Despite improvements in our understanding of transplant immunology and clinical and supportive care, acute graft-versus-host disease (GVHD) remains a clinical challenge and a major cause of morbidity and mortality for patients after allogeneic hematopoietic stem-cell transplantation. While systemic corticosteroid is standard primary therapy for acute GVHD, there is no established standard treatment in the steroid-refractory setting. New generations of monoclonal antibodies, biologics, and chemotherapeutics with immunomodulatory effects have been developed over the past decade, and are being tested as novel therapies in this disease. Many of these agents – including, among others, mycophenolate mofetil, anti-tumor necrosis factor-α antibodies, denileukin diftitox, and anti-interleukin-2Rα-chain antibodies – have demonstrated promising activity in steroid-refractory acute GVHD. Despite the high response rates, however, long-term survival remains poor due to a high incidence of infections. The key to improving acute GVHD outcomes may, in fact, rest upon successful initial therapy, and timely taper of corticosteroids to promote healthier immune reconstitution. Clinical trials combining these newer agents with systemic corticosteroids as initial treatment are under way, and will determine whether fortifying initial therapy will indeed reduce the development of steroid-refractory GVHD and improve long-term outcomes. In this article, we review current and novel agents available for acute GVHD, and discuss newer investigational approaches – such as phototherapy and cellular therapies – in the management of this common transplant complication.

Key words: GVHD; BMT; stem cell transplant; HSCT.

As acute graft-versus-host disease (GVHD) is believed to be mediated by donor T cells that are co-infused with the stem-cell graft, therapeutic strategies for this condition have primarily targeted lymphocytes of the T lineage. However, the pathogenesis of acute

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GVHD is complex, and involves intricate interactions between cellular and cytokine components of the immune system. The current view of the pathogenesis of acute GVHD is that it involves three phases: (1) tissue damage from the conditioning regimen; (2) the donor T-cell activation phase; and (3) the inflammatory effector phase. Recent studies demonstrating the importance of chemokines and regulatory T cells (Tregs) in acute GVHD have added further complexity to this model. Within this context, clinical strategies that mitigate host tissue damage, down-regulate activated effector donor T cells, and reduce inflammatory cytokines in the early post-transplant period should be effective in treating or preventing this condition. Indeed, strategies based, at least in part, on this model have continued to aid in the development of newer agents with promise in acute GVHD. In this chapter we will review the current literature with regard to the initial and secondary treatments of acute GVHD, and discuss the role of supportive care in the management of patients with this disease.

PRIMARY THERAPY FOR ACUTE GVHD

As corticosteroids are lympholytic and inhibit inflammatory cytokine cascades, this class of drugs is considered standard primary therapy for acute GVHD. The dose and route of administration of corticosteroids may vary depending on the organs involved and the severity of the GVHD. For example, isolated cutaneous GVHD with less than 50% body surface area involvement (stage-I or -II skin disease, overall grade-Ia or -Ib acute GVHD) can usually be treated with the topical medium- or high-potency glucocorticoid creams alone. However, individuals with multi-organ involvement, as well as individuals with over 50% body surface cutaneous involvement, require systemic administration to achieve adequate GVHD control. There is also some variability among investigators and transplant centers regarding the starting dose of corticosteroids to be used, particularly in early-stage GVHD. The recommended initial dose of corticosteroids for moderate to severe (grade-II–IV) acute GVHD is 2 mg/kg/day of methylprednisolone or an equivalent steroid. The response rate to single-agent corticosteroid therapy, when analyzed in large retrospective reviews, is approximately 50%. Doses >2 mg/kg/day have not been associated with improvement in response rates. In a prospective trial comparing methylprednisolone at 2 mg/kg/day with 10 mg/kg/day in 94 patients with grade-II–IV acute GVHD, response rates, progression to grade-III–IV disease, non-relapse mortality and overall survival were similar in both treatment groups. Treatment is generally continued in responders for at least 1–2 weeks before a gradual taper is initiated. The pace of the steroid taper should generally be no greater than a 10% reduction/week. However, this could be modified by factors such as the durability of the response to corticosteroids and the toxicity of high-dose steroid administration. Despite an initial response, many patients will experience a flare of their GVHD upon steroid taper, and the durability of response is often substantially lower. In acute GVHD developing after matched unrelated and related donor transplantation, durable remission of acute GVHD with steroid alone were reported in only 24% and 40% of patients, respectively.

It has long been recognized that the outcome of acute GVHD is correlated with the initial stage at presentation. Long-term survival for patients with grade-0–I disease approaches 50%, while for those with grade-IV disease the long-term survival rate has been reported to be as low as 11%. Response to initial treatment is a key predictor of outcome, as mortality in patients with grade-II–IV acute GVHD is lowest among those who fail to achieve a complete response to initial treatment. A very early response, as evidence by the ability to begin a steroid taper on day 5 of therapy,
has also been shown to be associated with a favorable prognosis; however, this study included patients with grade-I disease.\textsuperscript{11} It is possible that early responders do better at least in part because the steroid taper begins sooner and reduces the risk of complicating opportunistic infections, which are a common cause of death. In general, cutaneous disease responds promptly, but lower gastrointestinal and hepatic involvement responds poorly to therapy.\textsuperscript{5} Other risks for failure of initial therapy include early onset of GVHD, increasing human leukocyte antigen (HLA) disparity, and age.\textsuperscript{5,6}

The suboptimal response and long-term survival associated with corticosteroids alone has prompted investigation of additional immunosuppressive agents in the initial therapy of acute GVHD. Unfortunately, this strategy has generally been unsuccessful, as the benefit of better initial GVHD control is often offset by a greater risk of infection or other side-effects, thus resulting in no net survival benefit. The most widely studied agent in this context is anti-thymocyte globulin (ATG). In single-arm phase-II studies, Dugan et al reported a response rate of 67% in patients treated with ATG and prednisone as initial therapy of acute GVHD\textsuperscript{12}, and Graziani et al reported a response rate as high as 80%.\textsuperscript{13} However, in a study randomizing patients to receive prednisolone/prednisolone ± equine ATG as initial therapy of grade-II–IV acute GVHD, there was no difference in response rates (76% in both arms) or survival at 1 and 2 years, but infectious morbidity, especially cytomegalovirus (CMV) disease and pneumonitis, was higher in the combined immunosuppression group.\textsuperscript{14}

Several biologic agents have been studied as an adjunct to corticosteroids as initial therapy for acute GVHD. Lee et al randomized 102 patients to receive the monoclonal anti-CD25 – the interleukin 2 (IL-2) receptor \(\alpha\) chain – antibody, daclizumab (1 mg/kg) on days 1 and 4, and weekly thereafter, or placebo in conjunction with corticosteroids. While response rates were similar in both groups (53 versus 51%), survival at 100 days and 1 year was inferior in the daclizumab group.\textsuperscript{15} A previous randomized study evaluating another antibody against the IL-2 receptor (BT563) also did not demonstrate an advantage over placebo when combined with prednisone and cyclosporine.\textsuperscript{16} In another randomized trial of 143 patients, methylprednisolone plus placebo yielded similar clinical results as methylprednisolone combined with a CD5-specific immunotoxin.\textsuperscript{17} Manifestations of acute GVHD responded more quickly in the immunoconjugate arm, but benefits were not durable. Finally, Uberti et al reported a 75% response rate in 20 patients with biopsy-proven acute GVHD when etanercept, a recombinant tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)) receptor fusion protein capable of neutralizing TNF, was given in conjunction with corticosteroids with tacrolimus.\textsuperscript{18} However, this was a small uncontrolled study that is subject to selection bias, especially since a majority of patients had grade-II GVHD after related donor transplantation.

While none of these studies to date has deposed corticosteroids alone as standard initial therapy of acute GVHD, there remains great interest in the transplant community to find better adjunctive treatments to corticosteroids as the initial treatment of this disease. Towards this effort, the Bone Marrow Transplant Clinical Trials Network is conducting a large multicenter randomized phase-II trial evaluating four promising novel agents with activity in acute GVHD (denileukin diftitox, etanercept, mycophenolate mofetil and pentostatin) in combination with corticosteroids for the initial therapy of acute GVHD. This study may identify of a new treatment combination for acute GVHD to be validated in future phase-III trials.

An alternative adjunctive strategy that has attracted recent attention is the incorporation of topical steroid therapy as an adjunct to systemic corticosteroids as treatment of intestinal acute GVHD. In a randomized placebo-controlled trial involving 129 patients with gastrointestinal acute GVHD, 62 patients were randomized to receive
oral beclomethasone (oral BDP 8 mg/day) with systemic corticosteroids, and 69 were randomized to receive systemic corticosteroids with placebo. Prednisone was tapered starting on day 10 if clinical improvement was observed. The risk of treatment failure at days 50 and 80 was reduced in the BDP arm, and there was a significant reduction in mortality (hazard ratio 0.30, \( P = 0.03 \)) at day 200 in favor of the group receiving oral BDP. Aside from adrenal axis suppression, no significant adverse reactions or increase in infection rates were observed with the combination of oral BDP plus prednisone. These results suggest that oral high-potency steroid therapy with BDP can limit intestinal epithelial injury and allow for earlier withdrawal of systemic corticosteroid treatment. Further studies with topical high-potency steroid agents are warranted to confirm these results and assess the durability of these GVHD responses.

SECONDARY THERAPY FOR ACUTE GVHD

There is currently no established consensus for defining failure of primary therapy in acute GVHD. A set of criteria common to some clinical trials define steroid-refractory acute GVHD as: (1) progression after 3 days; (2) no change after 5–7 days; or (3) incomplete response after 14 days of steroid treatment with methylprednisolone at a dose of 2 mg/kg/d or equivalent. For patients with steroid-refractory GVHD, there is no clear standard for salvage treatment, and survival remains poor despite seemingly high response rates to certain second-line therapeutic agents. It is important to note that the pace of response to primary therapy varies depending on the organ(s) involved. While erythematous cutaneous acute GVHD may show improvement in 24 h after initiation of therapy, it is exceedingly unlikely that intestinal or hepatic GVHD would respond within the same time frame. Table 1 provides a summary of therapeutic agents available for the treatment of steroid-refractory acute GVHD.

Biologic agents targeting T lymphocytes

Antithymocyte globulin

The agent traditionally most commonly employed in steroid-refractory GVHD is anti-thymocyte globulin (ATG). ATG use has been associated with response

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<th>Table 1. Therapeutic agents in steroid-refractory acute graft-versus-host disease (GVHD).</th>
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PUVA, psoralen and ultraviolet irradiation.

\(^{a}\) Not commercially available.
rates of 30–54%, with responses of 60–75% in cutaneous GVHD. However, these responses have not translated into a reduction in mortality, as 1-year overall survival in this population is only about 10%, primarily as a result of infections, lymphoproliferative disease associated with Epstein–Barr virus (EBV), and other consequences of severe immune suppression.23–25 As such, it is possible that survival may be improved if the ATG is administered earlier in the course of the GVHD.26 Despite its popularity as an agent in steroid-refractory GVHD, there is great variation in clinical practice with regard to this agent. In a survey of transplant centers worldwide that routinely employ ATG for steroid-refractory GVHD, Hsu and colleagues found that there are 14 different formulations of ATG (equine or rabbit), and that the dose and schedule of ATG is highly variable from center to center. Furthermore, only 6–24% of transplant centers administered ATG at doses and schedules as reported in the literature. This variation in clinical practice, along with the inconsistent titers among different brands or lots of ATG, render the use of ATG problematic in steroid-refractory GVHD, and points to the need for better, more consistent agents for this condition.

**Anti-T-cell monoclonal antibodies**

The monoclonal murine anti-CD3 antibody, OKT3, is one of the earlier monoclonal antibodies found to be effective as second-line therapy for GVHD.27 The benefit of OKT3 is offset by toxicity, including a cytokine release syndrome28 and a higher-than-anticipated risk of EBV-associated lymphoproliferative disease.29 In a recent trial of OKT3 with high-dose methylprednisolone (10 mg/kg), in comparison with high-dose methylprednisolone alone, the response rate to the combination was higher (53% versus 33%); however, this did not result in an improvement in overall survival at 1 year (45% versus 36%, \( P = 0.41 \)).30 To minimize cytokine release, a humanized anti-CD3 antibody that does not bind the human Fc receptor, visilizumab (HuM291), was developed and tested in the setting of steroid-refractory GVHD. In a phase-I study, pharmacokinetic studies demonstrated significant accumulation and delayed clearance of visilizumab after multiple daily dosing, resulting in prolonged lymphopenia and high rates of infection and EBV-associated lymphoproliferative disorder. Subsequently, a single infusion schedule of 3 mg/m² was adopted in a cohort of 11 patients, with six (67%) patients achieving a complete response (CR). However, toxicity remained problematic, as four patients died from infections or EBV-associated lymphoproliferative disorder.31 In a follow-up phase-II study of 44 patients, the overall response to visilizumab was 32% at 7 weeks, and overall survival was 32% at 6 months.32 In both studies, the incidence of EBV reactivation was between 40–50%.

In a multicenter trial, investigators from Seattle have also tested a murine IgM monoclonal antibody against CD147 – known as ABX-CBL – in patients with steroid-refractory GVHD. ABX-CBL targets neurothelin, a glycoprotein weakly expressed on leukocytes that is up-regulated in activated B and T lymphocytes, monocytes, and dendritic cells.33 In a phase-I trial of 59 patients treated with ABX-CBL, the most common toxicity was myalgias, and extended overall responses lasting at least 14 days were achieved in 41%, with overall survival of 30%, which was better than a historical control group treated with equine ATG.33 Based on this pilot study, a recent phase-II/III study was performed comparing ABX-CBL with ATGAM in 92 patients with steroid-refractory acute GVHD, but no difference in response rate or day 180 survival was detected.34
In an attempt to target activated T cells, biologic therapies directed against the \( \alpha \)-subunit of the IL-2 receptor (CD25) have been studied extensively as treatment for acute GVHD. The first antibody (anti-Tac antibody) was reported in 1981\textsuperscript{35,36}, however, the humanized form (daclizumab), first reported upon in 1989\textsuperscript{37}, is used more commonly today. The original trials of anti-Tac and other anti-IL-2 monoclonal antibodies yielded similar results, with complete responses noted in 10–65% of treated patients\textsuperscript{38–42}. The largest of these trials, which evaluated 85 patients treated with the murine antibody BT563 (inolimomab), demonstrated a complete response in 29% and a partial response in an additional 34%, for an overall response rate of 63%.\textsuperscript{42} Three phase-II trials of the humanized form of the IL-2 receptor \( \alpha \)-chain antibody, daclizumab, have been published for steroid-refractory acute GVHD. In the original phase-I/II trial, daclizumab was associated a response rate of 40%, with a predilection for improvement in cutaneous and gastrointestinal disease.\textsuperscript{43} A subsequent study reported a response rate of 50% in a small cohort of patients with grade-III–IV acute GVHD.\textsuperscript{44} In the largest series reported, daclizumab demonstrated a complete response rate of 29% for patients treated weekly for 5 consecutive weeks, and a complete response rate of 47% for patients treated on a more accelerated schedule (1 mg/kg on days 1, 4, 8, 15 and 22).\textsuperscript{45} A chimeric murine/human monoclonal IL-2 receptor antibody, basiliximab, has also been used in steroid-refractory acute GVHD. In phase-II studies using different doses and schedule of basiliximab, the overall response rate was uniformly high (71–82.5%), with the complete response rate varying between 17.5% and 53%.\textsuperscript{46–48}

In an effort to target T cells as well as antigen-presenting cells, the monoclonal antibody against CD52, alemtuzumab, has also been reported to be effective as therapy of steroid-refractory acute GVHD.\textsuperscript{49–52} Because alemtuzumab also depletes donor and host B lymphocytes, the risk of EBV reactivation and post-transplant lymphoproliferative disorder is low.\textsuperscript{53} However, depending on the dose employed, the risks of CMV reactivation and other infection may remain substantial.\textsuperscript{54}

Alefacept (Amevive), a novel fusion protein composed of the extracellular CD2-binding domain of the human leukocyte function antigen-3 (LFA-3) fused with the Fc portion of IgG1, has selective activity against human memory T cells. Given its activity in psoriasis and other T-cell-mediated autoimmune diseases, alefacept has attracted interest as a potential therapeutic agent in acute GVHD. Two small case series totaling 10 patients have been reported with alefacept, with encouraging GVHD responses and few immediate side-effects.\textsuperscript{55,56} However, late complications from fungal and viral infections were observed.\textsuperscript{55}

**Immunotoxin/conjugates**

Denileukin diftitox (Ontak) is a newer biologic toxin conjugate that targets activated T cells through its affinity for the high-affinity IL-2 receptor. Approved by the Food and Drug Administration (FDA) for the treatment of CD25\( ^+ \) cutaneous T-cell lymphoma, denileukin diftitox is a genetically engineered recombinant protein composed of human IL-2 fused to the membrane translocation and catalytic domains of diphtheria toxin. In a phase-I study of Ontak in steroid-refractory acute GVHD, 71% of patients had a clinical response to therapy, with 46% of patients achieving a complete response at the maximum tolerated dose level of 9 \( \mu \)g/kg administered on days 1, 3, 5, 15, 17 and 19.\textsuperscript{57} Dose-limiting toxicity was hepatic transaminase elevation, which was transient, and generally peaked about 1 week after administration. Infusion reactions and vascular leak syndrome were also reported, and could be mitigated by steroid
premedication. A similar dose-escalation trial that administered 4.5 μg/kg daily for 5 days followed by weekly therapy for 1 month showed a complete response rate of 41% at 36 days.58

Cytokine blockade

A different approach to therapy of steroid-refractory acute GVHD is to target the inflammatory cytokines that lead to inflammation and T-cell activation and proliferation, with TNF-α having been the primary successful target to date. Two different commercially available agents that target TNF-α have reported activity in steroid-refractory GVHD. Etanercept (Enbrel), a genetically engineered molecule comprising two p75 extracellular domains of the human TNF-α fused with human IgG1, has been tested in steroid-refractory GVHD. Busca et al treated 13 patients with steroid-refractory acute GVHD with 25 mg of etanercept administered subcutaneously twice weekly for 4 weeks. Six of the 13 patients responded (46%), with five of six responses being complete.59 Combination therapy with daclizumab and etanercept has been reported, with a response rate of 66%.60 A recent retrospective study of 16 patients given ATG in combination with etanercept for steroid-refractory visceral acute GVHD suggested that the addition of etanercept improved overall response rate and survival compared to historical patients treated with ATG.61 The chimeric antibody, infliximab, has been used more extensively than etanercept. The antibody both neutralizes TNF-α and lyses cells that produce it. Initial case series and dose-escalation trials documented the potential effectiveness of this agent62–65, and larger series confirmed that this drug may be effective, with response rates of 59–67% noted, with a predilection for improvement in gastrointestinal GVHD.66,67 A high incidence of invasive fungal infection has been noted following infliximab therapy.67,68

Chemotherapy

The T-cell cytotoxic agent pentostatin has been used as therapy in steroid-refractory acute GVHD. The accumulation of 2'-deoxyadenosine 5'-triphosphate after pentostatin administration leads to impaired growth and apoptosis of dividing lymphocytes. In a phase-I dose-escalation study, the MTD was determined to be 1.5 mg/m², and the complete response rate was 63%.69 Reduction of pentostatin dosing was required in patients with renal dysfunction. Aside from prolonged lymphopenia and a suggestion of higher risk for CMV and other viral infections, pentostatin was well tolerated in these GVHD patients. Despite the encouraging response rate, only 26% were alive at 1-year follow-up.

Mycophenolate mofetil (MMF) is another agent commonly used in the treatment of steroid-refractory GVHD. Similarly to pentostatin, MMF suppresses T-cell proliferation by reversibly inhibiting the synthesis of the purine guanosine triphosphate. Basara et al initially reported a 65% response rate in 17 patients with steroid-refractory acute GVHD and updated the series to include 36 patients.70,71 Similar response rates were noted in other small studies.72,73 Common toxicities associated with MMF administration include nausea, diarrhea, myelosuppression, and opportunistic infections.74

Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is a T-cell immunosuppressant via a reduction in DNA transcription, DNA translation, protein
synthesis and cell cycling. Sirolimus may also be immunosuppressive through the maintenance of regulatory T-cell populations and via inhibition of dendritic-cell activity through a reduction in antigen uptake, cellular maturation, intracellular signaling, and apoptosis induction. Benito et al reported that 12 of 21 steroid-refractory patients (57%) had an objective response to sirolimus (5 complete response, 7 partial response) given daily to achieve a target serum trough level of 17–25 ng/mL. Perhaps reflecting the higher drug levels used, toxicity was high in this series, including thrombotic microangiopathy, cytopenias, and hypertriglyceridemia. Whether sirolimus administered at lower doses (serum target 3–12 ng/mL), which is well tolerated and effective in the GVHD prophylaxis setting, is effective in the treatment of steroid-refractory acute GVHD needs further investigation.

**Phototherapy**

An alternative approach employs use of ultraviolet A with a psoralen sensitizer to control refractory cutaneous GVHD, where high response rates have been noted. More interest has focused on extracorporeal photopheresis (ECP) in management of refractory acute GVHD. Postulated mechanisms of action of ECP, in addition to apoptosis of treated lymphocytes, include a decrease in the production of pro-inflammatory cytokines and an increase in production of anti-inflammatory cytokines, both of which lead to a lower ability to stimulate T-cell responses. In addition, ECP may help eliminate CD8+ T effector cells while inducing regulatory T cells. In a series of 59 patients who received ECP as therapy of steroid-refractory grade-II–IV acute GVHD, Greinix et al reported complete response rates of 82%, 61%, and 61% for skin, liver, and intestinal disease. Furthermore, patients achieving CR after ECP had significantly better 4-year overall survival (59% versus 11%) compared to those who did not achieve a CR.

**Cellular therapy**

The use of cellular therapy to treat resistant acute GVHD has now been explored. Mesenchymal stem cells (MSCs) are immunosuppressive or immunomodulatory, and transplantation of these cells from haploidentical or third-party donors has been shown to improve GVHD in experimental models. The first report of haploidentical MSC infusion for therapy of resistant acute GVHD was by LeBlanc et al, who reported a single successful outcome. Since then, other case series reporting the successful use of MSCs in resistant visceral acute GVHD have been reported, the largest being a report where six of eight treated patients with grade-III–IV aGVHD responded to one or two infusions of MSCs. Multicenter clinical trials are now ongoing to confirm the activity of expanded third part MSCs as potential therapy in acute GVHD.

**Directed organ therapy**

Other experimental approaches under investigation in refractory acute GVHD include intra-arterial administration of steroid or methotrexate for gastrointestinal and hepatic GVHD. There is also evidence that topical therapy with oral non-absorbable corticosteroids —either beclomethasone or budesonide — may be of value in patients with gastrointestinal acute GVHD.
Supportive care

In addition to immunosuppressive therapy, supportive care is critical for the favorable outcome of acute GVHD. Organ-specific supportive measures for the skin include the use of topical emollient therapy and meticulous wound care, up to and including care in a burn unit. For the gastrointestinal tract, bowel rest and hyperalimentation are required. Anti-motility agents such as loperamide are often employed. Octreotide or other somatostatin analogs may be of benefit in controlling the secretory component of gastrointestinal GVHD. Development of bloody diarrhea often requires transfusion support, and should trigger further pathologic investigation to rule out secondary processes such as infectious colitis, CMV or adenovirus, or possible superimposed intestinal thrombotic microangiopathy. The use of ursodeoxycholic acid has been advocated as a supportive measure since it is associated with a reduction in hepatic acute GVHD in a randomized prophylaxis trial.

In light of the fact that a majority of patients with steroid-refractory GVHD will succumb to infection, systematic monitoring and judicious use of antibiotics for prophylaxis against infectious pathogens is paramount. Standard infection prophylaxis in patients with GVHD should include trimethoprim–sulfamethoxazole or equivalent agents to prevent Pneumocystis jirovecii pneumonia, and acyclovir to prevent herpesvirus reactivation. Routine serum viral load monitoring for viruses – including CMV, adenovirus, and EBV – is recommended. CMV or EBV reactivation should be treated preemptively to prevent progression to end-organ disease and post-transplant lymphoproliferative disorder. Finally, serial monitoring of serum galactomannan and β-glucan levels may be helpful to detect incipient invasive fungal disease. For patients who have steroid-refractory GVHD, especially those with intestinal involvement who are at risk for translocation of bacteria and fungi into the systemic circulation, empiric prophylaxis with broad-spectrum antibiotics and extended-spectrum antifungal agents, including voriconazole or posaconazole, or echinocandins with activity against Aspergillus species and other invasive molds, is recommended. The development of these sensitive tests for early detection of viruses and fungal infections, together with the arrival of novel extended-spectrum antibiotics and antifungal therapies, represent a major advance in transplant ancillary care, and should improve the clinical outlook for patients with acute GVHD.

SUMMARY

Despite improvements in transplant medicine and supportive care, acute GVHD remains the cardinal complication of allogeneic hematopoietic stem-cell transplantation. While our understanding of the pathophysiology of acute GVHD has improved and newer therapeutic agents have emerged over the past decade, our track record for treating this disease remains unsatisfactory. Corticosteroids are still the standard primary therapy for acute GVHD, and combination of secondary agents with corticosteroids in the primary treatment setting have, to date, failed to improve survival outcomes. Nonetheless, it is crucial that we continue to test new agents as adjuncts to corticosteroids in the up-front setting to prevent the development of steroid-refractory GVHD, since the latter is associated with extremely high mortality. The multicenter randomized trial testing the addition of MMF, pentostatin, denileukin diftitox, or etanercept in combination with corticosteroids for initial treatment of GVHD through the BMT Clinical Trials Network in North America
represents one such effort, and may eventually lead to a change in our treatment paradigm for this disease.

REFERENCES


