Infections in Patients with Multiple Myeloma in the Era of High-Dose Therapy and Novel Agents

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The introduction of stem cell transplantation and the novel anti-myeloma agents, bortezomib, thalidomide, and lenalidomide, have improved the outcome of patients with multiple myeloma. These advances have transformed myeloma into a chronic condition, with multiple relapses and salvage therapies, all of which result in cumulative immunosuppression and higher risk of infection.

In addition to the immunodeficiency related to myeloma and its complications, the type of anti-myeloma therapy used also plays a role in the development of infection. Therapy with bortezomib increases the risk for reactivation of herpes simplex and herpes zoster viruses, whereas the application of stem cell transplantation has broadened the spectrum of infection to include those caused by Clostridium difficile, cytomegalovirus, and opportunistic moulds. Key to the management of infection is the understanding of the specific risk factors and periods during which patients are at risk; this allows the anticipation of the likely pathogen(s) and the application of risk-adjusted prophylactic and treatment strategies.

MULTIPLE MYELOMA

Multiple myeloma has an annual incidence of 4.3 cases per 100,000 persons, with 15,000 new cases per year in the United States alone [1]. In the past decade, substantial progress in the treatment of myeloma has occurred, with a favorable impact on survival [2]. These advances include high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HCT), allogeneic HCT, and the most recently introduced drugs, bortezomib and the immunomodulatory agents thalidomide and lenalidomide [3]. These therapeutic strategies impact differently on the immune system, predisposing patients to various opportunistic infections. However, little has been reported on the prevention and management of infection associated with these novel forms of therapy.

RISK FACTORS FOR INFECTION

Infection is a significant cause of morbidity and the leading cause of death in patients with myeloma [4–6]. The increased susceptibility of patients with myeloma to infection results from the interplay between antineoplastic therapies and age- and disease-related complications (Table 1).

Myeloma-related innate immunodeficiency involves various arms of the immune system and includes B cell dysfunction (manifested as hypogammaglobulinemia), numerical and functional abnormalities of dendritic cells [3] and T cells (inversion of CD4:CD8 ratio [4], abnormal Th1/Th2 CD4+ ratio [5], and severe disruption of global T cell diversity [39]), and dysfunction of natural killer cells [40]. Although it remains unclear which mechanism is most relevant in vivo to the risk of infection, polyclonal hypogammaglobulinemia has been classically associated with infection by encapsulated bacteria, such as Streptococcus pneumoniae [6] and Haemophilus influenzae [41].

Myeloma and treatment-associated organ dysfunctions and comorbidities also increase the risk of infection. These dysfunctions and comorbidities include (1) renal failure (cast nephropathy, hypercalcemia, deposition disease, and others) [11, 39, 42]; (2) respiratory...
<table>
<thead>
<tr>
<th>Risk factor(s)</th>
<th>Effect(s) on the immune system</th>
<th>Pathogen(s) and/or infection(s)</th>
<th>Monitoring and/or prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease and receipt of MP-based regimens</td>
<td>Hypogammaglobulinemia</td>
<td>Encapsulated bacteria, <em>Staphylococcus aureus</em>, enterobacteriaceae, <em>Pseudomonas aeruginosa</em></td>
<td>Monitor serum Ig levels; antimicrobial prophylaxis against encapsulated and other bacteria (FQ, TMP-SMX)</td>
</tr>
<tr>
<td>Active disease and receipt of MP-based regimens</td>
<td>Neutropenia (neutrophils &lt;10% at diagnosis)</td>
<td>Bacteremia, pneumonia, sinusitis, otitis, meningitis</td>
<td>Consider vaccinating patients against <em>Haemophilus influenzae</em>; consider IVIG if serum IgG level &lt;500 mg/dL and recurrent serious infection despite prophylactic antibiotics</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Decrease in neutrophil function, CMI, and expression of TLR-4</td>
<td>Various infections; renal failure is an independent risk factor for infection in the first 2–4 months</td>
<td>Same as under active disease; immediate therapy for myeloma-related renal failure; avoid and treat conditions that may cause or worsen renal failure</td>
</tr>
<tr>
<td>Dexamethasone-based regimens</td>
<td>Decrease in CMI; severe hyperglycemia</td>
<td>Bacteria (encapsulated bacteria, <em>S. aureus</em>, enterobacteriaceae, <em>P. aeruginosa</em>); viruses (CMV, HSV, VZV, respiratory viruses); fungi (mucosal candidiasis, PJP); mycobacteria (tuberculosis); endemic infections</td>
<td>Same as during active disease; control of glycemia; prophylaxis for PJP (TMP-SMX), <em>Candida</em> species ( clotrimazole, fluconazole), influenza viruses (neuraminidase inhibitor during influenza season), HSV, VZV (acyclovir, valaciclovir, famciclovir)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Stimulation of T cells; increase in production of IL-2 and IFN-γ; increase in virus-specific CD8+ T cells, cytokine production, and cytotoxicity; stimulation of NK cells</td>
<td>No increased risk of infection [8, 16, 17]; potential risk factors include peripheral neuropathy, DVT at site of venous catheter [18]</td>
<td>Unclear whether antimicrobial prophylaxis needed; DVT prophylaxis (low-molecular weight heparin, aspirin, others)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Mild neutropenia; decrease in T cell proliferation; number and function of NK and CD8+ T cells; inhibition of function and viability of dendritic cells; alteration of cytokine secretion</td>
<td>Increase in HSV and VZV infections [26]; other infections similar to those observed with dexamethasone-based regimens</td>
<td>Same as active disease and dexamethasone-based regimens, with emphasis on prophylaxis against <em>Streptococcus pneumoniae</em> and influenza virus; closely monitor for skin lesions suggestive of VZV infection</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>...</td>
<td>When combined with dexamethasone, increase in bacterial infections in patients with relapsed myeloma [27, 28]</td>
<td>Adjust dose of lenalidomide in presence of renal dysfunction to avoid excessive myelotoxicity</td>
</tr>
<tr>
<td>Conditioning regimen for HCT, pre-engraftment</td>
<td>Neutropenia and severe alimentary tract mucositis; increase in infection in those with MBL deficiency</td>
<td>Enterobacteriaceae, <em>P. aeruginosa</em>, <em>Staphylococci</em>, streptococci, fungi (<em>Candida</em> and <em>Aspergillus</em> species); bacteria, pneumonia, colitis (<em>Clostridium difficile</em>)</td>
<td>Same as active disease and dexamethasone-based regimens; for mucositis suggest oral/dental hygiene, cryotherapy, laser therapy</td>
</tr>
</tbody>
</table>
compromise, caused by collapse of thoracic vertebra and opiate therapy (which may depress the central nervous system) given to patients with painful fractures [40]; (3) severe alimentary mucosal damage (caused by chemotherapy, radiation therapy, or graft-versus-host disease [43–45]); (4) hyperglycemia induced by dexamethasone [46]; (5) transfusional iron overload [34, 47]; and (6) the multisystem involvement by myeloma-associated deposition diseases (AL-amyloidosis and light chain deposit disease [48]).

Moreover, the prolonged survival resulting from novel therapies has transformed myeloma into a chronic condition [49], with multiple relapses and salvage therapies, all of which result in cumulative immunosuppression and higher risk for infection. Indeed, levels of CD4⁺ T cells, particularly naive and activated subsets, decrease significantly with increasing cycles of chemotherapy, a decrease strongly associated with opportunistic infections [50].

Finally, myeloma typically affects an older population, with a median age of 62–73 years [51]. These patients frequently experience an age-related decline in physiologic reserve of various organs and from other age-related conditions, including frailty, geriatric syndromes, cognitive dysfunction, and social isolation [52], all of which may increase the risk of infection.

Compared with therapy with oral melphalan plus prednisone-based regimens, current therapies (autologous and allogeneic HCT and the novel agents thalidomide, lenalidomide, and bortezomib) have improved the outcomes of patients with myeloma [49]. These therapies impact the immune system differently [14], and their application has resulted in the emergence of infections not previously associated with myeloma, such as those caused by cytomegalovirus (CMV) [15], Aspergillus species [53], Fusarium species [54], herpes simplex virus (HSV), and varicella-zoster virus (VZV) [26], the prevalence of the latter 2 significantly increased following treatment with bortezomib [55] (Table 1) [13–15, 20–22, 26, 56–62]. Although the newer agents are relatively well tolerated, their use has resulted in additional complications that may predispose recipients to infection, such as deep venous thrombosis (thaldomidomide, lenalidomide) and peripheral neuropathies (thalidomide, lenalidomide, and bortezomib) [25]. Indeed, the presence of deep venous thrombosis at the site of a central venous catheter increases the risk of septic thrombophlebitis following bacteremia [23, 63], and peripheral neuropathies increase the risk of trauma and soft-tissue infection, which may progress to osteomyelitis [24].

**OVERVIEW OF THE INFECTIOUS COMPLICATIONS IN PATIENTS WITH MULTIPLE MYELOMA**

Infections following therapy for multiple myeloma are variable and depend on the remission status of the underlying disease,
Table 2. Grade 3 and 4 Infection with Various Therapies in Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Treatment/patient group, study</th>
<th>Study design, no. of patients</th>
<th>Regimen</th>
<th>Dose-schedule</th>
<th>Rate of infection</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone, untreated patients*</td>
<td>RCT, 127</td>
<td>MP vs dexamethasone vs melphalan plus dexamethasone vs IFN-α plus dexamethasone; every 6 weeks</td>
<td>40 mg/day; cycles 1–2: days 1–4, 9–12, 17–20; cycles 3–12: days 1–4</td>
<td>11% with dexamethasone vs 10% with MP</td>
<td>...</td>
</tr>
<tr>
<td>Facon [64]</td>
<td>RCT, 127</td>
<td>Dexamethasone vs dexamethasone-thalidomide; every 4 weeks</td>
<td>40 mg/day; 4 cycles: days 1–4, 9–12, 17–20</td>
<td>NR</td>
<td>...</td>
</tr>
<tr>
<td>Rajkumar [38]</td>
<td>RCT, 102</td>
<td>Dexamethasone vs dexamethasone-thalidomide; every 4 weeks</td>
<td>40 mg/day; cycles 1–4: days 1–4, 9–12, 17–20; subsequent cycles: days 1–4</td>
<td>6% with dexamethasone vs 7% with dexamethasone-thalidomide</td>
<td>...</td>
</tr>
<tr>
<td>Rajkumar [65]</td>
<td>RCT, 234</td>
<td>Dexamethasone vs dexamethasone-thalidomide; every 4 weeks</td>
<td>40 mg/day; cycles 1–4: days 1–4, 9–12, 17–20; subsequent cycles: days 1–4</td>
<td>16% with high dexamethasone vs 8% with low dexamethasone</td>
<td>...</td>
</tr>
<tr>
<td>Rajkumar [66]</td>
<td>RCT, 220 vs 223</td>
<td>Lenalidomide plus dexamethasone high vs lenalidomide plus dexamethasone low; every 4 weeks</td>
<td>High dexamethasone: days 1–4, 9–12, 17–20; low dexamethasone: days 1, 8, 15, 22</td>
<td>6% with dexamethasone vs 11% with lenalidomide-dexamethasone</td>
<td>...</td>
</tr>
</tbody>
</table>

Dexamethasone, relapsed patients

<table>
<thead>
<tr>
<th>Treatment/patient group, study</th>
<th>Study design, no. of patients</th>
<th>Regimen</th>
<th>Dose-schedule</th>
<th>Rate of infection</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimopoulos [28]</td>
<td>RCT, 175</td>
<td>Dexamethasone vs lenalidomide-dexamethasone; every 4 weeks</td>
<td>Dexamethasone 40 mg/day; cycles 1–4: days 1–4, 9–12, 17–20; subsequent cycles: days 1–4</td>
<td>6% with dexamethasone vs 11% with lenalidomide-dexamethasone</td>
<td>...</td>
</tr>
<tr>
<td>Weber [27]</td>
<td>RCT, 175</td>
<td>Dexamethasone vs lenalidomide-dexamethasone; every 4 weeks</td>
<td>Dexamethasone 40 mg/day; cycles 1–4: days 1–4, 9–12, 17–20; subsequent cycles: days 1–4</td>
<td>12% with dexamethasone vs 21.5% with lenalidomide-dexamethasone</td>
<td>...</td>
</tr>
</tbody>
</table>

* Dexamethasone appears to pose the same risk of infection as does MP; lowering the dose of dexamethasone may decrease the rates of infection.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richardson [67]</td>
<td>RCT, 332</td>
<td>Dexamethasone vs bortezomib; every 4 weeks</td>
<td>Dexamethasone 40 mg/day; cycles 1–4: days 1–4, 9–12, 17–20 every 7 weeks; cycles 5 to 9: days 1–4</td>
<td>16% with dexamethasone vs 13% with bortezomib</td>
</tr>
</tbody>
</table>

### Thalidomide, untreated patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo [17]</td>
<td>RCT, 129</td>
<td>MP vs MPT</td>
<td></td>
<td>2% with MP vs 10% with MPT</td>
</tr>
<tr>
<td>Facon [16]</td>
<td>RCT, 124</td>
<td>MP vs MPT</td>
<td>Variable, not exceeding 400 mg/day</td>
<td>9% with MP vs 13% with MPT</td>
</tr>
<tr>
<td>Rajkumar [38]</td>
<td>RCT, 102</td>
<td>Dexamethasone vs dexamethasone-thalidomide</td>
<td>200 mg/day</td>
<td>NR</td>
</tr>
<tr>
<td>Rajkumar [65]</td>
<td>RCT, 234</td>
<td>Dexamethasone vs dexamethasone-thalidomide</td>
<td>50–200 mg/day</td>
<td>6% with dexamethasone vs 7% with dexamethasone-thalidomide</td>
</tr>
</tbody>
</table>

### Thalidomide, relapsed patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo [68]</td>
<td>Phase II, 24</td>
<td>MPT</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Gracia-Sanz [69]</td>
<td>Phase II, 71</td>
<td>Dexamethasone plus thalidomide plus cyclophosphamide</td>
<td>200–800 mg/day</td>
<td>7%</td>
</tr>
</tbody>
</table>

### Bortezomib, untreated patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Miguel [70]</td>
<td>RCT, 340</td>
<td>MP vs MP plus bortezomib</td>
<td></td>
<td>7% with MP vs 10% with MP plus bortezomib; VZV 4% with MP vs 13% with MP plus bortezomib; VZV infection rate reduced to 3% with prophylaxis</td>
</tr>
<tr>
<td>Mateos [55]</td>
<td>Phase I-II, 60</td>
<td>MP plus bortezomib</td>
<td></td>
<td>16%; VZV, 13% (7% with prophylaxis)</td>
</tr>
</tbody>
</table>

### Bortezomib, relapsed patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richardson [67]</td>
<td>RCT, 333</td>
<td>Bortezomib vs dexamethasone</td>
<td></td>
<td>13% with bortezomib vs 16% with dexamethasone; VZV, 13% with bortezomib vs 5% with dexamethasone</td>
</tr>
<tr>
<td>Palumbo [71]</td>
<td>Phase II, 64</td>
<td>Bortezomib plus dexamethasone plus doxorubicin</td>
<td>1.3 mg/m²</td>
<td>16%; VZV, 5% with prophylaxis</td>
</tr>
<tr>
<td>Palumbo [72]</td>
<td>Phase II, 30</td>
<td>MPT plus bortezomib</td>
<td></td>
<td>17%; VZV, 10% (none with prophylaxis)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Treatment</td>
<td>Dosage</td>
</tr>
<tr>
<td>-------</td>
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<td>--------</td>
</tr>
<tr>
<td><strong>Lenalidomide, untreated patients</strong>&lt;br&gt; Rajkumar [73]</td>
<td>RCT, 220 vs 223</td>
<td>Lenalidomide plus dexamethasone high vs lenalidomide plus dexamethasone low</td>
<td>25 mg/day</td>
<td>16% with high dexamethasone; 8% with low dexamethasone</td>
</tr>
<tr>
<td>Rajkumar [74]</td>
<td>Phase II, 34</td>
<td>Lenalidomide plus dexamethasone</td>
<td>25 mg/day</td>
<td>3%</td>
</tr>
<tr>
<td>Palumbo [75]</td>
<td>Phase II, 54</td>
<td>MP plus lenalidomide</td>
<td>5–10 mg</td>
<td>9%</td>
</tr>
<tr>
<td>Niesvizky [76]</td>
<td>Phase II, 72</td>
<td>Lenalidomide plus dexamethasone plus clarithromycin</td>
<td>25 mg/day</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Lenalidomide, relapsed patients</strong>&lt;br&gt; Richardson [77]</td>
<td>RCT, 102</td>
<td>Lenalidomide twice/day vs once/day</td>
<td>15 mg twice/day vs 30 mg once/day</td>
<td>1% (68 patients received dexamethasone)</td>
</tr>
<tr>
<td>Dimopoulos [28]</td>
<td>RCT, 176</td>
<td>Lenalidomide plus dexamethasone vs dexamethasone</td>
<td>25 mg/day</td>
<td>6% with dexamethasone vs 11% with lenalidomide plus dexamethasone</td>
</tr>
<tr>
<td>Weber [27]</td>
<td>RCT, 177</td>
<td>Lenalidomide plus dexamethasone vs dexamethasone</td>
<td>25 mg/day</td>
<td>12% with dexamethasone vs 21% with lenalidomide plus dexamethasone</td>
</tr>
<tr>
<td>Wang [78]</td>
<td>RCT, 353b</td>
<td>Lenalidomide plus dexamethasone vs dexamethasone</td>
<td>25 mg/day</td>
<td>8% with dexamethasone vs 15% with lenalidomide plus dexamethasone</td>
</tr>
</tbody>
</table>

**NOTE.** IFN, interferon; MP, melphalan-prednisone; MPT, melphalan-prednisone-thalidomide; NR, not reported; RCT, randomized clinical trial; VZV, varicella-zoster virus.

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*a* Prophylaxis with acyclovir.

*b* Reference [78] includes pooled results of other studies [27, 28].
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The first 2–4 months of treatment are associated with a greater risk of infection among patients treated with melphalan plus prednisone and high-dose dexamethasone–based regimens [83, 84]. When dexamethasone is used, infection caused by a depression of cell-mediated immunity is more likely to occur, including mucosal candidiasis, HSV or VZV infection, and others [64, 84, 85]. However, the overall infection rate with dexamethasone was similar to that with melphalan plus prednisone in a randomized controlled trial [64], although lower cumulative doses of dexamethasone (once a week) significantly decrease the incidence of grade 3–4 infection, compared with the usual high dose (3 cycles of 4 days each, every month) [66].

Thalidomide is not significantly myelotoxic [86] and exerts both immunomodulatory and immunosuppressive effects on T cells (Table 1) [21, 22, 60]. Overall, thalidomide does not increase the risk for infection in newly diagnosed patients, as shown in 2 randomized controlled trials of dexamethasone versus dexamethasone plus thalidomide [87] and melphalan plus thalidomide [88]. Conventional therapy is still used by some as primary treatment for patients who are not candidates for autologous HCT [82], although this practice is being supplanted by high-dose dexamethasone, usually in combination with thalidomide [2], and more recently by bortezomib, thalidomide, or lenalidomide alone or in combination with dexamethasone [2].

Table 3. Dosage schedule of Antimicrobial Agents Used in the Prophylaxis and Treatment of Infection in Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prophylaxis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenic</td>
<td>FO²</td>
<td>Antipseudomonal β-lactam antibiotic°²</td>
</tr>
<tr>
<td>Nonneutropenic</td>
<td>TMP-SMX 800 mg/160 mg orally daily [102] or daily FO³</td>
<td>Broad spectrum antibiotic (FO, β-lactam, other)²⁸; if FO not used in prophylaxis, add a FO² or macrolide° for pneumonia°²</td>
</tr>
<tr>
<td>CDAD</td>
<td>Consider metronidazole prophylaxis (500 mg orally 3× daily) if prior history of CDAD⁷</td>
<td>Metronidazole 500 mg orally 3× daily or vancomycin 125 mg orally 4× daily; treat for 2–4 weeks [103]</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Isoniazid 300 mg orally daily [104]</td>
<td>Various regimens [105]</td>
</tr>
<tr>
<td><strong>Fungal infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral and/or esophageal candidiasis</td>
<td>Clotrimazole troches (10 mg 5× per day) or fluconazole 100–200 mg orally daily [106]</td>
<td>Fluconazole 200–400 mg orally daily for 7–10 days [106]</td>
</tr>
<tr>
<td><strong>Viral infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Acyclovir 200–400 mg orally twice or 3× daily,³ valacyclovir 500 mg orally 3× daily,³ or famciclovir 500 mg orally 3× daily³ [107]</td>
<td>7–14 days of acyclovir 250 mg/m² IV 3× daily³ valacyclovir 1 g orally 3× daily,³ or famciclovir 500 mg orally 2× daily³ [107]</td>
</tr>
<tr>
<td>Herpes zoster virus</td>
<td>Acyclovir 400 mg orally twice or 3× daily,³ valacyclovir 500 mg orally 3× daily,³ or famciclovir 500 mg orally 3× daily³ [107]</td>
<td>7–14 days of acyclovir 500 mg/m² IV 3× daily,³ valacyclovir 1 g orally 3× daily,³ or famciclovir 500 mg orally 2× daily³ [107]</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Ganciclovir 5 mg/kg IV twice daily,³ or valganciclovir 900 mg/day orally,³ or foscarnet 60 mg/kg IV twice daily³ [107]</td>
<td>14–21 days of ganciclovir IV 5 mg/kg IV twice daily,³ or valganciclovir 900 mg/day orally twice daily,³ or foscarnet 90 mg/kg IV twice daily [107]</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Oseltamivir 75 mg orally twice daily for the duration of the Influenza season [107]</td>
<td>Oseltamivir 75 mg orally twice daily for 5–7 days [107]</td>
</tr>
</tbody>
</table>

**NOTE.** Unless otherwise stated, the duration of treatment depends on clinical response and persistence or resolution of immunosuppression. CDAD, Clostridium difficile–associated diarrhea; FO, fluoroquinolone; IV, intravenously; TMP-SMX, trimethoprim-sulfamethoxazole.

a Includes ciprofloxacin 500 mg orally twice daily, levofloxacin 500 mg orally daily, moxifloxacin 400 mg orally daily, and others.

b Recommendation based on randomized trial.

c Antipseudomonal β-lactam antibiotics: ceftazidime, cefepime, piperacillin-tazobactam, imipenem, or meropenem.

d Recommendation based on cohort studies or case series.

e Erythromycin 500 mg orally twice daily, azithromycin 400 mg/day orally or IV, clarithromycin 500 mg twice daily orally or IV.

f Recommendation based on expert advice.

g Oseltamivir-resistant influenza A H1N1 strains remain susceptible to zanamivir and ramantadine/amantadine. The influenza A strain (H1N1) responsible for the swine flu outbreaks is susceptible to the neuraminidase inhibitors, including oseltamivir.

type of therapy applied, extent of prior therapy, and presence of comorbidities and organ dysfunctions (Table 1).
prednisone versus melphalan plus prednisone with thalidomide [16]. The results of the latter study contrasted with those of another melphalan plus prednisone versus melphalan plus prednisone with thalidomide trial in which thalidomide-treated patients had significantly higher rates of infection than did control patients [28]. Notably, the rate of infection in the thalidomide arm did not differ in these 2 melphalan plus prednisone with thalidomide studies (13% and 10%, respectively [16, 17]) but was unexpectedly lower in the melphalan plus prednisone arm in the latter study (9% vs 2%) (Table 2) [16, 17].

Bortezomib exerts potent immunosuppressive effects on T cells (Table 1) [7, 22–25, 80], as evidenced by the 13% incidence of VZV infection observed among newly diagnosed patients [59, 78]. However, except for infection with VZV, no increase in the risk of infection was observed in 1 randomized controlled trial, and the rates of VZV infection were similar to those of the comparator arm after the institution of VZV prophylaxis [78].

Lenalidomide has more potent costimulatory effects on CD4+ and CD8+ T cells than does thalidomide [56, 88]. In a trial of 34 newly diagnosed patients treated with lenalidomide plus dexamethasone, grade III-IV neutropenia was uncommon (12%), and only 1 patient developed severe infection [74]. In another study, 68% of patients receiving melphalan plus prednisone and lenalidomide developed neutropenia, but only 9% developed serious infection, a rate comparable to that observed in patients receiving melphalan plus prednisone [16, 70]. Higher cumulative doses of dexamethasone increase the infectious morbidity, as shown in a recent randomized controlled trial, in which the combination of lenalidomide with high-dose dexamethasone (3 cycles of 4 days every month) was associated with higher infection rates, compared with lenalidomide plus low-dose dexamethasone (1 dose per week) [73].

HCT

**Autologous transplantation.** The risk of infection in autologous HCT recipients may be divided into 2 periods: pre-engraftment, which is associated with neutropenia and mucositis, and post-engraftment, which is related to a slow recovery of cell-mediated immunity [29]. Prior to engraftment, infections consist mainly of bacteremia, pneumonia, cellulitis, and gastrointestinal infection (including *Clostridium difficile*–associated diarrhea) [29]. The risk factors for infection prior to beginning conditioning chemotherapy include renal failure, iron overload, and smoking, whereas the duration of neutropenia is the main risk factor after the conditioning regimen is given [34, 89, 90]. The association between iron overload and higher risk of infection has been increasingly reported, including serious infection in autologous HCT recipients [34], invasive aspergillosis [91], and infection-related death in allogeneic HCT recipients [86].

Following engraftment, infection associated with depressed cell-mediated immunity predominate. T cell reconstitution occurs slowly and is influenced by the myeloma remission status,
Table 4. General Measures to Prevent Infections in Severely Immunosuppressed Myeloma Patients

<table>
<thead>
<tr>
<th>Maintaining Good Personal Hygiene</th>
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<tbody>
<tr>
<td>Handwashing, frequent, preferably with liquid soap, before eating and after contact with contaminated materials</td>
</tr>
<tr>
<td>Maintaining good dental hygiene; brushing teeth with soft bristle toothbrush after meals, and flossing daily; not sharing toothbrushes and changing toothbrush every three months, particularly in patients treated with bisphosphonates</td>
</tr>
<tr>
<td>Avoiding unprotected sexual exposure (HIV, Human papillomavirus, Herpes simplex virus, Hepatitis B virus, and others)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Avoiding At-Risk Environmental Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals (visitors, household members/caregivers, and health care workers)</td>
</tr>
<tr>
<td>Avoiding exposure to individuals with any of the following:</td>
</tr>
<tr>
<td>Signs and symptoms of infection including respiratory infections (fever, cough, etc)</td>
</tr>
<tr>
<td>Skin lesions (herpes simplex, varicella zoster, other)</td>
</tr>
<tr>
<td>Infectious conjunctivitis</td>
</tr>
<tr>
<td>Recent vaccination with the oral polio vaccine (3–6 weeks)</td>
</tr>
<tr>
<td>In endemic areas: individuals with tuberculosis, hepatitis A infection, measles, other endemic infections</td>
</tr>
<tr>
<td>Encouraging influenza virus vaccination of close contacts before the influenza season</td>
</tr>
<tr>
<td>Avoiding crowded places</td>
</tr>
<tr>
<td>Food and water</td>
</tr>
<tr>
<td>Food should be thoroughly cooked and fruits and vegetables washed before eating</td>
</tr>
<tr>
<td>Avoiding drinking potentially contaminated water</td>
</tr>
<tr>
<td>Recreational activities</td>
</tr>
<tr>
<td>Avoiding swimming in public places, particularly in stagnant water</td>
</tr>
<tr>
<td>Avoiding outdoor activities at risk for infections (eg, exploring caves)</td>
</tr>
<tr>
<td>Occupational settings</td>
</tr>
<tr>
<td>Avoiding working in jails, homeless shelters and other health care institutions that may cause exposure to pathogens (consultation with an infectious disease physician)</td>
</tr>
<tr>
<td>Pets</td>
</tr>
<tr>
<td>Travel (consultation with an infectious disease physician)</td>
</tr>
</tbody>
</table>

Consultation, before travel, with an infectious disease physician and/or researching the CDC Web site for specific recommendations including prophylactic agents, patterns of resistance for certain pathogens and vaccination needed when traveling overseas

NOTE. Consider these measures in patients undergoing sequential intensive therapy that includes high-dose dexamethasone, tandem autologous stem cell transplantation (SCT) or allogeneic SCT, and in patients with relapsed disease after SCT who are receiving immunosuppressive therapy. CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

a For a complete list of food and water precautions and avoidance of potentially infectious pets, see reference [96].

stem cell manipulation, the conditioning regimen (especially the addition of total body irradiation), and the intensity of subsequent anti-myeloma therapy [29]. Serious late infection after autologous HCT can be caused by C. difficile, VZV, CMV, and Pneumocystis jirovecii, which causes pneumonia [15, 92].

Allogeneic transplantation. Allogeneic HCT in myeloma patients with use of myeloablative conditioning is classically associated with transplant-related mortality exceeding 40%, mostly caused by infection [93], although transplant-related mortality was reduced to 10% only when a reduced intensity conditioning regimen was applied [94]. The spectrum of infections that occur after allogeneic HCT is comparable to that seen with other diseases and has been recently reviewed [95]. A detailed description of infectious complications is beyond the scope of this review.

Consolidation and/or Maintenance Therapy

The strategy of total therapy (ie, induction with multiagent chemotherapy and autologous HCT followed by consolidation and maintenance) significantly prolongs event-free and overall survival of patients with myeloma but is associated with higher risk of infection, including some occurring during consolidation and maintenance therapy [3, 96, 97].

Salvage Therapy for Relapsing Myeloma

Because of the cumulative immunosuppressing resulting for extensive prior therapy, infection tends to be more common after salvage therapy [50]. However, the frequency of infection reported in clinical trials involving patients experiencing relapse is not significantly higher than that reported in untreated patients (Table 2).

Bortezomib is commonly used in salvage therapy [87] and increases the risk of VZV and HSV infections. Compared with patients treated with high-dose dexamethasone, bortezomib recipients had a 4-fold higher incidence of VZV infection (13% vs 2%; P < .001) [12, 26]. The association between bortezomib and VZV infection was further confirmed in a retrospective study in which the rate of VZV infection doubled among bort-
tezomib recipients, compared with control patients (22% and 11%, respectively) [81].

Lenalidomide plus dexamethasone versus dexamethasone alone has been evaluated in the setting of relapse in 2 randomized controlled trials [98, 99]. In both trials, lenalidomide recipients experienced significantly higher rates of grade 3–4 neutropenia with a nonsignificant trend toward increased grade 3–4 infection [27, 28]. The rate of grade 3–4 infection doubled with lenalidomide and dexamethasone, compared with dexamethasone (15% vs 8%), in a pooled analysis of these 2 trials [78]. A high rate of neutropenia and infection (79% and 38%, respectively) was reported when arsenic trioxide was given as salvage therapy for myeloma [100].

Prevention and Management of Infection

Risk Stratification prior to Initiation of Anti-Myeloma Therapy

Patients with myeloma should undergo risk stratification on the basis of tumor- and host-related factors. Tumor-related factors likely to affect treatment decisions include complex cytogenetic abnormalities, elevated serum β2-microglobulin and lactic dehydrogenase levels, and others [101]. Evaluation of host-related factors includes a detailed medical history (with emphasis on infections), a complete physical examination, and a comprehensive evaluation of organ function. Consideration should be given to obtaining a serum mannose-binding lectin measurement, because of the strong association between mannose-binding lectin deficiency and severe infection in myeloma patients undergoing autologous HCT (Table 1) [30].

Prevention of Complications

Antimicrobial prophylaxis. The need for antimicrobial prophylaxis is based on various factors including the risk for, timing and seriousness of infections and outlined in Table 1 (Table 3 and Figure 1). Patients treated with corticosteroid-containing regimens should receive prophylaxis for P. jirovecii pneumonia, preferably with daily trimethoprim-sulfamethoxazole [109, 110], because trimethoprim-sulfamethoxazole also prevents other bacterial infection [102]. For antibacterial prophylaxis, an oral fluoroquinolone can be used if prophylaxis for P. jirovecii pneumonia is not indicated [111, 112]. Because of the increasing incidence and severity of C. difficile–associated diarrhea, metronidazole prophylaxis should be considered in patients with a history of such infection [91].

Prophylaxis for HSV and VZV should be provided to patients who are seropositive or have a history of recurrent fever blisters,
Cold sores, or documented HSV or VZV infection, particularly if their CD4 counts are low (<50 cells/mm³) [102]. All patients treated with bortezomib-containing regimens should receive prophylaxis for HSV and VZV infection [113]. Preemptive therapy for CMV infection should be applied on the basis of weekly monitoring (pp65 antigenemia or polymerase chain reaction assays) of CMV-seropositive patients who are at highest risk of CMV reactivation and disease. Such monitoring is recommended for heavily pretreated patients [50], including recipients of tandem autologous HCT, allogeneic HCT, or single autologous HCT followed by repeated courses of intensive chemotherapy. Patients with a history of CMV reactivation or disease should also undergo CMV monitoring. Prevention of candidiasis can be accomplished with clotrimazole troches or fluconazole. Heavily pretreated patients may develop invasive mold infection, such as aspergillosis, and should either receive mold-active prophylaxis or preemptive therapy on the basis of the results of serial monitoring for Aspergillus antigenemia [114]. Targeted secondary prophylaxis should be given to patients with history of prior infection [92].

**Immune enhancement strategies.** Vaccination of patients with myeloma against influenza A and B viruses, *S. pneumoniae*, and *H. influenzae* remains controversial. Among patients treated with less-immunosuppressive conventional regimens, such as melphalan plus prednisone, responses to pneumococcal and to influenza vaccine were suboptimal [93, 94] and failed to improve when a booster dose was given [94], although 1 study suggested that adequate response to *H. influenzae* type B vaccine could be elicited [93]. Preventing influenza virus infection is important and is best accomplished by vaccinating health care workers, caregivers, and household members and by providing patients with neuraminidase-inhibitor prophylaxis during the influenza season (October–March in the United States) [95]. Following HCT, patients should undergo revaccination as recommended by the Centers for Disease Control and Prevention [96].

Vaccination against VZV may become an attractive option. An inactivated VZV vaccine has been used investigationally in severely immunocompromised patients [97]. Studies are ongoing to further define what role, if any, it will have.

In 1 study, prophylactic intravenous immunoglobulin (400 mg/kg every 4 weeks) prevented serious infection during the plateau phase of myeloma [115]. However, antibiotic prophylaxis was not given in that study, and chemotherapy consisted of mildly immunosuppressive conventional chemotherapy. Because of the high cost of intravenous immunoglobulin and the protection conferred by antibiotics, intravenous immunoglobulin should be limited to patients with immunoglobulin G levels <500 mg/dL who suffer recurrent infection despite appropriate antimicrobial prophylaxis. Older recipients of myelosuppressive chemotherapy may benefit from prophylaxis with colony-stimulating factors [99].

**Other preventive measures.** Because renal failure is a risk factor for infection in myeloma patients, conditions likely to cause renal dysfunction should be immediately reversed (Tables 1 and 4). Iron overload and smoking increase the risk of serious infection in patients undergoing autologous HCT. Therefore, such patients should be encouraged to quit smoking, and the risk of transfusional iron overload should be minimized by giving erythropoetin-stimulating agents [34]. Iron chelation may be considered when clinically significant iron overload is present [98]. Fractures may increase the risk of osteomyelitis and may be prevented by employing bisphosphonates in patients with severe osteopenia and a history of fractures [24].

### Table 5. Antimicrobial Agents that Should Be Used with Caution in Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 and CYP3A4 inducers (nafcillin and rifampin)</td>
<td>May increase metabolism of bortezomib; monitor therapy</td>
</tr>
<tr>
<td>CYP2C19 and CYP3A4 inhibitors (fluconazole, erythromycin, doxycycline, metronidazole, norfloxacin, isoniazid, and tetracycline)</td>
<td>May decrease metabolism of bortezomib; consider therapy modification</td>
</tr>
<tr>
<td>Drugs that prolong QT interval (macrolides [erythromycin, clarithromycin, telithromycin, azithromycin], intravenous pentamidine, quinolones [levofloxacin, moxifloxacin], and azoles [fluconazole, itraconazole, voriconazole, posaconazole])</td>
<td>Monitor QT interval and use with caution in patients with cardiac amyloidosis or light chain deposition disease</td>
</tr>
<tr>
<td>Nephrotoxic drugs (aminoglycosides, glycopeptides, amphotericin B, foscarin, and immunomodulators*)</td>
<td>Use alternative therapies in patients with impaired renal function</td>
</tr>
<tr>
<td>Drugs that suppress bone marrow function (linezolid, pirmethamine, and TMP-SMX)</td>
<td>Avoid when possible in patients with poor marrow reserve particularly after receipt of myelosuppressive therapies (including myeloablative conditioning regimens for HCT)</td>
</tr>
</tbody>
</table>

**NOTE.** HCT, hematopoietic stem cell transplantation; TMP-SMX, trimethoprim-sulfamethoxazole.

* Immunomodulators include cyclosporin A and tacrolimus.
Bisphosphonates have been associated with the development of osteonecrosis of the jaw [100, 101, 116]. This complication is frequently accompanied by signs of local infection. Osteonecrosis of the jaw can be prevented with intensive oral hygiene and by holding bisphosphonates several weeks before and after major dental procedures. Early identification and treatment with antibiotics is critical [36–38]. Practical guidelines for diagnosis, prevention, and management of osteonecrosis of the jaw have been recently published [30]. Additional measures that may decrease the risk of infection in patients with myeloma include strict glycemic control during corticosteroid therapy and deep venous thrombosis prophylaxis, because of the association between deep venous thrombosis at central venous catheter site and septic thrombophlebitis.

Management of Infection

Infection in patients with myeloma represents a clinical challenge. The list of potential pathogens is long and changes over the disease course [50]. A cumulative suppression of cell-mediated immunity is particular to myeloma and results from the combined effect of multiple applications of high-dose corticosteroids, the chronic nature of the disease with multiple relapses requiring salvage therapies (almost always containing dexamethasone), and the addition of bortezomib, a powerful immunosuppressive agent (Table 3 and Figure 2) [20, 21, 26, 59].

Because of severe cell-mediated immunity defects, manifestations of infection may be masked, rendering the diagnosis of infection difficult. Fever in patients with myeloma should be considered to be of infectious etiology until proven otherwise. Occasionally, fever may be a manifestation of myeloma [117]. These patients are usually clinically stable, with evidence of extensive myeloma. Other noninfectious causes of fever include venous thromboembolism [18, 118] and the engraftment syndrome that coincides with marrow recovery in HCT recipients [119].

Work-up of infection starts with an understanding of the pathogens and spectrum of infections associated with various disease stages and therapies (Table 1). Critical to the optimal management of infection is the application of diagnostic tools that take into consideration the clinical findings and geographical determinants of pathogens and the selection of antimicrobial therapy on the basis of local epidemiological trends.

Figure 2 describes the framework for managing fever in patients with myeloma.

Drug Interactions when Managing Infection

Myeloma-effective agents may be P450 competitors or inducers (corticosteroids thalidomide and bortezomib) [120–122]. Therefore, caution should be exercised when prescribing P-450-related antimicrobial agents (macrolides, antifungal triazoles, rifampin, doxycycline, isoniazid, and others) [114]. Furthermore, the QT interval should be carefully monitored in patients with myeloma-related cardiac pathology (AL amyloidosis and light chain deposition disease) who commonly receive antimicrobial agents associated with QT prolongation (antifungal triazoles and fluoroquinolones). Finally, the use of potentially myelosuppressive agents in the early post-HCT period (such as linezolid, trimethoprim-sulfamethoxazole, and others) should be limited because of concerns about delaying engraftment (Table 5) [27, 123].

CONCLUSION

Infection continues to represent a major challenge for clinicians caring for myeloma patients. The introduction of novel life-prolonging therapies has transformed myeloma into a chronic disease. The resulting cumulative immunosuppression has increased the risk of infection and expanded the spectrum of potential pathogens in this patient population. Managing infection begins with a risk-adapted selection of anti-myeloma therapy, taking into consideration tumor- and host-related factors, with particular emphasis on disease- and age-related organ dysfunction.

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