Purpose. The most important articles on infectious diseases (ID) pharmacotherapy published in the peer-reviewed literature in 2015, as nominated and selected by panels of pharmacists and others with ID expertise, are summarized.

Summary. Members of the Houston Infectious Diseases Network were asked to nominate articles published in prominent peer-reviewed journals in 2015 that were thought to have a major impact in the field of ID pharmacotherapy. A list of 55 nominated articles on general ID-related topics and 10 articles specifically related to human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) was compiled. In a national online survey, members of the Society of Infectious Diseases Pharmacists (SIDP) were asked to select from the list 10 general ID articles believed to have made a significant contribution to the field of ID pharmacotherapy and 1 article contributing to HIV/AIDS pharmacotherapy. Of the 361 SIDP members surveyed, 153 (42%) and 76 (21%) participated in the selection of general ID-related articles and HIV/AIDS-related articles, respectively. The 11 highest-ranked publications (10 general ID-related articles and 1 HIV/AIDS-related article) are summarized here.

Conclusion. With the growing number of significant ID-related publications each year, it can be challenging to stay current with the literature. This review of important ID pharmacotherapy publications in 2015 may be helpful in identifying key articles and lessening this burden.

Keywords: antifungal agents, communicable diseases, drug therapy, microbiology, publications, therapeutic use

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A vast amount of information regarding the diagnosis and treatment of infectious diseases (ID) is published in the literature each year. A PubMed search conducted in January 2016 using the keywords infectious diseases and HIV identified 24,046 and 16,436 articles on those respective topics published in 2015. These numbers are only expected to increase as researchers aim to keep up with the challenges of multidrug-resistant pathogens and emerging ID.

The Houston Infectious Diseases Network (HIDN) consists of ID clinicians, including physicians, pharmacists, microbiologists, and researchers, the majority of whom practice at Texas Medical Center and other institutions in the greater Houston area. The purposes of HIDN are to establish and foster collaborative research and education, share best-practice models, and host presentations from national ID experts. In addition, HIDN mentors residents, fellows, and young practitioners with an interest in ID.

To support ongoing efforts to identify and summarize important recent ID pharmacotherapy-related publications, HIDN members were asked to nominate articles published in 2015 that they believed had a significant impact on ID pharmacotherapy, including articles on human immu-
nodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). All nominated articles were published between January 1 and December 31, 2015, in prominent peer-reviewed journals (e.g., *Antimicrobial Agents and Chemotherapy*, *Clinical Infectious Diseases*, *Journal of the American Medical Association*, *New England Journal of Medicine*).

In late December 2015, an invitation to participate in an electronic survey was e-mailed to members of the Society of Infectious Diseases Pharmacists (SIDP). Members were directed to a list of the nominated articles (55 general ID pharmacotherapy-related and 10 HIV/AIDS pharmacotherapy-related articles) and were asked to select the top 10 articles that they believed contributed the most to the field of ID pharmacotherapy in general as well as 1 article pertaining to HIV/AIDS pharmacotherapy specifically. Voters were allowed to nominate articles not included in the survey; each nomination was counted as a single vote. In order to minimize responses from members not current with the literature, voters were given the opportunity to opt out of voting in either or both categories. The final article rankings were determined by total survey response counts. The survey closed in early January 2016. Of the 361 SIDP members surveyed, 153 (42%) and 76 (21%) members voted for general ID-related articles and HIV/AIDS-related articles, respectively. The highest-ranked articles of 2015 encompassed a wide range of ID topics, and the 11 highest-ranked papers (10 general ID-related articles and 1 HIV/AIDS-related article) are summarized below in alphabetical order according to the lead author’s last name. Ranked lists of the top 20 general ID-related and 10 HIV/AIDS-related articles appear in Tables 1 and 2, respectively.7-37

**Baddour et al. Infecive endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association**

Infecive endocarditis (IE) is defined by an infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling catheter.38 Hospital admissions for IE rose from 9.3 per 100,000 population in 1998 to 12.7 per 100,000 population in 2009, with no change in the 15-day average length of hospitalization over the 12-year period.39 The epidemiology and patient characteristics have changed since publication of the latest version of American Heart Association (AHA) guidelines on IE in 2005. *Staphylococcus aureus* has emerged as the leading etiologic agent in IE, mostly due to increased healthcare contact ([e.g., intravascular catheters, surgical wounds, indwelling prosthetic devices, hemodialysis]) in the industrialized world. The characteristic profile of patients with IE also has shifted over the past decade toward an increased mean patient age, an increased proportion of patients with prosthetic valves or other cardiac devices, and a decreased proportion of patients with rheumatic heart disease.4 The AHA IE Writing Committee conducted reviews of the literature published between January 2005 and October 2013 to update the previous 2005 version of the AHA IE guidelines.

The 2015 guideline update emphasizes that the recommendations are intended to support but do not supersede clinical decision-making with regard to the management of individual patients due to high variability in the clinical presentation and course of IE. Patients with suspected IE should be clinically evaluated using the modified “Duke criteria” as a diagnostic guide. The updated guidelines recommend initial transthoracic echocardiography in all patients with suspected IE, followed by transesophageal echocardiography (TEE) as soon as possible in patients at high initial risk for IE (including those with prosthetic heart valves, previous IE, or heart failure), in patients for whom there is moderate- to-high clinical suspicion of IE, and in “difficult imaging candidates” for whom TEE is not clinically possible or must be delayed.

The 2015 update has a new section focused on antimicrobial therapeutic principles that highlights the importance of bactericidal antibiotics, the role of the inoculum effect, and the penetrability of drugs into the vegetations of IE. Pharmacokinetic (PK) and pharmacodynamic (PD) dosing considerations are included in an effort to fully optimize antibiotic dosing to increase the likelihood of treatment success and reduce the potential for treatment selection pressure favoring resistant pathogens.

For patients with IE involving a native or prosthetic valve or other pros-
Table 1. Results of SIDP Member Ranking of Significant Publications on Infectious Diseases Pharmacotherapy in 2015

<table>
<thead>
<tr>
<th>Rank</th>
<th>Ref.</th>
<th>Article</th>
<th>No. (%) Individuals Ranking Article in Top 10 (n = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>Britt NS et al. Comparison of the effectiveness and safety of linezolid and daptomycin in vancomycin-resistant enterococcal bloodstream infection: a national cohort of Veterans Affairs patients.</td>
<td>83 (54)</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Baddour LM et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association.</td>
<td>80 (52)</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>Sawyer RG et al. Trial of short-course antimicrobial therapy for intraabdominal infection.</td>
<td>79 (52)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>McDanel JS et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible Staphylococcus aureus bloodstream infections among 122 hospitals.</td>
<td>77 (50)</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>Tamma PD et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia.</td>
<td>72 (47)</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>Dulhunty JM et al. A multicenter randomized trial of continuous infusion versus intermittent beta-lactam infusion in severe sepsis.</td>
<td>64 (42)</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>Marr KA et al. Combination antifungal therapy for invasive aspergillosis.</td>
<td>59 (39)</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>Lee NY et al. Cefepime therapy for monomicrobial Enterobacter cloacae bacteremia: unfavorable outcomes in patients infected by cefepime-susceptible dose-dependent isolates.</td>
<td>58 (38)</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>Rao SN et al. Treatment outcomes with cefazolin versus oxacillin for deep-seated methicillin-susceptible Staphylococcus aureus bloodstream infections.</td>
<td>53 (35)</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>Paul M et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial.</td>
<td>52 (34)</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>Cai T et al. Asymptomatic bacteriuria treatment is associated with higher prevalence of antibiotic resistant strains in women with urinary tract infections.</td>
<td>49 (32)</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>Hobbs AL et al. Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics.</td>
<td>48 (31)</td>
</tr>
<tr>
<td>13</td>
<td>19</td>
<td>Rokas KE et al. The addition of intravenous metronidazole to oral vancomycin is associated with improved mortality in critically ill patients with Clostridium difficile infection.</td>
<td>47 (31)</td>
</tr>
<tr>
<td>14</td>
<td>20</td>
<td>Bai AD et al. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteremia: results from a large multicenter cohort study.</td>
<td>45 (29)</td>
</tr>
<tr>
<td>14</td>
<td>21</td>
<td>Berbari E et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults.</td>
<td>45 (29)</td>
</tr>
<tr>
<td>16</td>
<td>22</td>
<td>Casapao AM et al. Association between vancomycin day 1 exposure profile and outcomes among patients with methicillin-resistant Staphylococcus aureus infective endocarditis.</td>
<td>40 (26)</td>
</tr>
<tr>
<td>18</td>
<td>24</td>
<td>Trautner BW et al. Effectiveness of an antimicrobial stewardship approach for urinary catheter-associated asymptomatic bacteriuria.</td>
<td>36 (24)</td>
</tr>
<tr>
<td>20</td>
<td>26</td>
<td>Prybylski JP. Vancomycin trough concentration as a predictor of clinical outcomes in patients with Staphylococcus aureus bacteremia: a meta-analysis of observational studies.</td>
<td>30 (20)</td>
</tr>
<tr>
<td>20</td>
<td>27</td>
<td>Tumbarello M et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicenter study.</td>
<td>30 (20)</td>
</tr>
</tbody>
</table>

*SIDP = Society of Infectious Diseases Pharmacists, MSSA = methicillin-susceptible Staphylococcus aureus, KPC = Klebsiella pneumoniae carbapenemase.*
Table 2. Results of SIDP Member Ranking of Significant Publications in HIV/AIDS Pharmacotherapy in 2015a

<table>
<thead>
<tr>
<th>Rank</th>
<th>Ref.</th>
<th>Article</th>
<th>No. (%) Individuals Selecting Article (n = 76)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>Lundgren JD et al., for the INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection.</td>
<td>31 (41)</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>Sax PE et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised double-blind, phase 2, non-inferiority trials.</td>
<td>9 (12)</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>Molina JM et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection.</td>
<td>8 (11)</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>McCormack S et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial.</td>
<td>7 (9)</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>Molina JM et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label phase 3b study.</td>
<td>7 (9)</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>Marrazzo JM et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women.</td>
<td>5 (7)</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>Mills A et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study.</td>
<td>5 (7)</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>Gallant JE et al. Cobicistat compared with ritonavir as a pharmacoenhancer for atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate: week 144 results.</td>
<td>3 (4)</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>Lalezari JP et al. Safety and efficacy of the HIV-1 attachment inhibitor produg BMS-663068 in treatment-experienced individuals: 24 week results of A1438011, a phase 2b, randomised controlled trial.</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>Renjifo B et al. Pharmacokinetic enhancement in HIV antiretroviral therapy: a comparison of ritonavir and cobicistat.</td>
<td>0</td>
</tr>
</tbody>
</table>

aSIDP = Society of Infectious Diseases Pharmacists, HIV = human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome.
bRaters were asked to choose one article only.
IE is now the third or fourth most common life-threatening infection, surpassed in frequency only by sepsis, pneumonia, and intraabdominal abscess. Patients with IE should be managed by a team of specialists in ID, cardiology, cardiovascular surgery, and clinical pharmacy.

**Britt et al. Comparison of the effectiveness and safety of linezolid and daptomycin in vancomycin-resistant enterococcal bloodstream infection: a national cohort of Veterans Affairs patients**

The optimal approach for treatment of vancomycin-resistant enterococcal bloodstream infection (VRE-BSI) is uncertain. Linezolid is the only drug with Food and Drug Administration (FDA)–approved labeling for treatment of VRE-BSI; however, significant concerns exist regarding its bacteriostatic activity, its unfavorable hematologic effects, and FDA approval of its use for VRE-BSI during an era when few treatment alternatives existed. Despite lacking an FDA-approved indication for use in VRE-BSI, daptomycin has become an important agent for treatment of VRE-BSI, largely due to its potent in vitro bactericidal activity and a growing body of clinical evidence supporting its use for that purpose.

Recent systematic reviews and meta-analyses showed that there was a tendency for linezolid to provide better survival than daptomycin in the context of VRE-BSI; however, the study methodologies have been heavily scrutinized, in part due to the inherent heterogeneity of pooled study data, small sample sizes, and lack of adjustment for potential confounders. The retrospective review by Britt et al. represents the most robust clinical and safety data comparing linezolid and daptomycin for the treatment of VRE-BSI published to date.

The investigators used the Veterans Affairs (VA) electronic medical record to generate a multicenter national cohort of patients treated for VRE-BSI between January 2004 and January 2013. Patients were carefully selected, with patients excluded from the cohort study if they received treatment with another anti-VRE agent, treatment with linezolid–daptomycin combination therapy (including sequential use), or treatment with daptomycin or linezolid for less than 48 hours. The primary outcome was composite treatment failure, including 30-day all-cause mortality, microbiological failure, and recurrence of VRE-BSI within 60 days of therapy completion. There were 644 patients in the final analysis, including 319 linezolid-treated and 325 daptomycin-treated patients. The study authors concluded that daptomycin (median dose, 6 mg/kg/day) offered a significant advantage over linezolid in terms of microbiological clearance ($p = 0.011$) and 30-day mortality ($p = 0.014$). The median duration of bacteremia was 4 days for linezolid-treated patients, compared with 3 days for the daptomycin group ($p = 0.033$). There were no significant between-group differences in the 60-day recurrence rate or hospital length of stay. Evaluation of platelet counts and creatine phosphokinase (CPK) data indicated no significant associations between treatment and thrombocytopenia or CPK elevations in either group. Poisson regression, Cox proportional analysis, and propensity score matching were conducted to adjust for treatment selection and potential confounders, which was a major strength of this study.

Of note, there were significant baseline differences between patients treated with linezolid versus daptomycin indicating greater severity of illness among linezolid–treated patients. Specifically, patients in the linezolid cohort were more likely than those in the daptomycin group to be receiving intensive care ($p < 0.001$), to be 65 years of age or older ($p = 0.027$), and to be receiving mechanical ventilation ($p < 0.001$); in addition, they had a higher median Acute Physiology and Chronic Health Evaluation II (APACHE II) score ($p = 0.005$).

A major limitation of this study was that only 60% of patients had follow-up blood cultures definitively proving microbiological eradication. Moreover, daptomycin susceptibility results were available for few isolates, as such testing was not routinely performed. Increasing evidence indicates that the rate of daptomycin treatment failure in VRE bacteremia is increased when the daptomycin MIC of an isolate is elevated but still considered to indicate susceptibility ($\leq 4$ mg/L, $>2$ mg/L). Furthermore, in vitro and clinical data suggest that outcomes may be improved with doses of daptomycin higher than the standard recommended dose of 6 mg/kg/day used in the study.

**Dulhunty et al. A multicenter randomized trial of continuous infusion versus intermittent beta-lactam infusion in severe sepsis**

Time-dependent killing with the use of β-lactam antibiotics is supported by in vitro, animal, and limited human data pointing to time above MIC as the important PD parameter with respect to clinical outcomes. While extended- and continuous-infusion regimens are used in an attempt to take advantage of the time-dependent PD of β-lactams, evidence to support the superiority of these regimens is inconclusive; in some cases, the relevant studies have been insufficiently powered or included populations who may have been less likely to benefit from those regimens, such as patients with low-severity illness. Nonetheless, a pooled analysis of studies comparing extended or continuous infusion versus intermittent administration of carbapenems or piperacillin–tazobactam
found a mortality advantage with use of the extended- or continuous-infusion regimens.⁶⁰

In this randomized, placebo-controlled study, conducted primarily in Australia and New Zealand intensive care units (ICUs), patients with severe sepsis undergoing treatment with piperacillin–tazobactam, ticarcillin–clavulanate, or meropenem were randomly assigned to receive either intermittent- (over 30 minutes) or continuous-infusion antibiotic administration.¹² The primary outcome was “alive ICU-free days” at 28 days after randomization. Secondary outcomes included day-90 mortality; clinical cure, assessed at day 14 after antibiotic cessation; “alive organ failure–free days” at day 14; and duration of bacteremia after randomization.

Overall, 212 patients were randomly assigned to continuous infusion and 220 to intermittent infusion, and the groups were well matched with regard to age, severity of illness, organ dysfunction, and source of infection. In both groups, the lungs were the most common site of infection, and most patients (around 74%) were in septic shock. Approximately 26% of patients required some form of renal replacement therapy during their ICU stay. While dosing was not discussed in detail, the study authors mentioned that the median 24-hour doses on day 1 were 13.5 g (interquartile range [IQR], 13.5–13.5 g) of piperacillin–tazobactam, 3.0 g (IQR, 2.0–3.0) of meropenem, and 12.4 g of ticarcillin–clavulanate in both groups. The results indicated no significant between-group difference in the primary outcome of alive ICU-free days at 28 days or in any secondary outcome, with the exception of median ICU length of stay, which was 1 day longer in the continuous-infusion group, a finding that was not correlated with any of the study variables.

This trial was notable because it was the largest randomized controlled trial to examine whether continuous versus intermittent administration of β-lactams improves outcomes to date and was well controlled for heterogeneity between the study groups. It was also conducted in a high-risk group of patients with severe sepsis in the ICU. The lack of a demonstrated overall benefit with the use of continuous-infusion therapy is disappointing but not entirely unexpected. There are many factors that influence PD target attainment, including PK differences, variable organism MICs, and host factors. The patients in this study, while critically ill, were primarily infected with highly susceptible organisms, and dosing was relatively aggressive. In addition, a specific pathogenic organism was not isolated in a substantial proportion of patients (81%), suggesting that noninfectious or nonbacterial infectious causes may have diluted the researchers’ ability to discern a difference between the groups. Further research is needed to identify specific patient populations that may benefit the most from PD regimen optimization, such as patients infected with multidrug-resistant gram-negative organisms, but this study provided good evidence that the broad application of extended- or continuous-infusion–based regimens is unlikely to be superior as a general strategy in the ICU setting.

Lee et al. Cefepime therapy for monomicrobial Enterobacter cloacae bacteremia: unfavorable outcomes in patients infected by cefepime-susceptible dose-dependent isolates¹⁴

With the emergence of multidrug-resistant pathogens, including those with chromosomally encoded AmpC β-lactamases and extended-spectrum β-lactamases (ESBLs), therapeutic options for the management of associated infections are becoming extremely limited. Enterobacter cloacae is among the pathogens with increasing resistance and often causes serious community- and healthcare-associated infections.⁶⁰⁻⁵²

Cefepime, in comparison to the other extended-spectrum cephalosporins, has greater stability against ESBL- and AmpC β-lactamase–producing organisms⁵⁰; hence, it is a viable option for treating infections caused by these organisms.⁵⁰,⁵⁴,⁵⁵ However, based on a better understanding of cefepime's PK and PD properties, it is now clear that the mechanism of resistance is not the only important factor in determining treatment failure and that drug-level target attainment should also be emphasized.⁶⁰ In response, the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing revised the Enterobacteriaceae susceptibility breakpoints for many of the β-lactams, including cefepime and the carbapenems.⁵⁷,⁵⁸ With the new breakpoints, CLSI no longer recommends that clinical laboratories routinely report the presence of ESBL phenotypes. In addition, CLSI introduced a new cefepime susceptibility category, “susceptible dose-dependent” (SDD), with an associated MIC of 4–8 µg/mL.⁵⁰ Higher doses of cefepime (2 g every 12 hours or 1–2 g every 8 hours to attain an MIC of 4 µg/mL and 2 g every 8 hours to attain an MIC of 8 µg/mL) are recommended for severe infections caused by Enterobacteriaceae associated with elevated cefepime MICs.

In this retrospective study, Lee et al.¹⁴ analyzed clinical outcomes of adult patients with bacteremia due to cefepime-SDD E. cloacae who were treated with cefepime or a carbapenem relative to outcomes in patients with cefepime-susceptible E. cloacae treated with cefepime. Overall, among 305 initially screened cases of documented E. cloacae bacteremia, 217 (79.8%) met the inclusion criteria for microbiological and clinical outcomes analysis. Therapy was classified as empirical or definitive. Empirical therapy was defined as receiving a first cefepime or carbapenem dose during the first 24 hours after blood sampling for cultures. Definitive therapy was defined as receiving cefepime or carbapenem monotherapy if the causative isolate was susceptible in vitro to
the prescribed drug, according to the CLSI breakpoint.

The primary outcome of the study was the crude 30-day mortality rate. The 30-day mortality rates were similar in patients empirically treated with cefepime and those treated with a carbapenem (24.5% [13 of 53 patients] versus 25.8% [8 of 31 patients]; \( p = 1.0 \)). Among 72 patients who received definitive cefepime therapy, the 30-day mortality rate of those infected by cefepime-susceptible isolates was significantly lower than that of patients infected by cefepime-SDD isolates (16.1% [9 of 56 patients] versus 62.5% [10 of 16 patients], \( p < 0.001 \)) but similar to that of 72 patients with definitive carbapenem therapy (16.1% [9 of 56 patients] versus 22.2% [16 of 72 patients], \( p = 0.50 \)). In a Cox regression model, empirical cefepime treatment at a higher dose (2 g every 8 hours) was associated with a prognosis and a clinical outcome similar to those with carbapenem use; in addition, relative to other evaluated dosages, the high-dose cefepime regimen was independently associated with a better outcome. However, in the SDD subgroup (\( n = 15 \)), empirical high-dose therapy resulted in a better, although not significantly better, outcome than other evaluated dosages (30-day mortality rate, 22.9% [2 of 9 patients] versus 66.7% [4 of 6 patients]; \( p = 0.14 \)). In a multivariate analysis, the presence of critical illness, rapidly fatal underlying disease, or ESBL-producing or cefepime-SDD isolates was independently associated with 30-day mortality.

The study authors concluded that cefepime, at the recommended doses, can be used as definitive carbapenem-sparing therapy in patients with cefepime-susceptible E. cloacae infections; however, cefepime should be used cautiously for cefepime-SDD E. cloacae infections. A strength of this study was that it included both microbiological and clinical outcomes. However, the study limitations included its retrospective observational nature and the availability of only in-hospital clinical data regarding the hospitalization period.

**Marr et al. Combination antifungal therapy for invasive aspergillosis**

A common complication seen in patients with hematologic malignancies (HMs) and patients who have undergone hematopoietic cell transplant (HCT) procedures is invasive aspergillosis (IA), which is often associated with poor clinical outcomes. Voriconazole, a triazole antifungal, is currently recommended in Infectious Diseases Society of America (IDSA) guidelines for treatment of IA based on improved outcomes relative to those with conventional amphotericin B therapy. To date, there have only been in vitro studies, animal models, and clinical series suggesting that administration of voriconazole in combination with an echinocandin may improve outcomes.

This study was a randomized, double-blind, placebo-controlled multicenter trial, funded by Pfizer Inc., designed to assess the safety and efficacy of voriconazole alone or in combination with anidulafungin in the management of IA in patients with HM and HCT recipients at low risk for death due to malignancy or organ failure. The primary endpoint of the study was all-cause mortality at 6 weeks. Secondary endpoints included all-cause mortality at 12 weeks and 6-week mortality in multiple prespecified subgroupings that were predicted to have prognostic significance at baseline.

The patients were randomly assigned in a 1:1 ratio to receive voriconazole in combination with either anidulafungin or a placebo for a minimum of 2 weeks, after which voriconazole monotherapy was administered for up to 4 weeks. Study data were vetted by an external data review committee (DRC). All patients received i.v. voriconazole (6 mg/kg every 12 hours on day 1, then 4 mg/kg every 12 hours) for the first week and then, if eligible, were switched to oral voriconazole (300 mg every 12 hours) to complete 6 weeks of treatment. All patients received treatment with either i.v. anidulafungin (200 mg on day 1, then 100 mg every 24 hours) or a placebo for at least 2 weeks and up to a maximum of 4 weeks.

A total of 454 patients with HM and HCT recipients with suspected or documented IA from 93 sites in 24 countries were enrolled in the study and received at least one dose of treatment. The intent-to-treat (ITT) population included 422 patients with DRC-confirmed possible, probable, or proven IA at study entry. The modified ITT (mITT) population included 277 patients (135 and 142 in the combination and monotherapy groups, respectively) with DRC-confirmed proven or probable IA by the end of the first study week. The mITT populations for both groups had similar baseline demographics, underlying conditions, and IA diagnoses.

In the primary endpoint analysis, mortality at 6 weeks in the mITT population was 19.3% (26 of 135 patients) with combination treatment and 27.5% (39 of 142 patients) with monotherapy (absolute difference, –8.2% [95% confidence interval [CI], –19.0% to 1.5%]; two-sided \( p = 0.087 \)). With regard to the secondary endpoints, mortality at 12 weeks was 28.9% (39 of 135 patients) with combination therapy and 38.7% (55 of 142 patients) with monotherapy (absolute difference, –10.1% [95% CI, –21.4% to 1.1%]; two-sided \( p = 0.077 \)). Post hoc univariate and multivariate analyses identified three independent predictors of mortality at 6 weeks: low Karnofsky score, low platelet count, and high serum galactomannan antigen index at baseline.

The investigators concluded that treatment of IA with a combination of voriconazole and anidulafungin was associated with a nonsignificant but clinically meaningful survival benefit in patients with HM and HCT recipients.
McDanel et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible Staphylococcus aureus bloodstream infections among 122 hospitals

Vancomycin is a common empirical therapy for BSI, but guidelines recommend switching from vancomycin to a β-lactam (cefazolin or an antistaphylococcal penicillin) if the causative pathogen is MSSA. This recommendation is based on small, single-center, observational cohort studies of patients with MSSA bacteremia demonstrating that definitive vancomycin therapy is associated with higher rates of mortality and recurrent infection than definitive therapy with a β-lactam. However, it is unclear whether vancomycin empirical therapy is also associated with worse outcomes relative to a β-lactam empirical therapy for MSSA bacteremia.

In this multicenter, retrospective cohort study of medical and surgical patients with MSSA bacteremia, McDanel et al. compared (1) empirical therapy with vancomycin and β-lactams and (2) definitive therapy with vancomycin and β-lactams. The study was performed at 122 acute care VA medical centers from 2003 to 2010. Patients were included in the analysis if they had at least one blood culture positive for MSSA and if they received vancomycin or a β-lactam with activity against S. aureus. Patients with multiple admissions involving MSSA bacteremia were included only once. Patients were excluded from the analysis if they had missing or inaccurate data or were admitted to a VA facility that treated fewer than 25 cases of S. aureus bacteremia during the study period.

The primary outcome was 30-day all-cause mortality, which was defined as death within 30 days after the collection of the first blood culture positive for MSSA; this included deaths that occurred outside the hospital or during subsequent admissions. Empirical therapy was defined as therapy administered during the period extending from 2 days before to 4 days after the collection of the first MSSA-positive blood culture. Definitive therapy was defined as therapy administered 4–14 days after the collection of the first blood culture positive for MSSA.

Three Cox proportional-hazards regression analyses were performed: empirical vancomycin therapy versus empirical β-lactam therapy, definitive vancomycin therapy versus definitive β-lactam therapy, and definitive vancomycin therapy versus definitive guideline-concordant β-lactam therapy (cefazolin or an antistaphylococcal penicillin). Patients were excluded from the empirical therapy analysis if they received both vancomycin and a β-lactam empirically and from the definitive therapy analyses if they received both agents as definitive therapy.

Of 16,973 patients with one or more episodes of MSSA bacteremia, 5,784 were included in the empirical therapy analysis; 46% received a β-lactam and 54% received vancomycin. The mortality rate was 14% in both groups (p = 0.65). After adjustment for confounders, patients who received empirical β-lactam therapy were found to have a risk of mortality similar to that of patients who received empirical vancomycin therapy (hazard ratio [HR], 1.03; 95% CI, 0.89–1.20). Among 5,633 patients included in the definitive therapy analysis, 83% received a β-lactam and 17% received vancomycin. The most commonly used β-lactams were antistaphylococcal penicillins (44%), cefazolin (30%), piperacillin–tazobactam (15%), and ceftriaxone (14%). In the univariate analysis, the mortality rate was slightly higher among patients who received a β-lactam (14% versus 12% in vancomycin-treated patients, p = 0.047). However, in the multivariate analysis, patients who received definitive β-lactam therapy had a 35% lower risk of mortality than those who received definitive vancomycin therapy after adjustment for confounders (HR, 0.65; 95% CI, 0.52–0.80). Patients who received cefazolin or an antistaphylococcal penicillin as definitive therapy had a 43% lower risk of mortality than those who received definitive vancomycin therapy after adjustment for confounders (HR, 0.57; 95% CI, 0.46–0.71). Half of the patients who received vancomycin definitive therapy had a β-lactam allergy.

Consistent with findings in previous studies, McDanel et al. demonstrated that definitive therapy with a β-lactam for MSSA bacteremia was associated with better patient outcomes than definitive therapy with vancomycin. This protective effect was augmented when patients received guideline-concordant β-lactam therapy (with cefazolin or an antistaphylococcal penicillin). The study’s strengths included a large sample size and multicenter design, both of which provided enhanced external validity relative to previous small, single-center cohort studies. However, the study also had important limitations. First, the results may not be generalizable to all patient populations, since 98% of the participants were male and all study centers were VA facilities. Second, data were collected from a database that did not capture potentially confounding influences on patient outcomes (e.g., dosing, ICU admissions, ID consultation, source of infection, source control). Third, the study did not adequately address one of its objectives, which was to determine whether vancomycin empirical therapy is associated with worse outcomes relative to empirical therapy with a β-lactam. Previous studies have shown that patients with MSSA bacteremia who were switched from vancomycin empirical therapy to β-lactam definitive therapy had better outcomes than patients who received vancomycin for both empirical and definitive therapy. However, it is unclear whether patients who are switched from vancomycin empirical therapy to β-lactam definitive therapy have similar or worse outcomes than patients who receive β-lactams for both empiri-
Antibiotics were continued for 7 days at the treating clinician’s discretion. The absolute trough concentration between 10 and 20 mg/L was maintained to prevent the development of resistance.

Vancomycin (a glycopeptide) twice daily or vancomycin (a glycopeptide) twice daily or trimethoprim–sulfamethoxazole was chosen for treatment of serious MRSA infections, including bacteremia, endocarditis, pneumonia, meningitis, and joint infections. However, clinical data supporting the use of trimethoprim–sulfamethoxazole for nonbacteremic MRSA infections is lacking.

Paul et al. Trimethoprim–sulfamethoxazole versus vancomycin for severe infections caused by meticillin-resistant Staphylococcus aureus: randomised controlled trial

Despite a decrease in the prevalence of MRSA among *S. aureus* bloodstream isolates in the United States from 2005 to 2011,20 MRSA remains a significant cause of bacteremia and other serious infections in the United States and worldwide.21 Although vancomycin is widely considered to be the drug of choice for serious MRSA infections, concerns regarding decreased vancomycin efficacy due to the “MIC creep” phenomenon and concerns regarding vancomycin nephrotoxicity have led clinicians to consider alternative therapeutic agents.22,23 Trimethoprim–sulfamethoxazole is an attractive option due to its proven efficacy in less serious MRSA infections and high degree of activity against MRSA bloodstream isolates.24,25 However, clinical data supporting the use of trimethoprim–sulfamethoxazole in the treatment of serious MRSA infections are lacking.

Paul et al.26 conducted a four-center, randomized, open-label noninferiority trial involving patients with severe MRSA infections, including bacteremia, who received either trimethoprim–sulfamethoxazole (320 mg of trimethoprim) twice daily or vancomycin (a starting dose of 1 g daily, with the dosage adjusted to maintain a trough concentration between 10 and 20 mg/L) at the treating clinician’s discretion. Antibiotics were continued for 7 days or longer, depending on the treatment indication. The primary outcome of interest was the rate of treatment failure (a composite of death, persistent fever, persistent hypotension, nonimprovement in Sequential Organ Failure Assessment [SOFA] score, and persistent bacteremia). Key secondary outcomes included all-cause mortality at 30 days, change in treatment, and development of resistance to either of the study agents. Safety outcomes, including acute kidney injury, rash, leukopenia, and *Clostridium difficile* infection, were also assessed. Notably, patients with left-sided endocarditis were excluded, as were patients with meningitis or chronic renal failure and certain neutropenic patients, including bone marrow transplant recipients.

A total of 252 patients were randomly assigned to receive either trimethoprim–sulfamethoxazole (n = 135) or vancomycin (n = 117). The groups were well balanced with regard to clinical characteristics, with the exception of bacteremia, which occurred at a high rate in the vancomycin-treated group (43% versus 30% in the trimethoprim–sulfamethoxazole group). The most common primary infectious sources were complicated skin and soft tissue infections (roughly one third of patients in both groups), bone and joint infections (also roughly one third of patients overall), pneumonia, endovascular infections, primary bacteremia, and other serious infections (each occurring at a rate of 6–14%). Patients were generally chronically ill (a median Charlson Comorbidity Index score of 2.6 in each group) with superimposed acute illness (approximately 50% of patients in each group had a SOFA score of ≥1).27 No significant difference was found in the rates of clinical failure in patients receiving trimethoprim–sulfamethoxazole and those receiving vancomycin (38% and 27%, respectively; risk ratio [RR], 1.38 [95% CI, 0.96–1.99]); however, the lower limit of the 95% CI for the absolute between-group difference (−1.2% to 21.5%) exceeded the prespecified noninferiority margin of 15%, and, therefore, the noninferiority of trimethoprim–sulfamethoxazole to vancomycin could not be established.

Based on several studies performed in different settings and patient populations, β-lactam–based therapy is generally considered to be superior to vancomycin for the treat-
ment of MSSA bacteremia. Due to in vitro and in vivo reports that cefazolin may be subject to an inoculum effect associated with high-level production of type A β-lactamases in deep-seated MSSA infections, there is clinical controversy surrounding the use of cefazolin (versus the antistaphylococcal penicillins oxacillin and nafcillin) for these infections. Previous studies exploring the relative efficacy of cefazolin in this setting have generally supported the use of cefazolin, although relatively few cases of endocarditis were assessed in those studies. As oxacillin and nafcillin are relatively poorly tolerated and cefazolin is substantially easier to administer than those drugs, additional information supporting the use of cefazolin for deep-seated MSSA infections is sorely needed.

In order to address that knowledge gap, Rao et al. performed a two-center, retrospective cohort review of outcomes data on adult inpatients with MSSA bacteremia who received more than 48 hours of definitive therapy with either cefazolin or oxacillin between January 2010 and April 2013. The primary outcome of interest was treatment failure, defined as (1) a switch in therapy away from cefazolin or oxacillin due to clinician documentation of ineffectiveness or (2) in-hospital mortality, with documentation of MSSA as the primary inciting factor. Additional outcomes analyzed were in-hospital mortality, duration of bacteremia, and documented adverse events. Outcomes were assessed based on the initial treatment of choice (i.e., cefazolin versus oxacillin) using multivariate logistic regression analysis with adjustment for confounding factors. A subgroup analysis was performed to assess the rate of treatment failure among patients with deep-seated infections (e.g., IE, bone and joint infections, osteomyelitis, pneumonia, vascular graft infections, deep-seated abscesses).

Overall, 161 patients were included in the analysis (103 treated with cefazolin and 58 with oxacillin). Notably, patients treated with cefazolin versus oxacillin were generally more acutely ill, with higher APACHE II scores (mean ± S.D., 13 ± 6.3 versus 10.3 ± 5.8; p = 0.009), and a higher proportion had acute renal dysfunction (49.5% versus 29.3%, p = 0.013). Additionally, patients treated with cefazolin were more likely than oxacillin-treated patients to have an implanted prosthetic device (21.4% versus 8.6%, p = 0.048) and to have a line-related infection (45.6% versus 24.1%, p = 0.007) but also had a higher rate of source control (76.7% versus 51.7%, p = 0.001). Deep-seated infections occurred in 31.1% of cefazolin-treated patients (53.1% of those with endocarditis), in comparison to 34.5% of patients (60.0% of those with endocarditis) in the oxacillin-treated group (p = 0.66). Overall, treatment failure occurred more frequently (but not significantly so) in the oxacillin-treated group (12.1% versus 5.8%; adjusted OR, 3.76 [95% CI, 0.98–14.4], p = 0.053), while a change in therapy to an alternative agent was significantly more common among oxacillin-treated patients (43.1% versus 20.4%, p = 0.002). The lack of a significant difference in rates of treatment failure persisted in the subgroup of patients with deep-seated infections (15.6% in the cefazolin group versus 20.0% in the oxacillin group, p = 0.72). None of the other outcomes of interest, including mortality, duration of bacteremia, or documented adverse effects, differed significantly between treatment groups; additionally, recurrent infection was not more frequent among cefazolin-treated patients.

The study results indicate that for patients with MSSA bacteremia (including those with a deep-seated focus), cefazolin and oxacillin appear to be equally effective options, with treatment failure rates numerically favoring cefazolin-treated patients. Moreover, a change in therapy to alternative agents occurred more than twice as frequently in patients treated with oxacillin as in patients receiving cefazolin. This study was notably limited by its retrospective nature and the observed differences in adequate source control favoring cefazolin; these factors preclude definitive conclusions about the effectiveness of cefazolin relative to oxacillin for the treatment of MSSA bacteremia. However, this study, in addition to previously published literature, yielded strong evidence that cefazolin is as effective as antistaphylococcal penicillins in the treatment of serious infections and may have the advantage of being far better tolerated.

Sawyer et al. Trial of short-course antimicrobial therapy for intraabdominal infection

The optimal duration of antibiotic therapy for complicated intraabdominal infections remains unclear. The mainstay of treatment is primarily surgical; once adequate source control is achieved, antibiotics play an important but secondary role. 2010 guidelines from the Surgical Infection Society (SIS) and IDSA recommended that antibiotics be continued no longer than 4–7 days after source control; however, this recommendation was based on expert opinion, and actual practice has varied widely.

Sawyer et al. conducted the Study To Optimize Peritoneal Infection Therapy (STOP-IT), an open-label, randomized, controlled multicenter trial investigating whether the administration of fixed-duration antibiotic therapy for 4 days after adequate source control could result in outcomes equivalent to those with the traditional strategy of administration of antibiotics until 2 days after resolution of systemic inflammatory response syndrome, with treatment continued for a maximum of 10 days.

A total of 518 patients from 23 institutions in the United States and Canada underwent 1:1 randomization from 2008 to 2013. The two groups were well balanced with respect to age (mean, 52.2 years in both groups), sex (55.8% male in both groups), ethnicity, infection characteristics, and surgical procedures. The most common site...
of origin for intraabdominal infection was the colon or rectum (34%). Adequate source control was achieved in approximately one third of the patients with percutaneous drainage. The mean APACHE II scores at the time of the index infection were 10.3 in the experimental group and 9.9 in the control group. Antibiotics were given for 4 days (IQR, 4–5 days) in the experimental group and 8 days (IQR, 5–10 days) in the control group. The protocol allowed for physician choice of antibiotics per the SIS–IDSA guidelines, with no specified minimum duration of i.v. therapy.\textsuperscript{84} Adherence to the Surviving Sepsis Campaign guidelines on use of nonantibiotic adjunctive therapies in the management of sepsis was encouraged.\textsuperscript{85}

No significant difference was found in the primary endpoint, a composite of surgical site infection, recurrent intraabdominal infection, and death within 30 days, in the experimental versus control group (rate of occurrence, 21.8% versus 22.3%; absolute difference, –0.5 percentage point; 95% CI, –7.0 to 8.0 points; \(p = 0.92\)). The primary outcome was largely driven by a high rate of recurrent intraabdominal infection in both groups (15.6% in the experimental group and 13.8% in the control group, \(p = 0.67\)). Adherence to the study protocol for specified antibiotic duration was 81.8% in the experimental group, as compared with 72.7% in the control group.

Study limitations included (1) enrollment of only half of the targeted total of 1010 patients deemed necessary for sufficient statistical power to detect a significant difference between the two groups and (2) moderately high protocol nonadherence, which created a bias favoring the null hypothesis of no difference in therapy. Since no significant between-group difference was demonstrated at the interim analysis, the study was defunded due to concern for futility, and the enrollment target was not attained. The results of the STOP-IT trial suggested but did not prove that a shorter (i.e., four-day) fixed course of antibiotic therapy will produce no clinically significant differences, as compared with traditional longer-duration antibiotic therapy tailored according to resolution of symptoms and markers of infection, in patients with intraabdominal infections once adequate source control is achieved by surgical intervention.

The release of an update of the current SIS–IDSA guidelines is expected in spring 2017.

**Tamma et al. Carbenapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum \(\beta\)-lactamase bacteremia\textsuperscript{11}**

Increased use of the third-generation cephalosporins in the 1980s contributed to the emergence of gram-negative organisms producing ESBLs capable of hydrolyzing many \(\beta\)-lactam antibiotics.\textsuperscript{86} Carbenapenems emerged as the drugs of choice based on improved outcomes (relative to outcomes with alternative regimens) in early studies, but overuse of carbenapenems is not without consequences, and broad use of carbenapenems may facilitate emergence of multidrug-resistant organisms such as carbenapenem-resistant Enterobacteriaceae.\textsuperscript{87} As a result, alternative therapies are needed to minimize treatment selection pressure due to excessive use of carbenapenems. A 2011 study in Spain provided some evidence that the use of \(\beta\)-lactam/\(\beta\)-lactamase inhibitor (BLBLI) combination therapies such as amoxicillin–clavulanate and piperacillin–tazobactam was associated with outcomes similar to those with use of carbenapenems, but that study primarily involved patients with bacteremia arising from the urinary or biliary tract and was potentially confounded by a lower severity of illness in the BLBLI group.\textsuperscript{88} Tamma et al.\textsuperscript{11} attempted to control for that and other potential confounders by focusing only on empirical therapy with either piperacillin–tazobactam or a carbenapenem followed by definitive therapy with a carbenapenem in patients with ESBL bacteremia at Johns Hopkins Hospital. Patients initiated on piperacillin–tazobactam whose therapy was subsequently modified to any noncarbenapenem regimen were excluded from the analysis, as were patients receiving piperacillin–tazobactam despite documentation of an isolate resistant to piperacillin–tazobactam (defined as a MIC of >16 \(\mu\)g/mL). Propensity scoring was used to control for confounding covariates, including age, Pitt bacteremia score, ICU placement, immunosuppression, infection source, and underlying medical conditions. The primary outcome was mortality within the first 14 days after bacteremia onset.

Overall, 103 patients received piperacillin–tazobactam and 110 a carbenapenem empirically. The groups differed with respect to the incidence of structural lung disease and baseline immunosuppression, but after adjustment with the use of propensity scores, the cohorts were very well matched. Approximately one third of patients were in the ICU on day 1 and had a mean Pitt bacteremia score of 2, and just over half of the patients in each group were immunocompromised. The most common source of bacteremia in both groups was central line–associated bacteremia, followed by urinary and intraabdominal sources. Mortality rates at 14 days were 17% in the piperacillin–tazobactam group and 8% in the carbenapenem group (HR, 1.78; 95% CI, 1.00–3.13); in the multivariable analysis, the adjusted HR for mortality with piperacillin–tazobactam use was 1.92. The study authors concluded that carbenapenems should be considered preferred therapy for patients suspected to have ESBL bacteremia.

This study was a valuable addition to the existing literature. The investigators addressed some limitations of the aforementioned study in Spain through excellent matching of the groups after controlling for im-

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important confounders and by focusing specifically on the role of empirical therapy by excluding patients who did not receive carbapenems as definitive therapy. Nonetheless, several study limitations are worth noting. The most important limitation was the exclusion of over 100 patients who were changed from piperacillin–tazobactam to other therapies (primarily ciprofloxacin and trimethoprim–sulfamethoxazole), indicating a patient population who may have been doing well on empirical piperacillin–tazobactam therapy; this exclusion could have resulted in selection bias. In addition, the most common source of infection was central line–related infection, but line management practices were not assessed. Given the study’s retrospective design, it is possible that important differences between patients empirically treated with piperacillin–tazobactam and those treated with carbapenems were not captured. Moreover, the study authors acknowledged that broad use of carbapenems for patients with suspected ESBL bacteremia is associated with the potential for further development of resistance to carbapenems. It is reasonable to assume that patients at the highest risk for ESBL bacteremia, such as those with prior infections due to ESBL-producing organisms, particularly those who are critically ill, may benefit from application of the study results, but further data to guide appropriate patient selection in order to limit carbapenem overuse are needed.

Lundgren et al., for the INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection

Recommendations regarding the threshold at which to initiate antiretroviral therapy (ART) in asymptomatic HIV-infected individuals have remained controversial. According to current U.S. federal and World Health Organization guidelines, ART should be started in all HIV-infected individuals to prevent disease progression. However, there is a lack of evidence from randomized trials to guide the optimal timing of ART initiation for patients with high CD4+ T-lymphocyte counts. A current recommendation to initiate ART in patients with CD4+ counts of >500 cells/mm³ is grounded in conflicting data from observational cohort studies and a randomized controlled trial involving the use of an ART deferral strategy that is no longer endorsed; thus, the recommendation is based on expert opinion and moderate-quality evidence.

The INSIGHT START Study Group conducted a randomized controlled trial in 35 countries to answer the question of whether early initiation of ART in asymptomatic HIV-infected individuals with high CD4+ counts can provide clinical benefits. From April 2009 to December 2013, patients with a baseline CD4+ count of >500 cells/mm³ were randomly assigned to either immediate or deferred ART initiation until a decline in the CD4+ count to 350 cells/mm³ or development of an AIDS-related condition that dictated the use of ART. The primary efficacy endpoint was a composite of any serious AIDS-related and non–AIDS-related events, including death. On May 15, 2015, the independent data and safety monitoring board determined that based on interim analyses, the study objective had been met.

The study population consisted of 2326 patients in the immediate-initiation group and 2359 patients in the deferred-initiation group; in each group, the median CD4+ count was 651 cells/mm³ at enrollment. The mean follow-up time was three years. Tenofovir, emtricitabine, and efavirenz were the most commonly prescribed antiretroviral medications; drug selection was based on guideline recommendations and available medications at the time the study was conducted. As for the primary endpoint, 42 patients in the immediate-initiation group and 96 patients in the deferred-initiation group experienced an AIDS-related or non–AIDS-related event (HR, 0.43; 95% CI, 0.30–0.62; p < 0.001). Although death from any cause was considered a component of the primary endpoint, no significant difference in mortality was observed between the two groups (HR, 0.58; 95% CI, 0.28–1.17; p = 0.13). The most common events in the immediate- and deferred-initiation groups were cardiovascular disease (29% versus 15%), non–AIDS-defining cancer (21% versus 19%), and tuberculosis (14% versus 20%). Patients in the immediate-initiation group had a 72% relative reduction in serious AIDS-related events (p < 0.001), which was mainly due to decreased rates of tuberculosis, Kaposi’s sarcoma, and malignant lymphomas. No significant difference in rates of symptomatic grade 4 events (defined as potentially life-threatening symptomatic events not attributable to AIDS that required medical intervention) was observed between the two groups.

Given the significant decrease in overall complications observed in the study, the study results support the guideline recommendation that ART should be initiated in HIV-infected patients with CD4+ counts of >500 cells/mm³.

Conclusion

With the growing number of significant ID-related publications each year, it can be challenging to stay current with the literature. This review of important ID pharmacotherapy publications in 2015 may be helpful in identifying key articles and lessening this burden.

Disclosures

Dr. Aitken has served on advisory boards for Astellas, Theravance, and Actavis. The other authors have declared no potential conflicts of interest.

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