1165

Monitoring For Antimicrobial Resistance in North American Haematology-Oncology Centers: Results from the CANCER Resistance Surveillance Program (USA; 2000-2002)

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AMENDED ABSTRACT

Background: The Chemotherapy Alliance for Neutropenics and the Control of Emerging Resistance (CANCER) program monitored susceptibility (S) of pathogens recovered in haematology-oncology centers from 2000-2002. Isolates from 32 hospitals were analyzed for trends in pathogen occurrence and S profiles.

Methods: 3,970 isolates recovered from neutropenic patients were analyzed centrally (JMI Laboratories, IA). MICs were determined using NCCLS methods and interpretive criteria, including those for extended spectrum ß-lactamase (ESBL) phenotypes (≥2 µg/ml).

Results: Ranking pathogens (%) included *S. aureus* (SA; 19.3), coagulase-negative staphylococci (CoNS; 14.1), *E. coli* (EC; 13.4), enterococci (10.2), *Klebsiella* spp. (KS; 9.5), *P. aeruginosa* (PSA; 8.8), *Enterobacter* spp. (ENT; 3.8), viridans group streptococci (2.5), *S. maltophilia* (SM; 2.4) and ß-haemolytic streptococci (2.2). 35.3 and 78.8% of SA and CoNS were oxacillin-R, respectively. 22% of enterococci were vancomycin-resistant. Among Gram-negatives, EC and KS were >90% S to piperacillin/tazobactam (P/T), third generation cephems, and levofloxacin (LEV) with 4.0 and 2.4% of these species, respectively, expressing ESBL phenotypes. ENT were less susceptible to P/T, ceftazidime (CTZ) and aztreonam (83.7 to 88.2%; Amp C), but EC, KS and ENT were fully S to cefepime (CEF), carbapenems (CRB) and amikacin (AK). PSA were variable with 82.6 to 89.5% S to P/T, CTZ, CEF, CRB, gentamicin and ciprofloxacin. Only AK, tobramycin and polymyxin B were more active (94.9 to 97.7% S). SM were only S to LEV (89.7%) and trimethoprim/sulfamethoxazole (100.0%).

Conclusions: R rates seen here do not reflect greater R in neutropenic patients compared with other hospitalized patients. The prevalence of Gram-negative pathogens (46.4%) is worrisome given the potential for more rapid R emergence in this group, warranting continued monitoring for these at-risk patients.

INTRODUCTION

During the previous two decades, significant changes have been documented in the prevalence of bacterial organisms occurring in oncology patients who experience neutropenia. The CANCER (Chemotherapy Alliance for Neutropenics and the Control of Emerging Resistance) surveillance program was developed as a three-year program to monitor the occurrence of bacterial and fungal pathogens and their antibiograms in hematology-oncology centers from diverse regions in North America.

During the initial year (2000-2001) of the study, *Staphylococcus aureus, Escherichia coli*, coagulase-negative staphylococci, *Enterococcus* spp., *Klebsiella* spp. and *Pseudomonas aeruginosa* represented the most frequently isolated pathogens. While resistance rates were found to generally mimic those found in non-neutropenic hospitalized patients, the continued increase in resistance among the common Gram-positive pathogens and emerging high-level resistance in Gram-negatives via horizontal transfer of genetic elements warranted continued monitoring. Significant age-related variations in pathogen occurrence and species-specific resistance patterns were also documented with isolates from patients ≤ 14 years of age displaying greater susceptibility.

This report summarizes the results of an examination of all data collected during 2000-2002, analyzing for pathogen prevalence and susceptibility patterns, including the presence of isolates with extended spectrum beta-lactamase (ESBL) occurring in neutropenic patients.

MATERIALS AND METHODS

Specimen Collection. A total of 3,970 non-duplicate bacterial strains were submitted from patients hospitalized in one of the 32 participating oncology treatment centers. Specimens originated from bloodstream infections, pneumonias, urinary tract infections and skin and from soft tissue infections and were either nosocomial- or community-acquired. Isolates were initially identified by the submitting laboratory and subsequently shipped to the monitoring laboratory (The JONES Group/JMI Laboratories, Iowa, USA) where identifications were confirmed using standard biochemical algorithms.

Susceptibility Testing. All strains were tested by the National Committee for Clinical Laboratory Standards (NCCLS) reference broth microdilution method in Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci) against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of febrile neutropenia. Interpretation of quantitative MIC results was in accordance with NCCLS methods and criteria. Enterobacteriaceae with elevated MICs (≥2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase-producing phenotypes according to NCCLS criteria. Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *Streptococcus pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212. All recorded QC results were within ranges as established by NCCLS.

RESULTS

- The 10 ranking pathogens (Table 1) recovered included *S. aureus* (19.3), coagulase-negative staphylococci (14.1), *E. coli* (13.4), enterococci (10.2), *Klebsiella* spp. (9.5), *P. aeruginosa* (8.8), *Enterobacter* spp. (3.8), viridans group streptococci (2.5)*, Stenotrophomonas maltophilia* (2.4) and ß-haemolytic streptococci (2.2). Gram-negative pathogens comprised 46.4% of all isolates studied.
- Oxacillin resistance was detected in 35.3% (increase from 29.4% in 2000/2001) and 78.7% of *S. aureus* and coagulase-negative staphylococci, respectively (Table 2).
- 22% of enterococci were resistant to vancomycin, remaining unchanged from the first year of the study.
- Among Gram-negative species, *E. coli* and *Klebsiella* spp. were >90% susceptible to piperacillin/tazobactam, third generation cephems, and levofloxacin, with 4.0 and 2.4% of these species, respectively, expressing ESBL phenotypes (Table 3).
- *Enterobacter* spp. were less susceptible to piperacillin/tazobactam, ceftazidime and aztreonam (83.7 to 88.2%) due to the typical presence of cephalosporinases, but along with *E. coli* and klebsiellae were fully susceptible to cefepime, carbapenems and amikacin.
- *P. aeruginosa* was variable in its antibiogram, with 82.6 to 89.5% being susceptible to piperacillin/tazobactam, ceftazidime, cefepime, carbapenems, gentamicin and ciprofloxacin; only amikacin, tobramycin, and polymyxin B were more active (94.9 to 97.7%).
- *S. maltophilia,* the fifth most prevalent Gram-negative organism, was only susceptible to levofloxacin (89.7%) and trimethoprim/sulfamethoxazole (100%).

Table 1. Frequency of occurrence of bacterial pathogens from medical centers participating in the CANCER Program (2000 - 2002).

Organism	Occurrences, n(%)	Site of infection[a] (% for the top two sites)
Staphylococcus aureus	768 (19.3)	58.1 BSI; 20.8 SSTI
Coagulase-negative staphylococci	561 (14.1)	86.1 BSI; 4.5 UTI
Escherichia coli	531 (13.4)	61.8 BSI; 26.7 UTI
Enterococcus spp.	405 (10.2)	65.9 BSI; 14.3 UTI
Klebsiella spp.	377 (9.5)	67.4 BSI; 14.6 UTI
Pseudomonas aeruginosa	351 (8.8)	48.7 BSI; 19.1 PNEU
Enterobacter spp.	153 (3.8)	64.1 BSI; 10.5 UTI
viridans group streptococci	101 (2.5)	84.2 BSI; 1.0 SSTI/1.0 UTI
Stenotrophomonas maltophilia	97 (2.4)	52.6 BSI; 17.5 PNEU
ß-haemolytic streptococci	88 (2.2)	53.4 BSI; 12.5 SSTI
Other species	538 (13.8)	62.5 BSI; 20.6 PNEU

a. BSI = bloodstream infection; SSTI = skin and soft tissue infection; UTI = urinary tract infection; PNEU = pneumonia.

Table 2. Activity and spectrum of 10 ß-lactam antimicrobial agents tested against the five most prevalent causes of Gram-positive infection in the CANCER Program (48.3% of all isolates).

Organism (no. tested)/antimicrobial agent	MIC (µg/ml) 50%	90%	Range	Category: % susceptible	% resistant
S. aureus (768)					
Oxacillin	0.5	>8	≤0.06->8	64.5	35.5
Penicillin	16	32	≤0.016->32	11.8	88.2
Piperacillin/Tazobactam	2	64	≤0.5->64	-[a]	-
Cefazolin	≤2	>16	≤2->16	-[a]	-
Ceftazidime	8	>16	2->16	-[a]	-
Ceftriaxone	4	>32	1->32	-[a]	-
Cefepime	4	>16	0.25->16	-[a]	-
Imipenem	≤0.06	8	≤0.06->8	-[a]	-
Ciprofloxacin	0.5	>2	≤0.25->2	61.7	37.0
Gatifloxacin	0.12	>4	≤0.03->4	70.2	17.2
Levofloxacin	0.25	>4	≤0.03->4	63.3	30.6
Clindamycin	0.12	>8	≤0.06->8	68.0	31.7
Erythromycin	>8	>8	≤0.06->8	48.0	51.5
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-2	99.9	0.0
Teicoplanin	0.5	1	≤0.12-4	100.0	0.0
Vancomycin	1	1	0.25-4	100.0	0.0
Chloramphenicol	8	8	≤2-16	92.6	0.0
Gentamicin	≤2	≤2	≤2->8	95.3	4.2
Linezolid	2	2	0.25-4	100.0	-[a]
Rifampin	≤0.25	≤0.25	≤0.25->2	98.3	1.2
Tetracycline	≤4	≤4	≤4->8	94.5	4.8
coagulase-negative staphylococci (561)					
Oxacillin	4	>8	≤0.06->8	21.2	78.8
Penicillin	4	32	≤0.016->32	10.3	89.7
Piperacillin/Tazobactam	2	8	≤0.5->64	-[a]	-
Cefazolin	≤2	>16	≤2->16	-[a]	-
Ceftazidime	16	>16	2->16	-[a]	-
Ceftriaxone	8	>32	≤0.25->32	-[a]	-
Cefepime	4	16	≤0.12->16	-[a]	-
Imipenem	0.5	>8	≤0.06->8	-[a]	-
Ciprofloxacin	>2	>2	≤0.25->2	32.1	66.6
Gatifloxacin	2	>4	≤0.03->4	79.3	14.1
Levofloxacin	4	>4	≤0.06->4	36.5	48.8
Clindamycin	0.12	>8	≤0.06->8	59.9	39.6
Erythromycin	>8	>8	≤0.06->8	24.8	74.3
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-2	99.5	0.0
Teicoplanin	2	8	≤0.12->16	95.7	0.7
Vancomycin	2	2	0.25-8	99.8	0.0
Chloramphenicol	4	8	≤2->16	95.7	3.0
Gentamicin	≤2	>8	≤2->8	68.8	19.6
Linezolid	1	2	0.12-2	100.0	-[a]
Rifampin	≤0.25	≤0.25	≤0.25->2	94.7	5.0
Tetracycline	≤4	>8	≤4->8	83.4	16.0
Enterococcus spp. (405)					
Ampicillin	2	>16	≤2->16	68.3	31.7
Ciprofloxacin	>2	>2	≤0.25->2	37.1	27.5
Gatifloxacin	>4	>4	0.06->4	44.3	53.5
Levofloxacin	>4	>4	0.25->4	43.6	55.0
Erythromycin	>8	>8	≤0.06->8	8.9	65.4
Quinupristin/Dalfopristin	8	0.25->8	32.9	62.7	
Teicoplanin	0.25	>16	≤0.12->16	80.7	15.1
Vancomycin	1	>16	≤0.12->16	78.0	22.0
Chloramphenicol	8	8	≤2->16	91.4	6.7
Gentamicin	<500	>1000	≤500->1000	72.8	27.2
Linezolid	2	2	≤0.06-4	99.8	0.0
Rifampin	2	>2	≤0.5->2	35.3	42.0
Streptomycin	≤1000	>2000	≤1000->2000	56.3	43.7
Tetracycline	>8	>8	≤4->8	41.5	56.2
viridans group streptococci (101)					
Penicillin	0.06	2	≤0.016-8	69.3	7.9
Ceftriaxone	≤0.25	2	≤0.25-4	88.1	5.0
Cefepime	≤0.12	2	≤0.12->16	87.1	5.9
Gatifloxacin	0.25	4	≤0.03->4	86.1	11.9
Levofloxacin	1	>4	≤0.03->4	86.1	12.9
Clindamycin	≤0.06	0.06	≤0.06->8	96.0	2.0
Erythromycin	0.5	4	≤0.06->8	48.5	46.6
Quinupristin/Dalfopristin	0.5	1	≤0.06-8	99.0	1.0
Vancomycin	0.5	0.5	≤0.12-1	100.0	0.0
Chloramphenicol	≤2	4	≤2-8	99.0	0.0
Linezolid	1	1	0.12-2	100.0	-[a]
Tetracycline	≤4	>8	≤4->8	70.3[b]	29.7
ß-haemolytic streptococci (88)					
Penicillin	0.03	0.06	≤0.016-0.12	100.0	-[a]
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	-[a]
Cefepime	≤0.12	≤0.12	≤0.12-0.5	100.0	-[a]
Gatifloxacin	0.25	0.5	0.06-0.4	100.0	0.0
Levofloxacin	0.5	1	0.25-2	100.0	0.0
Clindamycin	≤0.06	≤0.06	≤0.06->8	92.0	8.0
Erythromycin	0.06	4	≤0.06->8	78.4	21.6
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-0.5	100.0	0.0
Vancomycin	0.5	0.5	≤0.12-1	100.0	-[a]
Chloramphenicol	≤2	≤2	≤2-4	100.0	0.0
Linezolid	1	1	0.5-2	100.0	-[a]
Tetracycline	>8	>8	≤4->8	44.3[c]	55.7

a. Susceptibility of the ß-lactams would be predicted from the oxacillin MIC results [NCCLS, 2004].
b. No interpretive criteria for this category are available from NCCLS [2004].
c. Includes susceptible and intermediate results.

Table 3. Activity and spectrum of 14 ß-lactam antimicrobial agents tested against the five most prevalent causes of Gram-negative infection in the CANCER Program (39.3% of all isolates).

Organism (no. tested)/antimicrobial agent	MIC (µg/ml) 50%	90%	Range	Category: % susceptible	% resistant
E. coli (531)					
Ampicillin	4	>16	≤2->16	58.0	40.1
Amoxicillin/Clavulanate	4	16	≤2->16	85.1	6.8
Piperacillin	2	>128	≤1->128	63.8	27.5
Piperacillin/Tazobactam	2	4	≤0.5->64	97.1	2.1
Ticarcillin	8	>128	≤1->128	59.1	38.8
Ticarcillin/Clavulanate	4	64	≤1->128	81.0	4.5
Cefazolin	≤2	16	≤2->16	89.6	7.0
Cefuroxime	4	8	≤0.12->16	93.2	3.8
Cefoxitin	4	8	1->32	92.7	5.0
Ceftazidime	≤2	≤2	≤2->16	97.7	1.1(3.9)[a]
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	98.3	0.6(2.6)[a]
Cefepime	≤0.12	≤0.12	≤0.12->16	99.8	0.2
Aztreonam	≤0.12	0.25	≤0.12->16	98.1	1.1(4.0)[a]
Imipenem	0.12	0.25	≤0.06-2	100.0	0.0
Meropenem	≤0.06	≤0.06	≤0.06-1	100.0	0.0
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	90.8	8.8
Gatifloxacin	≤0.03	≤0.03	≤0.03->4	91.5	7.2
Levofloxacin	≤0.03	0.25	≤0.03->4	91.3	7.5
Amikacin	2	4	≤0.25-16	100.0	0.0
Gentamicin	≤2	≤2	≤2->8	95.5	4.5
Tobramycin	0.5	2	0.25->16	96.6	2.0
Polymyxin B	≤1	≤1	≤1->8	99.8[b]	0.2[c]
Tetracycline	≤4	>8	≤4->8	72.9	26.7
Trimethoprim/Sulfamethoxazole	≤0.5	>1	≤0.5->2	76.4[c]	23.6[c]
Klebsiella spp. (377)					
Ampicillin	>16	>16	≤2->16	6.6	70.3
Amoxicillin/Clavulanate	≤2	8	≤2->16	96.0	1.9
Piperacillin	4	128	≤1->128	85.1	10.9
Piperacillin/Tazobactam	2	4	≤0.5->64	97.9	1.3
Ticarcillin	128	>128	2->128	5.3	69.5
Ticarcillin/Clavulanate	4	16	≤1->128	94.2	1.3
Cefazolin	≤2	8	≤2->16	93.1	4.8
Cefuroxime	2	8	≤0.12->16	95.2	2.7
Cefoxitin	2	8	≤0.25->32	93.4	2.6
Ceftazidime	≤2	≤2	≤2->16	98.4	1.3(2.4)[a]
Ceftriaxone	≤0.25	≤0.25	≤0.25-32	99.2	0.0(2.1)[a]
Cefepime	≤0.12	≤0.12	≤0.12-8	100.0	0.0
Aztreonam	≤0.12	0.25	≤0.12->16	98.7	1.3(2.4)[a]
Imipenem	0.12	0.25	≤0.06-1	100.0	0.0
Meropenem	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	97.9	1.9
Gatifloxacin	0.06	0.12	≤0.03->4	97.9	0.5
Levofloxacin	≤0.03	0.25	≤0.03->4	98.1	0.5
Amikacin	1	2	0.5-8	100.0	0.0
Gentamicin	≤2	≤2	≤2->8	98.4	1.1
Tobramycin	0.5	1	≤0.12->16	98.4	0.8
Polymyxin B	≤1	2	≤1->8	97.4[b]	2.6[c]
Tetracycline	≤4	>8	≤4->8	87.5	10.3
Trimethoprim/Sulfamethoxazole[d]	≤0.5	≤0.5	≤0.5->2	94.1[c]	5.9[c]
Enterobacter spp. (153)					
Ampicillin	>16	>16	R->16	3.3	81.0
Amoxicillin/Clavulanate	>16	>16	≤2->16	3.9	94.1
Piperacillin	2	64	≤1->128	81.0	7.9
Piperacillin/Tazobactam	2	32	≤0.5->64	88.2	2.6
Ticarcillin	4	>128	≤1->128	74.5	18.9
Ticarcillin/Clavulanate	4	128	≤1->128	80.4	15.0
Cefazolin	>16	>16	≤2->16	3.3	95.4
Cefuroxime	8	>16	1->16	55.6	26.8
Cefoxitin	>32	>32	≤0.25->32	1.3	96.1
Ceftazidime	≤2	>16	≤2->16	83.7	13.1
Ceftriaxone	≤0.25	16	≤0.25->32	86.3	5.9
Cefepime	≤0.12	≤0.12	≤0.12-8	100.0	0.0
Aztreonam	≤0.12	>16	≤0.12->16	85.6	10.5
Imipenem	0.5	1	0.12-4	100.0	0.0
Meropenem	≤0.06	0.12	≤0.06-4	100.0	0.0
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	98.7	1.3
Gatifloxacin	≤0.03	0.25	≤0.03->4	98.7	0.7
Levofloxacin	≤0.03	0.25	≤0.03->4	98.7	0.7
Amikacin	2	2	0.5-16	100.0	0.0
Gentamicin	≤2	≤2	≤2->8	98.7	1.3
Tobramycin	0.5	1	0.25->16	97.4	2.0
Polymyxin B	≤1	>8	≤1->8	71.6[b]	28.3[c]
Tetracycline	≤4	8	≤4->8	86.3	9.2
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	95.4	4.6
P. aeruginosa (351)					
Piperacillin	8	>128	≤1->128	86.9	13.1
Piperacillin/Tazobactam	4	>64	≤0.5->64	88.6	11.4
Ticarcillin	32	128	≤1->128	80.3	19.6
Ticarcillin/Clavulanate	32	128	≤1->128	80.6	19.4
Ceftazidime	2	>16	≤2->16	85.5	12.3
Ceftriaxone	>32	>32	≤0.25->32	8.5	64.4
Cefepime	2	16	≤0.12->16	84.0	6.3
Aztreonam	8	>16	≤0.12->16	67.0	19.1
Imipenem	1	8	≤0.06->8	88.0	8.0
Meropenem	0.5	8	≤0.06->8	89.5	6.0
Ciprofloxacin	>0.25	>2	≤0.25->2	82.6	12.5
Gatifloxacin	0.5	>4	≤0.03->4	78.6	14.3
Levofloxacin	0.5	>4	≤0.03->4	80.6	12.8
Amikacin	4	8	≤0.25->32	97.7	1.7
Gentamicin	≤2	8	≤2->8	88.9	5.7
Tobramycin	0.5	1	≤0.12->16	94.9	4.3
Polymyxin B	≤1	2	≤1->8	97.4[b]	2.6[c]
S. maltophilia (97)					
Piperacillin	>128	>128	16->128	2.1	78.4
Piperacillin/Tazobactam	>64	>64	1->64	15.5	55.7
Ticarcillin	128	>128	2->128	7.2	59.8
Ticarcillin/Clavulanate	32	128	≤1->128	42.3	15.5
Ceftazidime	8	>16	≤2->16	54.6	37.1
Ceftriaxone	>32	>32	≤0.25->32	1.0	93.8
Cefepime	16	>16	≤0.12->16	33.0	40.2
Aztreonam	>16	>16	4->16	4.1	90.7
Imipenem	>8	>8	0.12->8	1.0	99.0
Meropenem	>8	>8	4->8	1.0	96.9
Ciprofloxacin	2	>2	≤0.016->2	38.5	35.5
Gatifloxacin	1	4	≤0.03->4	89.7	5.2
Levofloxacin	1	4	≤0.03->4	89.7	5.2
Amikacin	>32	>32	4->32	18.6	68.0
Gentamicin	>8	>8	≤2->8	16.5	78.4
Tobramycin	>16	>16	1->16	15.5	75.2
Polymyxin B	2	8	≤1->8	70.1[b]	29.9[c]
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0	0.0

a. Percent resistance in parenthesis indicates those strains meeting the NCCLS [2004] screening criteria (MIC ≥ 2 µg/ml) for an ESBL-producing isolate.
b. Published susceptibility breakpoint of ≤ 2 µg/ml [Gales et al., 2001].
c. Based on 517 isolate results.
d. Based upon 371 isolate results.

CONCLUSIONS

- Bacterial resistance rates seen in neutropenic patients are comparable to those of other hospitalized patients.
- Among all Gram-positive pathogens reported here, linezolid was the most active (99.8 to 100.0% susceptible); with the exception of enterococci, vancomycin and quinupristin/dalfopristin also provided near-complete coverage.
- Among the four most common Gram-negative pathogens, the carbapenems, cefepime, piperacillin/tazobactam and the aminoglycosides provided the most comprehensive coverage.
- Continued monitoring of this at-risk and ever-increasing patient population is warranted given the changes in species trends and antibiograms.
- Guidelines for empiric regimens of antimicrobics in hematology/oncology patients must consider pathogen frequency, contemporary resistance rates and age factors when being established.

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