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Trends in Antimicrobial Resistance in Canada Over Ten Years; Not All Bad News

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ABSTRACT

Background: Changes in antimicrobial resistance over time are important because they help inform decisions on antimicrobial stewardship and help identify potential future needs in new antimicrobial discovery and development. We describe trends observed in antimicrobial resistance in key pathogens in Canada over the past 10 years.
Methods: CANWARD is an annual, ongoing, national surveillance study assessing antimicrobial resistance from clinically relevant isolates in Canadian hospitals. Tertiary-care centers from across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. 33,527 isolates collected between 2007 and 2016 were analyzed as part of this study. Isolates were tested for resistance to 18 different antimicrobials using microbroth methods and interpreted according to CLSI 2017 criteria. A multiple regression model considering possible changes in demographic variables occurring through the years of the study (patient age, specimen source and hospital ward (Inpatient, Outpatient or ICU)) was used to ensure changes in antibiotic resistance over time were independent of changes in other variables.
Results: Observed trends are summarized in the results tables.
Conclusions: Resistance rates to several key antimicrobials have decreased over the past ten years for *P. aeruginosa*, *S. aureus*. Resistance to third generation cephalosporins has significantly increased in *E. coli* and *K. pneumoniae*. Efforts to reduce increasing resistance should focus on *E. coli* and *K. pneumoniae* while maintaining vigilance for the emergence of other relevant antibiotic-resistant pathogens.

BACKGROUND

Antimicrobial resistance patterns change over time and longitudinal surveillance studies provide insight into these trends. We sought to describe the important trends in antimicrobial resistance in key pathogens across Canada to provide useful information to clinicians, policy makers and industry to assist in optimizing antimicrobial therapy, formulary choices and drug development.

MATERIALS & METHODS

Isolates were collected as part of the CANWARD study between January 2007 and December 2016. Up to 15 Canadian centers in 8 provinces contributed clinically relevant isolates. To ensure sufficient statistical power for the analysis, only organisms where >1000 isolates were submitted during the whole study period were considered. These included: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, Streptococcus pneumoniae,* and *Staphylococcus aureus*. Susceptibility testing to key antimicrobials for each species was performed using broth microdilution in accordance with the CLSI M07-A10 document (1). Susceptibility breakpoints were defined in accordance with the CLSI M100-S27 (2) document. For the purpose of statistical analysis, isolates were defined to be either susceptible or non-susceptible. Variables included year of study, age group, gender, hospital location and specimen type. A second degree factorial multivariate logistic regression analysis using available demographic variables was used to isolate the effect of time on susceptibility from changes in demographic variables that may have occurred in the dataset as well as second degree interactions among the variables. Only p values less than 0.01 were considered significant. Statistical analysis was performed using JMP 11 software by SAS (Cary, NC, USA).

RESULTS

FIGURE 1: Distribution of isolates (n = 26,910), age of patients, patient location, specimen type, and gender.

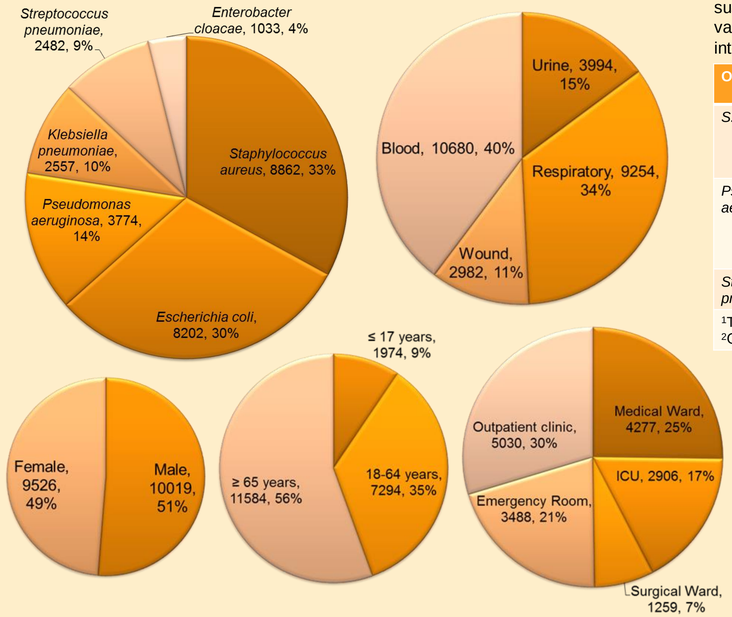

TABLE 1: Organism-antimicrobial combinations showing trends for **non-susceptibility** in the 10 year study. The change in total proportion of non-susceptible isolates may not appear significant due to interactions between variables. These are nevertheless significant when controlled for these interactions. These variables are explained in the methods.

Organism	Antibiotic	Non-susceptible (2007)	Non-susceptible (2016)	P value
Escherichia coli	Amox-clav Ceftriaxone Ceftazidime Cefepime	9.2% 5.8% 5.0%[1] 3.4%	21.3% 13.8% 9.1% 7.2%	<0.001 <0.001 <0.001 <0.001
Klebsiella pneumoniae	Ceftazidime Cefepime	3.2%[1] 3.3%	8.3% 9.2%	0.003 <0.001
Streptococcus pneumoniae	Clarithromycin	9.0%	19.1%	0.001

[1]Data available from 2008-2016 only.

TABLE 2: Organism-antimicrobial combinations showing trends for **susceptibility** in the 10 year study. The change in total proportion of non-susceptible isolates may not appear significant due to interactions between variables. These are nevertheless significant when controlled for these interactions. These variables are explained in the methods.

Organism	Antibiotic	Non-susceptible (2007)	Non-susceptible (2016)	P value
S. aureus	MRSA Clindamycin Clarithromycin TMP-SMX[1]	26.1% 22.8% 43.6% 3.7%	14.1% 10.1% 31.3% 0.0%	<0.001 <0.001 <0.001 <0.001
Pseudomonas aeruginosa	Ciprofloxacin Cefepime Amikacin Gentamicin Colistin	34.0% 32.6% 14.4% 39.7% 11.0%	16.8% 9.2% 5.5% 10.5% 2.9%	<0.001 <0.001 <0.001 <0.001 <0.001
Streptococcus pneumoniae	Penicillin[2]	20.8%	9.6%	0.003

[1]Trimethoprim-sulfamethoxazole
[2]Oral breakpoints (susceptible ≤0.06µg/mL).

TABLE 3: Organism-antimicrobial combinations showing **no significant trends** in resistance at the p<0.01 significance level in the 10 year study.

Organism	Antibiotic	
Escherichia coli	Cefazolin Ciprofloxacin Ertapenem Gentamicin Meropenem	Nitrofurantoin Piperacillin-tazobactam Tobramycin TMP-SMX
Klebsiella pneumoniae	Amox-clav Cefazolin Ceftriaxone Ciprofloxacin Ertapenem Gentamicin	Meropenem Nitrofurantoin Piperacillin-tazobactam Tobramycin TMP-SMX
Enterobacter cloacae	Cefazolin Ceftriaxone Ceftazidime Cefepime Ciprofloxacin Ertapenem	Gentamicin Meropenem Nitrofurantoin Piperacillin-tazobactam Tobramycin TMP-SMX
Pseudomonas aeruginosa	Tobramycin Ceftazidime[1]	Meropenem Piperacillin-tazobactam
Streptococcus pneumoniae	Ceftriaxone Cefuroxime TMP-SMX	Vancomycin Clindamycin Levofloxacin
Staphylococcus aureus	Vancomycin Daptomycin	Linezolid Doxycycline

[1]Data available from 2008-2013 only.

CONCLUSIONS

We have observed an increase in resistance phenotypes for *E. coli* and *K. pneumoniae*. In particular *E. coli* has demonstrated an alarming trend towards increasing resistance to several key antimicrobials include third generation cephalosporins and amoxicillin-clavulanate. This observation has been made globally, and is partially related to the expansion of ESBL and AmpC producing strains (3).

We observed increasing resistance to clarithromycin in *S. pneumoniae*. This may reflect the emergence of resistant serotypes reported by us and others (4).

We observed a significant reduction in resistance phenotypes for *P. aeruginosa* to several key antibiotics. Although the explanation is not known, a reduction in the prevalence of strains expressing the MexX-MexY-OprM efflux system, which has specificity for cefepime, ciprofloxacin and aminoglycosides (5), may explain the observation.

We observed a significant reduction in the proportion of MRSA, trimethoprim-sulfamethoxazole-, macrolide- and clindamycin-resistant *S. aureus* over the 10 year study. Given the concurrent significant reduction in MRSA proportions, the trends are likely explained by a reduction in the prevalence of MRSA, which has been observed by others and may be related to clonal replacement of MRSA by MSSA strains (6).

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