

Antibiotic-Resistant Gram-Negative Bacterial Infections in Patients With Cancer

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Patients with cancer are at high risk for infections caused by antibiotic resistant gram-negative bacteria. In this review, we summarize trends among the major pathogens and clinical syndromes associated with antibiotic resistant gram-negative bacterial infection in patients with malignancy, with special attention to carbapenem and expanded-spectrum β -lactam resistance in *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*—all major threats to our cancer patients. Optimal therapy for these antibiotic-resistant pathogens still remains to be determined.

Keywords. infections; neutropenia; carbapenem-resistant Enterobacteriaceae; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*.

A dramatic evolution has recently occurred in the significance of infections caused by gram-negative bacteria. Decades of progress in the care of patients with cancer, concomitant to the development of safe and effective antimicrobials, are being undermined. Patients with cancer, particularly those with hematologic malignancies, remain exquisitely vulnerable to infection with gram-negative bacteria as a result of neutropenia, lymphocyte dysfunction, mucositis, and the use of invasive devices [1]. At the same time, the effectiveness of our current prophylactic and empiric antibiotic regimens is compromised by the emergence of gram-negative bacteria that exhibit multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) phenotypes (Table 1) [2]. This trend is exacerbated by the successful global dissemination of “high-risk clones” of MDR gram-negative bacteria [3]. In this review, we focus on relevant examples of gram-negative bacteria that cause infections in patients with cancer, and point to important developments in their treatment.

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

Bacteria originating from the gastrointestinal tract are often responsible for infections in cancer patients with neutropenia. Broad-spectrum β -lactam agents are the cornerstone of treatment of cancer patients with suspected infection by Enterobacteriaceae. Therefore, the increasing prevalence in our healthcare system of carbapenem-resistant Enterobacteriaceae (CRE), also resistant to other β -lactams, poses an urgent threat [4].

The impact of CRE on patients with cancer is highlighted by the recent outbreak of carbapenem-resistant *Klebsiella pneumoniae* at the US National Institutes of Health Clinical Center, where patients with lymphoma or solid tumors did not survive bloodstream infections caused by CRE [5]. In patients with hematologic malignancies who were treated at a referral cancer center, CRE bloodstream infection was associated with an 89% chance of ineffective empiric therapy, a 55-hour delay in the institution of appropriate antibiotics, and a 69% mortality rate [6].

The chief mechanism of carbapenem resistance in Enterobacteriaceae from the United States is hydrolysis by the serine enzyme *K. pneumoniae* carbapenemase (KPC) [7]. Multilocus sequence typing of KPC-producing *K. pneumoniae* reveals the predominance of sequence

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Table 1. Antibiotic-Resistant Phenotypes of *Pseudomonas aeruginosa* Considered Multidrug Resistant, Extensively Drug Resistant, and Pandrug Resistant

Antibiotic Class	Antibiotic	Multidrug Resistant	Extensively Drug Resistant	Pandrug Resistant
Phosphonic acids	Fosfomycin			X
Polymyxins	Polymyxin B			X
	Colistin			X
Carbapenems	Imipenem	X	X	X
	Meropenem		X	X
Aminoglycosides	Tobramycin		X	X
	Amikacin		X	X
	Gentamicin	X	X	X
Cephalosporins	Ceftazidime	X	X	X
	Cefepime		X	X
Fluoroquinolones	Ciprofloxacin	X	X	X
	Levofloxacin	X	X	X
β -lactam + β -lactamase inhibitors	Piperacillin-tazobactam		X	X
	Ticarcillin-clavulanate		X	X

An X indicates resistance to the corresponding antibiotic.
Source: Based on definitions by Magiorakos et al [2].

type (ST) 258 containing the Tn4401 transposon, with variations upstream of the *bla*_{KPC} gene. This mobile genetic element is also found in isolates from around the world [8]. The recent worldwide dissemination of the New Delhi metallo- β -lactamase (NDM) and other metallo- β -lactamases is also noteworthy [9].

FLUOROQUINOLONE-RESISTANT *ESCHERICHIA COLI*

The prevention of infection through the prophylactic use of fluoroquinolones has been effective in the subset of “high-risk” cancer patients [10]. Since the inception of fluoroquinolone prophylaxis, controversy has arisen regarding its long-term impact on fluoroquinolone use and resistance [11]. The proportion of fluoroquinolone-resistant *Escherichia coli* in a comprehensive cancer center in the United States increased from <15% of isolates in the 1990s to 46% in 2009 [12]. In England, fluoroquinolone-resistant isolates are much more frequent in patients with hematologic malignancy than in other oncology patients [13]. These patterns bode poorly for the future of fluoroquinolone prophylaxis.

ESCHERICHIA COLI ST131 PRODUCING CTX-M-15

Studies have linked fluoroquinolone-resistant *E. coli* with the emergence of the virulent strain ST131. Furthermore, *E. coli* ST131 frequently harbors CTX-M-15 (cefotaximase-Munich), an extended-spectrum β -lactamase (ESBL) [14]. Detailed genomic

analysis suggests that the clonal expansion of ST131 and its subclone H30 is the main “driver” of the epidemic of fluoroquinolone-resistant *E. coli* worldwide [15]. Fluoroquinolone-resistant *E. coli* ST131 is also implicated as the cause of pyomyositis in patients with hematological malignancy [16]. Although ESBL production is present in <10% of *E. coli*, this phenotype accounts for up to 20% of bloodstream isolates among cancer patients, and is the most common mechanism behind bloodstream infections caused by MDR gram-negative bacteria [17]. Interestingly, fecal carriage of ESBL-producing *E. coli* was as high as 29% in a Spanish cohort of neutropenic patients with leukemia or hematopoietic stem cell transplant, but was not associated with bloodstream infection, mortality, or length of hospital stay [18].

PSEUDOMONAS AERUGINOSA

Another peril of fluoroquinolone prophylaxis in neutropenic patients is the risk of bloodstream infections caused by *Pseudomonas aeruginosa* [19]. Concomitantly, the prevalence of MDR *P. aeruginosa* has markedly increased, in association with infection-related death in patients with hematologic malignancy [20].

In general, resistance to β -lactam antibiotics in *P. aeruginosa* is due to hyperproduction of the cephalosporinase AmpC (from ampicillin-resistant mutant C), with the interplay of mutations in OprD (outer membrane protein D) and upregulation of drug-efflux pumps in the case of carbapenem-resistant strains. Acquired carbapenemases, such as metallo- β -lactamases, are only detected sporadically in the United States [21]. The first US isolate of metallo- β -lactamase-producing *P. aeruginosa*

was obtained from a patient with breast cancer and possessed VIM-7 (Verona integron–encoded metallo- β -lactamase), a distinct member of the VIM family. In the same cancer center, VIM-2–producing *P. aeruginosa* was later isolated from a patient from the Near East [22, 23]; indeed, carbapenem resistance in *P. aeruginosa* mediated by VIM-2 has long been common in the Mediterranean basin [24]. More recently in Italy, the fatal outcome of infection with NDM-1–producing *P. aeruginosa* was reported in a patient with leukemia previously hospitalized in Serbia [25]. This isolate belonged to *P. aeruginosa* ST235, associated with VIM throughout Europe and identified as an internationally successful XDR “high-risk clone” [26].

ACINETOBACTER BAUMANNII

Our understanding of the genetic diversity and the population structure of *Acinetobacter* has given rise to the concept of MDR clonal lineages. The predominant clone type has shifted from clonal cluster 3 (CC3 in the Pasteur scheme, or CC110 in the Oxford scheme) to clonal cluster 2 (CC2 or CC92), associated with carbapenem resistance mediated by the β -lactamase OXA-23 (oxacillinase) [27]. In Pittsburgh, where CC2 is prevalent, the mortality rate of patients with cancer and MDR *Acinetobacter baumannii* infection reached 55% [28]. Interestingly, a multivariate analysis revealed that the risk factors for acquisition of MDR *A. baumannii* were related to healthcare exposure, such as need for dialysis and length of previous intensive care, rather than to the underlying cancer [28]. In patients undergoing hematopoietic stem cell transplant, pneumonia (occurring after engraftment) was the main source of MDR

A. baumannii bloodstream infections, with overwhelming mortality (95%) [29].

STENOTROPHOMONAS MALTOPHILIA

The hallmark of *Stenotrophomonas maltophilia* is intrinsic antibiotic resistance. Its chromosome harbors 2 β -lactamases: L1, a metallo- β -lactamase with carbapenemase activity that does not hydrolyze aztreonam; and L2, a serine cephalosporinase that is inhibited by clavulanic acid. Additionally, *S. maltophilia* possesses a relatively impermeable membrane, and like *P. aeruginosa*, expresses efflux pumps and acquires additional resistance determinants in class 1 integrons. Trimethoprim-sulfamethoxazole (TMP-SMX) remains the main reliable antibiotic option to treat infections caused by *S. maltophilia*, although resistance to TMP-SMX has emerged; tigecycline, minocycline, moxifloxacin, and, in particular, colistin may offer activity [30]. Bloodstream infection with *S. maltophilia* is associated commonly with central lines, and strong consideration should be given to catheter removal [31]. Patients with hematologic malignancy may develop fulminant hemorrhagic pneumonia caused by *S. maltophilia* [32].

IMPLICATIONS FOR PRESENT AND FUTURE ANTIBIOTIC THERAPY

At the present time, clinicians struggle to devise effective guidelines that assist with the choice of therapy for infections caused by antibiotic resistant gram-negative bacteria in cancer patients [33]. The notion that in the immunologically impaired cancer patient “the first dose of antibiotics must really count” should

Table 2. Potential Combination Antibiotic Regimens and Examples of Novel Antibiotics Against Select Multidrug-Resistant Gram-Negative Bacteria

Bacteria and Phenotype	Suggested Antibiotic Combinations	Mechanism of β -Lactam Resistance	Novel Antibiotics
MDR and carbapenem-resistant Enterobacteriaceae	Carbapenem + tigecycline + (aminoglycoside or polymyxin) [35–37]	KPC in <i>Klebsiella pneumoniae</i> ST258	Ceftazidime/avibactam [38] MK-7655 + imipenem [38] Biapenem + RPX7009 [38]
		NDM	Aztreonam/avibactam [38]
MDR and carbapenem-resistant <i>Pseudomonas aeruginosa</i>	Carbapenem + polymyxin \pm rifampin [39–41] Carbapenem + intravenous fosfomycin [41]	AmpC hyperproduction	Ceftolozane/tazobactam [42] Ceftazidime/avibactam [43]
		OprD2 changes	Ceftolozane/tazobactam [42] BAL30072 + meropenem [44] MK-7655 + imipenem [45]
		Metallo- β -lactamases	BAL30072 + meropenem [44]
MDR and carbapenem-resistant <i>Acinetobacter baumannii</i>	Carbapenem + polymyxin [46] Sulbactam + polymyxin [47] Tigecycline + polymyxin [48]	OXA-23 in clone 2 (CC2/CC92)	BAL30072 + meropenem [49] (no other OXAs)

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug resistant; NDM, New Delhi metallo- β -lactamase; OprD, outer membrane protein D; OXA, oxacillinase-type β -lactamase; ST, sequence type.

remain the prevailing wisdom [34]. Although clinical evidence needs to be stronger in this regard, we suggest the use of combination antibiotic chemotherapy for empiric and definitive treatment of serious infections where certain MDR pathogens are suspected or recovered (Table 2). The risk of selection of antibiotic-resistant pathogens and the inability of current microbiological methods to deliver their timely identification merit giving consideration to this approach.

It is clear that the introduction of novel antibiotics will lead to improvements in the treatment of MDR, XDR, and PDR gram-negative bacterial infections, recognizing that a “magic bullet” does not exist and that therapeutic needs will remain unsatisfied (Table 2). The future use of novel agents will be informed and molded by developments in rapid molecular diagnostic testing. For instance, the rapid detection of *K. pneumoniae* in the bloodstream with the simultaneous confirmation of KPC and exclusion of a metallo- β -lactamase would permit the confident use of an antibiotic active against the former, but not the latter, carbapenemase. Such an approach is also a blueprint for clinical investigations where rapid molecular testing enhances patient selection and targeted use of antibiotics. Presently, the implementation of effective antimicrobial stewardship [50] and infection control programs remains essential. Regardless of how these practices develop and how the landscape of antimicrobial resistance evolves, we anticipate that fundamental lessons on how to treat gram-negative bacterial infections will continue to be learned from patients with cancer and neutropenia [51].

Notes

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