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Chemotherapy Alliance for Neutropenics and Control of Emerging Resistance (CANCER) Program: Initial Report From Haematology-Oncology Hospitals in North America

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ABSTRACT

Background: The CANCER Program was founded (2001) to monitor resistance (R) in antimicrobial and antifungal therapies used for cancer patients.
Methods: 1,992 bacterial isolates from bloodstream (BSI) and other infections were isolated at 32 oncology centers, sent to a central laboratory and tested by NCCLS methods against 41 antimicrobials.
Results: *S. aureus* (SA; n=361, 18.1%), *E. coli* (EC; 285, 14.3%), CoNS (282, 14.1%), *Enterococcus* spp. (ESP; 197, 9.9%), and *Klebsiella* spp. (KSP; 191, 9.6%) were the top 5 pathogens during 2001. Vancomycin (VAN; MIC_{90}, 1 µg/ml), linezolid (LZD; 2 µg/ml), quinupristin/dalfopristin (Q/D; 0.5 µg/ml), chloramphenicol (8 µg/ml) and rifampin (<0.25 µg/ml) demonstrated no R among SA. For CoNS (MIC_{90} in µg/ml), LZD (1), VAN (2), and Q/D (0.5) showed no R, while LZD (2) was completely active against ESP. Among agents tested against EC and KSP, carbapenems (MIC_{90}, ≤0.25 µg/ml), cefepime (≤0.12 µg/ml) and amikacin (AMK; 2-4 µg/ml) provided 100% activity. For other cephalosporins and fluoroquinolones, susceptibility (S) was: cefoxitin (92-95%), ceftazidime (98-99%), ceftriaxone (98-100%), ciprofloxacin (93-98%) and gatifloxacin (92-98%). Gentamicin (96-99% S; MIC_{90}, ≤1 µg/ml) and tobramycin (TOB; 97-99%;1 µg/ml) also provided high activity and the ESBL rate ranged from 2-5% in EC and KSP. Piper/tazo (P/T; MIC_{90}, 4 µg/ml) had high S rates for EC (96%) and KSP (98%). AMK and TOB along with polymyxins were the only agents with S rates (94, 98 and 95%) higher than the best ß-lactam (P/T; 90%) against *P. aeruginosa*. Yeast BSI (50; 6 spp.) showed complete S to amphotericin B, but 22% fluconazole-R (usually *C. krusei* or *glabrata*). Molecular studies detected a unique metallo-ß-lactamase in a *P. aeruginosa* isolate (Texas).
Conclusions: Elevated R rates were not observed in monitored CANCER centers during the baseline year of this novel, longitudinal surveillance program. BSI were the most frequent infection type (78% of isolates). Newer antifungals such as caspofungin have a wider spectrum than azoles.

INTRODUCTION

The assessment of empiric and culture-directed therapies for neutropenic patients is constantly changing and requires prudent antimicrobial usage. Treatment regimens for patients presenting with neutropenic fever require the integration of national guidelines with comprehensive risk assessments based on individual patient characteristics. Previous findings suggest that the successful therapeutic outcomes differ from institution to institution, and warrant special consideration based on local results, which are supplemented by data obtained from large surveillance programs.

Former concerns over the influence of methicillin-resistant staphylococcus and vancomycin-resistant enterococcus strains have been complicated by newer resistance mechanisms such as extended-spectrum and metallo ß-lactamases, efflux pumps and bacterial membrane alterations. Additionally, the continued dominant prevalence of Gram-positive organisms in the haematology/oncology population increases the need for novel antimicrobials for this patient population.

The Chemotherapy Alliance for Neutropenics and Control of Emerging Resistance (CANCER) Surveillance Program was developed as a three-year program to monitor a wide variety of broad-spectrum antimicrobial agents in haematology-oncology centers from diverse geographic regions in North America. The following report represents the experience from the initial, benchmark year of this innovative, longitudinal surveillance program.

MATERIALS AND METHODS

A total of 32 regional oncology centers and hospitals in North America submitted 1,992 bacterial and 50 yeast isolates to a central monitoring laboratory (JMI Laboratories) for testing. Over 1500 pathogens from 2001 and an additional 538 strains from 2000 were tested from cancer patients receiving treatment for nosocomial- or community-acquired infections. Infection sites included: blood stream, skin and soft tissue, respiratory tract and urinary tract. Primary species identification was performed at each participating medical center using their routine methodologies. Confirmation of organism identification was performed at the central monitoring laboratory using Vitek® Automated Microbial Identification system (bioMerieux, Hazelwood, MO) or other standardized methods.

Bacterial strains were tested against 41 antimicrobial agents and interpreted using reference broth microdilution standards as described by the NCCLS. Organisms were suspended in Mueller Hinton broth with the appropriate supplements and a final inoculum of approximately 5 X 10^5 CFU/ml was achieved using Sensititre® automated inoculators (TREK Diagnostics, Westlake, OH).

Suspected ESBL-producing phenotypes of enteric bacilli, based on NCCLS criteria of ceftazidime or ceftriaxone or aztreonam MICs at ≥2 µg/ml, were confirmed using Etest ESBL strips (AB BIODISK, Solna, Sweden). A positive result was identified when a ≥ eight-fold decrease was observed in the cephalosporin MIC in the presence of clavulanic acid. Suspected metallo ß-lactamase producing phenotypes of non-fermentors were based on high level resistance to carbapenems and ceftazidime. Confirmation using an investigational Etest MBL strip was identified when a ≥ eight-fold decrease was observed in the imipenem MIC in the presence of EDTA. Susceptibility testing for yeast isolates was performed using Etest strips and NCCLS interpretations.

A novel metallo-ß-lactamase producing strain of *P. aeruginosa* containing a VIM-4 metallo enzyme and a subsequent OXA-41 ß-lactamase enzyme was submitted to the CANCER Program in July of 2001. The blood culture isolate of *P. aeruginosa* from this patient in Houston, Texas was submitted to the central reference laboratory at JMI Laboratories. Primary identification was performed using Vitek® GNI+ cards, bionumber: 61704000440. The organism was tested against broth microdilution panels (MIC; µg/ml):

Ceftazidime	>16	Aztreonam	>16
Imipenem	>8	Amikacin	>32
Meropenem	>8	Gentamicin	>8
Amox/clav	>16	Tobramycin	>16
Piperacillin	128	Ciprofloxacin	>2
Pip/tazo	>64	Levofloxacin	>4
Ticarcillin	>128	Gatifloxacin	>4
Ticar/clav	>128	Garenoxacin	>4
Cefuroxime	>16	Tetracycline	>8
Ceftriaxone	>32	Nitrofurantoin	>32
Cefoxitin	>32	Trim/sulfa	>2/38
Cefepime	>16	Polymyxin B	2

The potential metallo¶-lactamase activity was confirmed utilizing Etest MBL strips; imipenem results > 256 µg/ml and 6 - 12 µg/ml for imipenem with EDTA.

The VIM-4 enzyme has a novel "VIM-like" metallo¶-lactamase displaying 69% identity with the VIM-1 enzyme, but demonstrates significant amino acid divergence from the European VIM-1. The gene sequences of such enzymes encoding resistance were carried on mobile gene cassettes and inserted into plasmid or chromosomal class 1 integrons. The OXA-41 enzyme was similar to class D (Bush group 2d) ß-lactamases which utilizes a serine active site residue. More closely related to previously categorized OXA-18 than any other oxacillinase, its origin is likely to be from *Salmonella* spp. rather than a strain of *P. aeruginosa*.

RESULTS

- Overall, 53% of the bacterial isolates submitted to the CANCER Program in the initial year were Gram-positive organisms. The rank order of the top five pathogens was: *S. aureus* (18.1%), *E. coli* (14.3%), CoNS (14.1%), *Enterococcus* spp. (9.9%) and *Klebsiella* spp. (9.6%), Table 1.

- Imipenem (MIC_{90}, 0.25 µg/ml), cefepime (MIC_{90}, ≤ 0.12 µg/ml) and amikacin (MIC_{90}, 2 - 4 µg/ml) showed activity against all *E. coli* and *Klebsiella* spp. The next most active agents by % susceptibility were: ceftriaxone (98.9 - 100%), ceftazidime (98.2 - 99%), gentamicin (96.1 - 99%), tobramycin (96.8 - 99%) and piperacillin/tazobactam (96 - 98.4%). ESBL phenotype rates for *E. coli* and *Klebsiella* spp. were 5.6 and 2.8% respectively.

- Against *P. aeruginosa* isolates, amikacin (97.7%), tobramycin (94.3%) and polymyxin B (94.6% using a suggested breakpoint of ≤ 2 µg/ml) were the only agents with susceptibilities better than the best ß-lactam, piperacillin/tazobactam (89.8%). Trimethoprim/ sulfamethoxazole (100%) and gatifloxacin (90.7%) were the only other agents providing >90% coverage for *S. maltophilia*.

- No vancomycin (MIC_{90}; 1-2 µg/ml), linezolid (MIC_{90}; 1 - 2 µg/ml), or quinupristin/dalfopristin (MIC_{90}; 0.5 µg/ml) resistance was observed among isolates of *S. aureus*, CoNS or *Streptococcus* spp. *Enterococcus* spp. displayed almost complete susceptibility to linezolid (99.5%), while 21% of the strains were resistant to vancomycin. The quinupristin/dalfopristin resistance rates approached 60% due to the dominant numbers of *E. faecalis* isolates.

- Linezolid displayed the broadest coverage (> 99.5%) against the top five Gram-positive pathogens, while amikacin (94.4%) and gatifloxacin (93.4%) displayed the broadest activity for the five prevailing Gram-negative pathogens.

Table 1. Frequency of occurrence of bacterial pathogens from medical centers participating in the 2001 CANCER Program.

Rank	Organism	No. of occurrences (%)
1	*Staphylococcus aureus*	361/(18.1)
2	*Escherichia coli*	285/(14.3)
3	Coagulase negative staphylococci[a]	282/(14.1)
4	*Enterococcus* spp.	197/(9.9)
5	*Klebsiella* spp.	191/(9.6)
6	*Pseudomonas aeruginosa*	176/(8.8)
7	Other streptococci[a]	111/(5.6)
8	*Enterobacter* spp.	78/(3.9)
9	*Stenotrophomonas maltophilia*	54/(2.7)
10	*S. pneumoniae*	52/(2.6)

a. Includes ß-haemolytic streptococci (41 strains) and viridans group streptococci (70 strains).

Table 2. Activities and spectrum for activity of 22 antimicrobial agents tested against the five most prevalent causes of Gram-negative infection in the CANCER Program (39.3% of all isolates).

Antimicrobial class/ agent tested	Activity[a] by organism (no. tested): *E. coli* (285) $MIC_{50/90}$	% S/R	*Klebsiella* spp. (191) $MIC_{50/90}$	% S/R	*P. aeruginosa* (176) $MIC_{50/90}$	% S/R	*Enterobacter* spp. (78) $MIC_{50/90}$	% S/R	*S. maltophilia* (54) $MIC_{50/90}$	% S/R
Penicillins										
Ampicillin	4/>16	61.4/36.5	>16/>16	6.3/70.2	>16/>16	0.0/100.0	>16/>16	3.8/75.6	>16/>16	1.9/94.4
Amoxicillin/Clavulanate	4/16	84.6/8.1	≤2/8	96.3/1.0	>16/>16	6.6/89.4	>16/>16	5.1/93.6	>16/>16	1.9/94.4
Piperacillin	2/>128	68.4/23.9	4/128	82.7/12.0	8/>128	88.1/11.9	>2/64	83.3/8.9	>128/>128	24.1/75.9
Piperacillin/Tazobactam	1/4	96.0/2.5	2/4	98.4/0.5	4/>64	89.8/10.2	2/32	89.7/2.6	>64/>64	46.3/53.7
Ticarcillin	4/>128	63.5/35.1	128/>128	6.8/71.2	32/128	84.1/15.9	4/>128	78.2/17.9	128/>128	42.6/57.4
Ticarcillin/Clavulanate	4/64	82.1/4.6	4/16	93.2/0.5	32/128	85.8/14.2	4/128	84.6/12.8	32/128	85.2/14.8
Cephalosporins										
Cefazolin	≤2/16	89.5/7.7	≤2/4	95.3/3.7	>16/>16	1.7/98.3	>16/>16	5.1/93.6	>16/>16	0.0/100.0
Cefuroxime	4/8	94.4/3.5	2/8	95.3/2.1	>16/>16	0.6/98.9	8/>16	59.0/23.1	>16/>16	0.0/100.0
Cefoxitin	4/8	94.4/4.6	2/8	92.1/2.6	>32/>32	0.6/99.4	>32/>32	2.6/93.6	>32/>32	0.0/100.0
Ceftazidime	≤0.12/0.25	98.2/1.4/(4.6%)[b]	0.12/0.5	99.0/0.5/(2.1%)[c]	≤2/>16	87.5/10.2	≤2/>16	85.9/11.5	2/>16	63.0/31.5
Ceftriaxone	≤0.25/≤0.25	98.9/0.7/(2.1%)[b]	≤0.25/≤0.25	100.0/0.0/(1.6%)[b]	>32/>32	11.9/60.2	≤0.25/16	85.9/7.7	>32/>32	1.9/90.7
Cefepime	≤0.12/≤0.12	100.0/0.0	≤0.12/≤0.12	100.0/0.0	2/16	86.4/5.7	≤0.12/1	100.0/0.0	16/>16	38.9/33.3
Other ß-lactams										
Aztreonam	≤0.12/0.25	98.2/0.7/(4.2%)[b]	≤0.12/0.25	98.4/1.6/(2.1%)[b]	8/>16	69.3/17.6	≤0.12/>16	87.2/10.3	>16/>16	5.6/87.0
Imipenem	≤0.12/0.25	100.0/0.0	≤0.12/0.25	100.0/0.0	1/8	88.6/6.1	0.5/1	100.0/0.0	>8/>8	1.9/98.1
Fluoroquinolones										
Ciprofloxacin	≤0.015/0.25	92.3/7.7	0.015/0.25	97.9/2.1	0.25/2	87.5/8.5	≤0.015/0.25	98.7/1.3	2/>2	41.5/34.0
Gatifloxacin	≤0.03/0.25	92.9/5.7	≤0.03/0.25	97.9/0.5	0.5/4	87.5/9.7	≤0.03/0.12	98.7/0.0	1/2	90.7/5.6
Aminoglycosides										
Amikacin	2/4	100.0/0.0	1/2	100.0/0.0	4/8	97.7/1.7	2/2	100.0/0.0	>32/>32	25.9/59.3
Gentamicin	≤1/≤1	96.1/3.9	≤1/≤1	99.5/0.5	2/8	88.1/5.7	≤1/≤1	97.4/2.6	>8/>8	20.4/72.2
Tobramycin	0.5/1	96.8/1.8	0.5/0.5	99.0/0.5	0.5/1	94.3/0.6	0.5/1	96.2/3.8	>16/>16	20.4/68.5
Miscellaneous										
Polymyxin B	≤1/≤1	-/-	≤1/≤1	94.2/5.8	2/2	94.6/5.4[c]	≤1/>8	-/-	2/8	65.9/34.1[c]
Tetracycline	≤4/>8	78.6/21.4	≤4/>8	-/-	>8/>8	2.8/89.8	≤4/8	88.5/7.7	>8/>8	5.6/77.8
Trimethoprim/ Sulfamethoxazole	≤0.5/>2	78.9/20.7	≤0.5/≤0.5	90.1/9.4	>2/>2	4.0/95.5	≤0.5/≤0.5	94.9/3.8	≤0.5/≤0.5	100.0/0.0

a. MIC_{50} and MIC_{90} in µg/ml at which 50 and 90% of the isolates, respectively, were inhibited; % S, percent of isolates susceptible per NCCLS [2002] criteria, % R percent of isolates resistant using NCCLS [2002] criteria.
Interpretive criteria for *S. maltophilia* were those applied to *P. aeruginosa* [NCCLS, 2002].
b. Percentage in parenthesis indicates the ESBL phenotype rates using MIC concentrations of ≥ 2 µg/ml for aztreonam or ceftazidime or ceftriaxone.
c. Interpretive criteria for polymyxin B was taken from Gales et al. (2001) for non-fermentative Gram-negative organisms only.

Table 3. Activities and spectrum for activity of 24 antimicrobial agents tested against the five most prevalent causes of Gram-positive infection in the CANCER Program (50.3% of all isolates).

Antimicrobial class/ agent tested	Activity[a] by organism (no. tested): *S. aureus* (361) $MIC_{50/90}$	% S/R	CoNS (282) $MIC_{50/90}$	% S/R	*Enterococcus* spp. (197) $MIC_{50/90}$	% S/R	Viridans gr. strept (70) $MIC_{50/90}$	% S/R	*S. pneumoniae* (52) $MIC_{50/90}$	% S/R
Penicillins										
Ampicillin	16/>16	[b]	4/16	[b]	≤2/>16	65.3/34.7	≤2/4	[b]	≤2/4	[d]
Amoxicillin/Clavulanate	≤2/16	[c]	≤2/8	[c]	≤2/>16	[b]	≤2/4	[b]	≤2/4	88.5/3.8
Oxacillin	0.5/>8	70.6/29.4	4/>8	22.0/78.0	>8/>8	[d]	≤0.06/2	[d]	≤0.06/8	[d]
Penicillin	8/32	11.6/88.4	4/32	9.9/90.1	4/>32	64.5/35.5	0.06/2	70.0/8.6	≤0.015/2	76.9/15.4
Piperacillin/Tazobactam	2/64	[c]	2/8	[c]	8/>64	[b]	≤0.5/8	[d]	≤0.5/4	[d]
Cephalosporins										
Cefazolin	≤2/>16	[c]	≤2/>16	[c]	>16/>16	[d]	>2/>16	[d]	≤2/8	[d]
Ceftazidime	8/>16	67.3/25.8	16/>16	[c]	>16/>16	[d]	≤2/>16	[d]	2/16	[d]
Ceftriaxone	4/>32	[c]	8/32	[c]	>32/>32	[d]	≤0.25/2	85.7/5.7	≤0.25/1	92.3/0.0
Cefepime	4/>16	[c]	4/16	[c]	>16/>16	[d]	≤0.12/2	85.7/8.6	≤0.12/1	92.3/0.0
Other ß-lactams										
Imipenem	≤0.06/2	[c]	0.25/>8	[c]	4/>8	[d]	≤0.06/0.12	[d]	≤0.06/0.25	82.7/0.0
Fluoroquinolones										
Ciprofloxacin	0.5/>2	67.3/31.0	>2/>2	29.1/69.9	>2/>2	33.7/62.2	2/>2	[d]	1/2	[d]
Gatifloxacin	0.06/>4	76.7/13.3	2/>4	78.4/13.8	>4/>4	40.3/56.6	0.25/4	82.9/17.1	0.25/0.5	100.0/0.0
Macrolides-Lincosamines-Streptogramins										
Clindamycin	0.12/>8	73.4/26.0	0.12/>8	57.8/41.8	>8/>8	[d]	≤0.06/≤0.06	98.6/0.0	≤0.06/>8	88.5/11.5
Erythromycin	0.5/>8	52.1/47.1	>8/>8	26.2/73.4	>8/>8	9.6/68.5	≤0.06/2	54.3/38.6	≤0.06/>8	69.2/30.8
Quinupristin/Dalfopristin	0.25/0.5	99.7/0.0	0.25/0.5	98.9/0.0	4/8	35.5/59.4	0.5/1	100.0/0.0	0.5/0.5	100.0/0.0
Glycopeptides										
Teicoplanin	0.5/1	100.0/0.0	2/8	94.3/1.1	0.25/>16	81.2/15.2	≤0.12/≤0.12	[d]	≤0.12/≤0.12	100.0/0.0
Vancomycin	1/1	100.0/0.0	2/2	99.6/0.0	1/>16	78.7/21.3	0.5/0.5	100.0/0.0	0.25/0.5	100.0/0.0
Other classes										
Chloramphenicol	8/8	90.6/0.0	4/8	95.0/3.2	8/8	92.4/4.6	≤2/4	100.0/0.0	≤2/4	96.2/3.8
Gentamicin[e]	≤1/≤1	95.3/4.2	≤1/>8	67.4/19.9	≤500/>1000	67.0/33.0[f]	2/8	[d]	8/>8	[d]
Linezolid	2/2	100.0/0.0	1/1	100.0/0.0	2/2	99.5/0.0	1/1	100.0/0.0	1/2	100.0/0.0
Rifampin	≤0.25/≤0.25	99.4/0.0	≤0.25/≤0.25	93.6/6.0	2/>2	39.1/39.6	≤0.25/≤0.25	[d]	≤0.25/≤0.25	100.0/0.0
Streptomycin[e]	-/-	[d]	-/-	2000/>2000	48.7/51.3[f]	-/-	[d]	-/-	[d]	[d]
Tetracycline	≤4/>4	93.6/5.3	≤4/>8	82.3/17.0	>8/>8	43.9/53.1	≤2/>8	74.3/25.7	≤2/8	88.5/11.5
Trimethoprim/ Sulfamethoxazole	≤0.5/≤0.5	95.0/3.6	>2/>2	41.8/56.4	1/>2	[d]	≤0.5/>2	[d]	≤0.5/>2	71.2/19.2

a. MIC_{50} and MIC_{90} in µg/ml at which 50 and 90% of the isolates, respectively, were inhibited, % S, percent of isolates susceptible per NCCLS [2002] criteria, % R percent of isolates resistant using NCCLS [2002] criteria.
b. Categorical criteria based on test results with penicillin (staphylococci and viridans group streptococci) or ampicillin (enterococci).
c. Categorical criteria based on test results with oxacillin, except where the spectrum would be inferior (example: ceftazidime versus S. aureus isolates).
d. No interpretive criteria have been published.
e. High-level resistance screen for synergy when combined with cell-wall active co-drugs.

Table 4. Susceptibility testing of six antifungal agents using the Etest method against 50 yeast isolates from blood stream infections.

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% susceptible/resistant
C. albicans (20)	Amphotericin B	0.19	0.25	0.064-0.25	100.0/0.0
	Fluorytosine	0.064	0.25	0.032-32	100.0/0.0
	Caspofungin	0.125	0.19	0.064-0.25	-
	Fluconazole	0.5	256	0.19-256	80.0/15.0
	Itraconazole	0.032	1	0.006-32	85.0/15.0
	Voriconazole	0.016	0.064	0.004-32	-
C. glabrata (13)	Amphotericin B	0.25	0.38	0.125-0.5	100.0/0.0
	Fluorytosine	0.016	0.023	0.012-0.02	100.0/0.0
	Caspofungin	0.19	0.25	0.125-0.38	-
	Fluconazole	16	256	6-256	7.7/23.1
	Itraconazole	32	32	8-32	0.0/100.0
	Voriconazole	0.38	12	0.19-12	-
C. parapsilosis (7)	Amphotericin B	0.5	-	0.125-2	85.7/14.3
	Fluorytosine	0.047	-	0.032-0.06	100.0/0.0
	Caspofungin	1	-	0.38-1.5	-
	Fluconazole	1.5	-	0.5-6	100.0/0.0
	Itraconazole	0.25	-	0.012-0.75	42.9/0.0
	Voriconazole	0.047	-	0.008-0.125	-
C. tropicalis (6)	Amphotericin B	0.25	-	0.125-0.5	100.0/0.0
	Fluorytosine	0.032	-	0.012-0.05	100.0/0.0
	Caspofungin	0.25	-	0.19-0.38	-
	Fluconazole	0.75	-	0.5-3	100.0/0.0
	Itraconazole	0.38	-	0.094-1.5	16.7/16.7
	Voriconazole	0.064	-	0.047-0.38	-
C. krusei (3) and *C. guilliermondii* (1)	Amphotericin B	0.38	-	0.094-0.5	100.0/0.0
	Fluorytosine	32	-	0.008-32	0.0/75.0
	Caspofungin	0.38	-	0.38-2	-
	Fluconazole	32	-	16-64	0.0/25.0
	Itraconazole	1	-	0.75-2	0.0/75.0
	Voriconazole	0.25	-	0.047-0.5	-

CONCLUSIONS

- Against *E. coli* and *Klebsiella* spp., imipenem, cefepime and amikacin provided complete coverage. Against non-fermentors like *P. aeruginosa*, amikacin, tobramycin, polymyxin B and piperacillin/tazobactam provided ≥ 90% coverage while isolates of *S. maltophilia* were most susceptible to trimethoprim/sulfamethoxazole and gatifloxacin.
- Linezolid demonstrated complete activity against the top five Gram-positive organisms.
- Amphotericin B displayed the greatest spectrum against submitted yeast isolates, whereas azoles like fluconazole displayed significantly reduced activity.
- Elevated resistance rates were not observed in this first year of the CANCER Program as compared to general hospital isolates of the same species.
- Two novel ß-lactamases were discovered in a strain of *P. aeruginosa* submitted to the CANCER Program. The isolate contained a VIM-4 metallo- and OXA-41 ß-lactamase enzymes.
- Longitudinal monitoring of pathogens infecting neutropenic patients, such as the CANCER Program can assist in the development of therapeutic strategies as it applies to future changes in the resistant patterns of bacteria and fungi.

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