Invasive Gram-Positive Bacterial Infection in Cancer Patients

Thomas Holland,¹ Vance G. Fowler Jr,¹ and Samuel A. Shelburne III²,³

¹Department of Medicine, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina; ²Department of Infectious Diseases, and ³Department of Genomic Medicine, MD Anderson Cancer Center, Houston, Texas

Systematic studies have shown that gram-positive organisms are the leading cause of invasive bacterial disease in patients with cancer. A broad range of gram-positive bacteria cause serious infections in the cancer patient with the greatest burden of disease being due to staphylococci, streptococci, and enterococci. The evolution of cancer therapy and the changing epidemiology of major gram-positive pathogens mean that ongoing efforts are needed to understand and mitigate the impact of these bacteria in patients with malignancy. The development of novel antibacterials, optimization of treatment approaches, implementation of improved vaccines, and manipulation of the microbiome are all active areas of investigation in the goal of improving the survival of the cancer patient through amelioration of the disease burden of gram-positive bacteria.

Keywords. gram-positive bacteria; infection; neutropenia; antimicrobial resistance.

Gram-positive bacteria account for at least half of all microbiologically documented infections in cancer patients [1]. Immunosuppression induced by the underlying cancer or its attendant therapy, such as neutropenia, and the breakdown in mucosal barriers, such as occurs following long-term vascular catheter placement or during graft vs host disease, synergize to make cancer patients particularly susceptible to gram-positive infections. Such infections are often caused by resistant organisms, such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) due to healthcare-associated exposure and selection from antimicrobial prophylaxis. Although a number of gram-positive organisms have been reported to cause disease in patients with malignancy, this article will focus on S. aureus, streptococci, and enterococci.

STAPHYLOCOCCUS AUREUS

Epidemiology

Although the prevalence of S. aureus as a cause of infection in cancer patients varies widely depending on the specific population, the type of infection studied, and geographic location, S. aureus has a major clinical impact on patients with malignancy [2]. A systematic analysis of bacteremia studies published since 2008 among all cancer patients found that S. aureus accounted for between 1.3% and 12% of all cases [3]. However, only looking at bloodstream infections may lead to significant underestimation of the impact of S. aureus. For example, among nonneutropenic cancer patients in 9 Asian countries, skin and soft tissue infection (26.7%) and pneumonia (25.4%) were the most common types of infections caused by S. aureus, whereas bacteremia only accounted for 14.0% [4]. Having pneumonia was an independent risk factor for mortality, and the observed 30-day mortality rate of both pneumonia and bacteremia approached 50%, which is substantially higher than that observed in patients who do not have cancer. The percentage of S. aureus isolates among cancer patients that are methicillin-resistant varies geographically but broadly appears to be on the rise [3]. This may, however, be at least partially offset by more...
encouraging data, suggesting that the incidence of invasive MRSA infections is declining overall, at least in the United States.

Treatment
Invasive methicillin-susceptible *S. aureus* (MSSA) infections should be treated with an anti-staphylococcal beta-lactam such as cefazolin or nafcillin. In a matched case control study in which approximately 40% of patients had cancer, treatment of MSSA bacteremia with vancomycin, as opposed to a beta-lactam, was associated with higher mortality [5]. Vancomycin remains the mainstay of treatment for MRSA; however, high vancomycin failure rates among patients with cancer and MRSA bloodstream infection have been reported [6]. Vancomycin minimum inhibitory concentrations (MIC) at the high end of the susceptibility range are associated with higher mortality in MRSA bloodstream infection, although there are limited data to suggest that alternative antibiotics are superior among high MIC isolates [7]. In a retrospective matched cohort of patients with MRSA bacteremia and MIC $\geq$ 1 μg/mL, only 5.9% of whom had active cancer, risk of clinical failure was lower among patients treated with daptomycin than with vancomycin [8]. Studies of newer anti-staphylococcal antibiotics (eg, daptomycin, ceftaroline) in cancer patients have thus far been limited, though generally favorable [9]. A randomized study of vancomycin vs linezolid for the treatment of febrile neutropenic patients with a suspected gram-positive infection included too few patients with *S. aureus* infection to make a clinically meaningful conclusion [10].

**STREPTOCOCCI**

**Epidemiology**
For this article, we will stratify streptococci into viridans group streptococci (VGS), β-hemolytic streptococci, and *Streptococcus pneumoniae*. Streptococci not classified into these groups rarely cause invasive disease in patients with cancer and thus will not be discussed further [11]. Many epidemiologic studies of infections in cancer patients do not subclassify streptococci, so precise epidemiology is limited. However, VGS, which are prominent members of the oral microbiome, are generally the most common cause of streptococcal infections in patients with cancer, particularly in the setting of neutropenia [12]. Although many VGS infections are relatively mild, a significant proportion of infected patients develop the VGS shock syndrome, characterized by diffuse pulmonary infiltrates, rash, and refractory hypotension with a high mortality rate [13]. Cancer is a risk factor for invasive disease due to β-hemolytic streptococci, particularly *S. agalactiae* or group B streptococci (GBS). Among cancer patients, GBS predominantly affects those with breast cancer in which recurrent bouts of postsurgical cellulitis are problematic [11]. Malignancy is also a risk factor for invasive disease due to *S. pneumoniae*, with persons having active leukemia, lymphoma, or myeloma, or those having undergone stem cell transplantation having the highest incidence [14]. Pneumonia is the most common source of *S. pneumoniae* bacteremia in cancer patients, but other sources of bacteremia, including occult, have been reported [11, 15]. Although most invasive infections due to *S. pneumoniae* in cancer patients are caused by serotypes found in the major pneumococcal vaccines, being immunocompromised has been found to be a risk factor for invasive pneumococcal disease caused by nonvaccine covered serotypes [16].

**ENTEROCOCCI**

**Epidemiology**
Although generally considered low virulence organisms, enterococci disproportionately affect patients with malignancy and are a major cause of difficult to treat infections in the cancer population [20]. The vast majority of enterococcal infections in cancer patients are bacteremias caused by either *E. faecium* or *E. faecalis* with recent data suggesting a predominance of *E. faecium* [9, 21]. Identified risk factors predisposing cancer patients to enterococcal infections have included nosocomial infection onset, prior antibiotic exposure, prolonged neutropenia, and stem cell transplantation [20–23]. Identification of vancomycin-resistant enterococci in the stool of cancer patients, particular at high levels, is a strong predictor of subsequent enterococcal bacteremia [22–24].

**Treatment**
Therapy of enterococcal infections in cancer patients is complicated by the propensity of the organism to develop antimicrobial resistance and its tolerance to β-lactam antimicrobials [25]. Although *E. faecalis* isolates may retain penicillin susceptibility, β-lactam resistance is nearly universal among *E. faecium* strains.
in cancer patients, and vancomycin resistance is common [21, 22, 26]. Most studies suggest poorer outcomes for patients with VRE infections compared to vancomycin-susceptible enterococci, but this finding may be derived more from host than pathogen factors [27, 28]. The most widely used antimicrobials for VRE bacteremia in cancer patients are daptomycin and linezolid, but the optimal drug and dose is not currently known [29, 30].

**ACTIVE INVESTIGATIVE AREAS AIMED AT DECREASING THE IMPACT OF GRAM-POSITIVE INFECTIONS IN CANCER PATIENTS**

There are a multitude of efforts underway that aim to mitigate the impact of gram-positive infections in patients with malignancy. A major ongoing study seeking to optimize treatment duration for patients with staphylococcal bacteremia will include a significant number of cancer patients [available at: http://clinicaltrials.gov/ct2/show/NCT01191840?term=staphylococcal+bacteremia&rank=12].

Similarly, strategies to optimize vaccine response against *S. pneumoniae* in the immunocompromised patient continue to evolve [31]. The high burden of MRSA and VRE colonization in cancer patients suggests that targeted screening and/or decolonization strategies might be particularly cost-effective in this group of patients, but data are needed to define optimal approaches [32]. Similarly, the high rate of antibiotic use and antimicrobial resistance in cancer patients means implementation of antimicrobial stewardship efforts are needed to mitigate the rise of drug-resistant pathogens [33]. Finally, characterization and manipulation of the host microbiome offers promising hope for preemptive therapeutics and prevention of gram-positive infections [24, 34].

**CONCLUSIONS**

The combination of cancer induced and cancer therapy-related immunosuppression predisposes patients with malignancy to serious infections caused by a vast array of gram-positive pathogens. The impact of particular gram-positive species on the cancer population is dynamic in terms of specific patient population, location, and geography. The significant influence of these organisms means that efforts aimed at reducing gram-positive infection-related morbidity and mortality need to continue to be supported and expanded in order to improve the outcome of the cancer patient.

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