SUNDAY - 96



Health Sciences Centre

Trends in Antimicrobial Resistance in Canada Over Ten Years; Not All Bad News P. LAGACÉ-WIENS^{1,2}, H. ADAM^{1,2}, M. BAXTER¹, J. KARLOWSKY^{1,2}, A. WALKTY^{1,2}, M. MULVEY^{1,3}, D. HOBAN^{1,2}, G. G. ZHANEL¹

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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. Tertiarycare 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 nonsusceptible. 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).





TABLE 1: Organism-antimicrobial combinations showing trends for **non**susceptibility in the 10 year study. The change in total proportion of nonsusceptible 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 nonsusceptible 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

¹Trimethoprim-sulfamethoxazole

²Oral breakpoints (susceptible ≤0.06µg/mL).

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Organism	Antibiotic					
Escherichia coli	Cefazolin Ciprofloxacin Ertapenem Gentamicin Meropenem	Nitrofu Pipera Tobra TMP-5				
Klebsiella pneumoniae	Amox-clav Cefazolin Ceftriaxone Ciprofloxacin Ertapenem Gentamicin	Merop Nitrofu Pipera Tobra TMP-5				
Enterobacter cloacae	Cefazolin Ceftriaxone Ceftazidime Cefepime Ciprofloxacin Ertapenem	Genta Merop Nitrofu Pipera Tobra TMP-3				
Pseudomonas aeruginosa	Tobramycin Ceftazidime ¹	Merop Pipera				
Streptococcus pneumoniae	Ceftriaxone Cefuroxime TMP-SMX	Vanco Clinda Levofl				
Staphylococcusaureus	Vancomycin Daptomycin	Linezo Doxyc				
¹ Data available from 2008-2013 only.						

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

ASM Microbe 2017, New Orleans, LA, June 1-5, 2017

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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).

ACKNOWLEDGMENTS

We acknowledge the contributions of the directors and technologists of the contributing site microbiology laboratories.

Funding for the CANWARD study was provided in part by the University of Manitoba, Health Sciences Centre (Winnipeg, Manitoba, Canada) and the National Microbiology Laboratory (Winnipeg, Manitoba, Canada).

REFERENCES

- CLSI. Methods for Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Eighth Edition. CLSI document M07-A10. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
- CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Sixth Informational Supplement. CLSI document M100-S27. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.
- 3. Denisuik AJ, Lagacé-Wiens PR, Pitout JD, et al. Molecular epidemiology of extendedspectrum β -lactamase-, AmpC β -lactamase- and carbapenemase-producing Escherichia coli and Klebsiella pneumoniae isolated from Canadian hospitals over a 5 year period: CANWARD 2007-11. J Antimicrob Chemother. 2013 May;68 Suppl 1:i57-
- 4. Wierzbowski AK, Karlowsky JA, Adam HJ, et al. Evolution and molecular characterization of macrolide-resistant Streptococcus pneumoniae in Canada between 1998 and 2008. J Antimicrob Chemother. 2014 Jan;69(1):59-66.
- 5. Aeschlimann JR. The role of multidrug efflux pumps in the antibiotic resistance of Pseudomonas aeruginosa and other gram-negative bacteria. Pharmacotherapy. 2003 Jul;23(7):916-24.
- 6. Lagacé-Wiens PR, Adam HJ, Low DE et al. Trends in antibiotic resistance over time among pathogens from Canadian hospitals: results of the CANWARD study 2007-11. J Antimicrob Chemother. 2013 May;68 Suppl 1:i23-9.

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