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Influence of Patient Age on the Occurrence and Antimicrobial Resistance Trends of Isolates from Haematology/Oncology Patients: Second Report from the CANCER Program (2001-2002)

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ABSTRACT

Background: The CANCER Program, established in 2001, is a surveillance study that monitors haematology/oncology (HEMONC) patients in North America. Concerns regarding increasing Gram-positive (GP) pathogens and resistance (R) need further examination by patient age-groups to facilitate improved therapeutic choices. Combined data from 2001-2002 were analyzed for trends in pathogen occurrence and susceptibility (S) patterns among four age groups.

Methods: Participating hospitals submitted significant isolates (3,970) from patients receiving HEMONC care. Species identification was confirmed and S testing performed (central lab) using NCCLS methods against 42 antimicrobials.

Results: The 7 most common pathogens (74% of total) and incidence trends follow:

	% by age group (years):			
Pathogen group (no. tested)	≤ 14	15 - 44	45 - 64	≥ 65
CoNS (505)	24.9	17.4	13.5	9.4
S. aureus (SA; 689)	13.0	21.5	19.2	19.2
E. coli (EC; 489)	10.7	12.2	12.2	18.2
Streptococci (ST; 237)	10.7	6.1	6.2	6.7
P. aeruginosa (PSA; 333)	8.3	8.2	10.3	10.0
Enterococci (ENT; 343)	5.9	7.4	10.4	11.5
Klebsiella spp. (KSP; 334)	5.1	8.2	10.3	10.1

The occurrence of SA, EC, ENT and KSP increased significantly (+48 to 98%); and CoNS and ST decreased markedly (-37 to 62%) with advancing age. GP pathogens declined (55 to 47%) from ≤ 14 to ≥ 65 years. All monitored pathogens were more S in the ≤ 14 yr group, except ST where PEN and macrolides had greater R (41 - 48%). Increased ß-lactam R was found in KSP, EC and PSA for adults; ciprofloxacin generally had decreased S with advancing age (P <0.05). MRSA rates with co-resistances increased with age (6 to 46%) and as did VRE (0 in ≤ 14 to 18 - 24% in adults). Greatest R among PSA was noted in the 15 - 44 age group. ESBL-EC and KSP were 0 - 5 and 1 - 8%, respectively (no age trend).

Conclusions: Significant age-related variations in pathogen occurrence and R-patterns by species were documented. Patients ≤ 14 yrs had more S isolates, except for ST where GP strains predominate. Empiric regimens in HEMONC patients must consider these contemporary age factors.

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 warrants continued monitoring. Examination of age-related effects on pathogen occurrence and susceptibility profiles to maximize treatment outcomes is one variable requiring further examination.

This report summarizes the results of an examination of data collected during 2001-2002, specifically analyzing for trends in pathogen occurrence and susceptibility patterns when patient isolates are stratified according to age.

MATERIALS AND METHODS

Specimen Collection. A total of 3,970 non-duplicate bacterial strains were submitted from patients hospitalized in one of the participating oncology treatment centers. Specimens originated from bloodstream infections, pneumonias, urinary tract infections and from skin and 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 ceftazideme 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 seven most common pathogens recovered included, in descending order, *S. aureus* (17.4%), coagulase-negative staphylococci (12.7%), *E. coli* (12.3%), enterococci (8.6%), *Klebsiella* spp. (8.4%) and *P. aeruginosa* (8.4%).
- The occurrence of *S. aureus, E. coli*, enterococci and *Klebsiella* spp. increased significantly (+48 to 98%) with advancing age whereas coagulase negative staphylococci and streptococci decreased markedly (-37 to 62%) (Figure 1).
- Gram-positive pathogens as a group declined from 55 to 47% with advancing age (≤ 14 to ≥ 65 years).
- All monitored pathogens were more susceptible in the youngest (≤ 14 years) group except for streptococci, where resistance to penicillin and macrolides was greater (41-48%) (Tables 1 and 2).
- In contrast, resistance to ß-lactams among *Klebsiella* spp. *E. coli* and *P. aeruginosa* was greater in adults as was resistance to ciprofloxacin (p< 0.05).
- Increases with the MRSA and VRE rates (6 to 46% and 0 to 18%) were also seen with increasing age.
- The greatest resistance among *P. aeruginosa* was apparent in the 15 to 44 year-old age group.
- ESBL phenotypes for *E. coli* and *Klebsiella* spp. were detected (0 to 5 and 1 to 8%, respectively) but no age-related trend was apparent.

Table 1. Antimicrobial activity of eight to 10 selected broad-spectrum agents tested against four Gram-positive pathogens isolated from four age groups of patients in the CANCER Program (2001 - 2002).

	MIC_{50}/% susceptible[a] by age group (years):			
Organism (no. tested)/antimicrobial	≤14	15-44	45-64	≥65
S. aureus (689)				
Ciprofloxacin	0.5/100	0.5/67	0.5/64	>2/48
Clindamycin	0.12/91	0.12/76	0.12/68	0.12/57
Erythromycin	0.5/64	0.5/51	8/49	>8/42
Gentamicin	≤2/100	≤2/95	≤2/95	≤2/95
Linezolid	2/100	2/100	2/100	2/100
Oxacillin	0.5/94	0.5/69	0.5/66	1/54
Q/D[b]	0.25/100	0.25/100	0.25/100	0.25/100
Vancomycin	1/100	1/100	1/100	1/100
Coagulase-neg staphylococci (505)				
Ciprofloxacin	0.25/60	>2/28	>2/33	>2/17
Clindamycin	0.12/62	0.25/51	0.12/67	0.12/58
Erythromycin	>8/18	>8/26	>8/31	>8/17
Gentamicin	≤2/75	≤2/66	≤2/76	≤2/61
Linezolid	1/100	1/100	1/100	1/100
Oxacillin	4/21	4/19	4/25	4/19
Q/D[b]	0.25/100	0.25/99	0.25/100	0.25/99
Vancomycin	2/100	2/100	2/100	2/100
Enterococci (343)				
Ampicillin	≤2/93	≤2/66	≤2/65	≤2/76
Ciprofloxacin	1/87	>2/34	>2/34	2/44
Gentamicin	≤500/93	≤500/72	≤500/71	≤500/77
Linezolid	2/100	2/100	2/100	2/100
Q/D[b]	8/13	8/34	8/38	8/24
Streptomycin	≤1000/87	>2000/48	≤1000/51	≤1000/63
Teicoplanin	≤0.12/100	0.25/81	0.25/80	≤0.12/83
Vancomycin	1/100	1/76	1/78	1/82
Streptococcus spp. (237)[c]				
Amoxicillin/Clavulanate	≤2/93	≤2/85	≤2/84	≤2/99
Cefepime	0.25/89	≤0.12/91	≤0.12/92	≤0.12/97
Ceftriaxone	≤0.25/93	≤0.25/89	≤0.25/92	≤0.25/98
Clindamycin	≤0.06/100	≤0.06/84	≤0.06/96	≤0.06/96
Erythromycin	≤0.06/52	≤0.06/56	≤0.06/70	≤0.06/70
Levofloxacin	0.5/96	1/98	1/92	1/94
Linezolid	1/100	1/100	1/100	1/100
Penicillin	0.06/59	0.03/67	0.03/79	≤0.015/80
Q/D[b]	0.5/100	0.5/100	0.5/99	0.5/100
Vancomycin	0.5/100	0.5/100	0.5/100	0.5/100

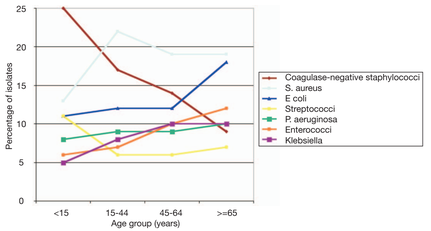
a. Susceptibility was defined by NCCLS [2004] criteria.
b. Q/D = quinupristin/dalfopristin.
c. Includes ß-haemolytic species (75 strains), *S. pneumoniae* (75 strains) and viridans group streptococci (87 strains). Susceptibility determined by applying the most conservative *S. pneumoniae* breakpoints [NCCLS, 2004] to all species.

Table 2. Antimicrobial activity of eight selected broad-spectrum agents tested against three Gram-negative bacilli isolated from four age groups of patients in the CANCER Program (2001 - 2002).

	MIC_{50}/% susceptible[a] by age group (years):			
Organism (no. tested)/antimicrobial	≤14	15-44	45-64	≥65
E. coli (489)				
Amoxicillin/Clavulanate	8/93	8/81	4/85	4/86
Cefepime	≤0.12/100	≤0.12/100	≤0.12/>99	≤0.12/100
Ceftazidime	≤2/100(0.0)[b]	≤2/97(3.6)[b]	≤2/97(5.2)[b]	≤2/98(3.9)[b]
Ceftriaxone	≤0.25/100(0.0)[b]	≤0.25/98(3.7)[b]	≤0.25/97(3.4)[b]	≤0.25/99(1.7)[b]
Ciprofloxacin	≤0.25/96	≤0.25/89	≤0.25/88	≤0.25/94
Gentamicin	≤2/89	≤2/95	≤2/96	≤2/97
Imipenem	0.12/100	0.12/100	0.12/100	0.12/100
Piperacillin/Tazobactam	1/100	1/96	2/97	2/97
Klebsiella spp. (334)				
Amoxicillin/Clavulanate	4/100	≤2/97	≤2/98	≤2/91
Cefepime	≤0.12/100	≤0.12/100	≤0.12/100	≤0.12/100
Ceftazidime	≤2/100(7.7)[b]	≤2/99(1.4)[b]	≤2/99(2.0)[b]	≤2/97(4.0)[b]
Ceftriaxone	≤0.25/100(7.7)[b]	≤0.25/100(1.4)[b]	≤0.25/99(1.4)[b]	≤0.25/99(4.0)[b]
Ciprofloxacin	≤0.25/100	≤0.25/99	≤0.25/97	≤0.25/97
Gentamicin	≤2/100	≤2/96	≤2/99	2/99
Imipenem	0.12/100	0.12/100	0.12/100	0.12/100
Piperacillin/Tazobactam	4/100	2/97	2/99	2/97
P. aeruginosa (333)				
Cefepime	2/86	2/82	2/85	2/86
Ceftazidime	2/86	2/83	2/89	2/86
Ciprofloxacin	≤0.25/100	≤0.25/84	≤0.25/80	≤0.25/81
Gentamicin	≤2/95	2/84	2/89	≤2/91
Imipenem	1/95	1/83	1/92	1/89
Meropenem	0.5/100	1/79	0.5/95	0.5/88
Piperacillin/Tazobactam	4/86	4/82	4/86	4/80
Tobramycin	0.5/100	0.5/92	0.5/95	0.5/96

a. Susceptibility criteria of the NCCLS [2004] was used throughout.
b. Percentage in parenthesis indicates those strains having a screening MIC that would be considered an extended spectrum ß-lactamase phenotype [NCCLS, 2004].

Figure 1: Frequency of bacterial pathogens (3,970 strains) in haemotology/oncology patients when stratified by age (North America; 2001-2002).



CONCLUSIONS

- Significant age-related variations in pathogen occurrence and species-specific resistance patterns were documented.
- Isolates from patients ≤ 14 years of age displayed greater susceptibility.
- Guidelines for empiric regimens of antimicrobics in hematology/oncology patients must consider contemporary age factors and related pathogen frequency and resistance rates when being established.

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