The European FA Research Group later studied 245 patients from 179 families in 2000, at a time when only 4 FA genes (\textit{FANCA, FANCC, FANCF} and \textit{FANCG}) had been cloned.\textsuperscript{15} Even so, specific (null) mutations were readily shown to be associ-
ated with earlier onset of hematologic abnormalities, higher incidences of leukemia and/or higher incidences of somatic abnormalities. Patients with the biallelic FANCD1 mutations (i.e., BRCA2) have particularly early onset of leukemia. Similarly, recent reports have provided helpful data on the incidence, prevalence, time to occurrence and outcome of a variety of malignancies in patients with marrow failure states. In some cases, the incidence of solid malignancies, such as squamous cell carcinomas in FA patients, is sufficiently high that routine surveillance seems clearly indicated. This cancer risk may be modified by treatment choices or sequelae of treatment. For example, secondary malignancies in FA patients and in AA patients appear increased in those having experienced graft-versus-host disease (GVHD). It is likely that this sort of data will increasingly drive clinical decision-making.

General Trends in Evaluation and Management

The above section is intended to convey the message that decision-making for pediatric patients with marrow failure is highly individualized. However, there are some general management precepts related simply to diagnosis per se. Children with SAA or VSAA, like younger adults, appear best served by matched family SCT, which results in 70%-90% chance of long-term survival. No alternative treatment comes close to achieving these results. However, the issues of substituting one chronic disease (GVHD) for another (aplasia) remain appreciable; while rates have decreased, acute GVHD grade II-IV and chronic GVHD of any severity still occur in approximately 20%-25% of patients. In general these percentages are lower, but not zero, for younger children. The long-term sequelae include uncertain effects on fertility and some increased risk of second malignancies such as skin and thyroid cancer, although radiation-free regimens commonly used in this setting are associated with high likelihood of preserved fertility and little second malignancy. For the child lacking such a donor, the data cited above support use of multiagent immunosuppression containing at least ATG, steroids and cyclosporine. If patients respond, slow weaning of cyclosporine and careful follow-up is advisable as the recurrence rate is substantial. For patients who do not have a clinically satisfactory response, another trial of ATG may be attempted or SCT from a suitably matched unrelated donor (URD) may be considered. Alternative SCT results have improved in recent years.

In my own experience, the likelihood of response to retreatment is less than that which is published and my experience with URD SCT significantly better, but each practitioner will need to weigh the literature against local results and opinions of other consultants in coming to closure with patients and families. While the rate of response to immunosuppression has remained relatively constant since the introduction of multiagent approaches, there has been significant improvement in alternative SCT outcomes and the most contemporary data should be reviewed. Use of cyclophosphamide absent stem cell support is controversial, but until fully resolved, this and other possible novel studies should also be discussed with the family. The decision of whether and when to proceed to the curative potential of SCT with its significant and unpredictable side effect profile is complex and depends upon an appropriate review of results and complications by the physician or consultants and subsequent interpretation of that information by patient/family groups with diverse beliefs and risk-taking profiles. In any case, non-transplanted patients require close assessment not only for hematologic status but also for evolution of MDS and other secondary malignancies.

The generic triage of therapy for patients with marrow failure states is even less orderly. The FA Research Foundation, for example, has sponsored two international consensus conferences to bring multidisciplinary subspecialists together with a view toward promulgating helpful clinical management guidelines (available at www.fanconi.org). In brief, these guidelines suggest critical hematologic values or findings at which therapy should be initiated and suggest an approach to the triage of therapies. In FA and Diamond-Blackfan anemia (DBA), the excellent results of matched sibling SCT in alleviating marrow failure mandate early consideration of this treatment where available. However, the sequelae of GVHD and conditioning toxicity in terms of quality of life and second malignancy remain considerable even in this group. Significant improvements in alternative donor SCT in FA have been reported, but these results are based on relatively few patients with still limited follow-up. Alternative donor SCT results in DBA appear unsatisfactory, but little experience with current regimens is reported. Both related and URD SCT for dyskeratosis congenita (DC) are associated with significant acute and chronic toxicity; similar to the situation with FA, SCT does not abrogate and may even exacerbate the other systemic complications of DC. Patients with SDS have also had excessive toxicity with SCT, although the outcome may be better for those with AA than those with hematologic malignancy.

The role of non-SCT supportive therapies is similar to that in SAA, requiring careful attention to blood products, iron and infectious propensity. This is similarly true for patients with DBA. The consequences of transfusion- and steroid-related toxicity have been clarified and need to be integrated into decision-making and subsequent management. For example, prospective counseling around high-risk activities (e.g., use of sunscreen, sexual transmission of papilloma virus) and the need for cancer screening are an extremely important component of care for patients with FA.

The non-hematological management of congenital marrow failure patients is also being informed by the improved patient recognition and characterization discussed above. Awareness of these non-hematologic issues, many of which are critical for maximal functioning and quality of life, falls squarely upon the hematologist as few other specialists have sufficient exposure to patients with these
diagnoses to spontaneously initiate appropriate evaluations or follow-up. Liaisons with other subspecialists, including adult head and neck specialists in the case of DC and FA, is critical in effecting the most appropriate management of these complex patients.

Thus, we are now in an era in which there is a richness of available detail regarding the natural history of patients with increasingly well understood, or at least classifiable, disorders. The availability of longitudinal clinical data for both acquired and congenital disease patients in concert with molecular and cytogenetic information provides an enormous resource that should rationalize the evaluation and management and assist hematologists in advocacy for this very complex patient group.

References


