Treatment outcome and predictors of poor clinical response in extensively drug-resistant gram-negative urinary tract infection among children: A single-institution experience

Carren Anne P. Batalla-Bocaling, MD[*1]; Patrick Vincent P. Tanseco, MD*[*2]; Michael E. Chua, MD*[3]

[1]Section of Infectious Diseases, Philippine Children's Medical Center, Quezon City, Philippines; [2]Insitute of Urology, St. Luke's Medical Center, Quezon City, Philippines; [3]Division of Urology, The Hospital for Sick Children, Department of Surgery, University of Toronto, Toronto, ON, Canada

*Equal contributors

Cite as: Batalla-Bocaling CAP, Tanseco PVP, Chua ME. Treatment outcome and predictors of poor clinical response in extensively drug-resistant gram-negative urinary tract infection among children: A single-institution experience. *Can Urol Assoc J* 2021;15(3):E148-52. http://dx.doi.org/10.5489/cuaj.6475

Published online August 7, 2020

Abstract

Introduction: Extensively drug-resistant (XDR) is defined as isolates sensitive only to two or fewer antimicrobial categories. This paper aims to present the treatment outcome and identify factors associated with poor clinical response among children with XDR gram-negative urinary tract infection (UTI).

Methods: This is a retrospective cohort conducted at a tertiary pediatric hospital from January 2014 to June 2017. All patients diagnosed with culture-proven XDR gram-negative UTI were identified and analyzed. Descriptive statistics were used to summarize demographic and clinical characteristics. Patients were categorized according to treatment outcomes: success vs. failure. Univariate analysis and multivariate logistic regression were used to assess statistical differences between the groups and determined patient variables that are predictive of poor response. Odds ratio (OR) and corresponding 95% confidence interval (CI) were generated.

Results: A total of 29 (19.2%) XDR gram-negative pediatric UTIs were identified within the 42-month study period. No significant differences were noted in demographic characteristics between the groups. Treatment outcome of XDR gram-negative UTI patients showed that combination therapy with colistin had the highest success rate (40.9%), followed by non-colistin (36.4%) and combination therapy without colistin (22.7%). However, univariate analysis showed no significant difference among the different treatment groups (p=0.65). On multivariate logistic regression, receiving immunosuppressant and the presence of indwelling urinary catheters were independent predictors of poor clinical response among pediatric patients with XDR gram-negative UTI (OR 19.44, 95% CI 1.50–251.4, p=0.023 and OR 20.78, 95% CI 1.16–371.28, p=0.039; respectively).

Conclusions: The treatment success rate of XDR gram-negative pediatric UTI ranged from 22.7–36.4%. This finding emphasizes the need to advocate antibiotic stewardship to prevent further increase in XDR UTIs. Indwelling urinary catheters and receipt of immunosuppressants are associated with poor clinical outcome.

Introduction

Urinary tract infection (UTI) is one of the most common infections, especially in children. It is estimated that 8% of girls and 2% of boys will experience at least one episode of UTI by age seven, and recurrence occurs in 12–30% of them within a year.[1] Septicemia, renal scarring, and end-stage renal dysfunction are the severe complications of UTIs. They are important causes of morbidity and mortality during the first two years of life.[2]

Throughout recent years, an increasing antimicrobial-resistant trend among UTIs in children has been noted.[3] In particular, UTI among hospitalized children has an increasing trend of antibiotic resistance.[4] In recent studies, a high prevalence of antibiotic resistance in pediatric UTI was reported among Asian countries.[5,6] Extensively drug-resistant (XDR) is defined as culture isolates with sensitivity limited only to two or fewer antimicrobial agents.[7] Difficulty in the clinical management of this condition has raised an important concern. We aim to present the treatment outcome of XDR gram-negative UTI among hospitalized children in a tertiary government institution and determine factors that are associated with poor clinical response. This study was conducted in a low-middle-income country (Philippines), where a national antibiotic pattern is currently reinforced. All included patients in the study were in-patient and being treated with intravenous antibiotics; hence, self-medication is unlikely. However, in the community, there is a possibility that these patients may have been previously self-medicated with oral antibiotics, although this was difficult to capture from a retrospective data collection.

Methods

This is a retrospective cohort conducted at a tertiary referral center for pediatrics. The study protocol was approved by the institutional scientific and ethics review committee (IRB# 18095). Likewise, the reporting of the study complies with the RECORD statement.

All the subjects of this research were based on the previous data collected in the study done by Batalla et al on XDR gram-negative bacteria in 2017.[8] All urine culture specimens with gram-negative bacteria isolate were identified and evaluated for potentially eligible cases. The medical records of patients diagnosed with XDR gram-negative UTI were further identified and included for analysis. Only urine specimens aseptically collected by suprapubic aspiration, catheterization, or clean catch mid-stream, were considered. Patients with culture-proven XDR UTI that were excluded from the study due to inability to assess the treatment outcome comprised of patients who were prematurely discharged, patients who died due to other conditions, patients who received treatment elsewhere, and patients that were lost to followup.

Collected demographic and clinical characteristics of patients included sex, age, nutritional status, underlying comorbidities, surgical intervention, intake of immunosuppresants (such as steroids and chemotherapeutics), accessory medical procedures (invasive vascular access, mechanical ventilator, blood transfusion, indwelling Foley catheter placement), culture source, growth organism, antimicrobial susceptibility, prior antibiotic intake, total hospital stay, number of hospital days prior to XDR gram-negative infection, treatment received and treatment outcome. The nutritional status was categorized according to the World Health Organization growth chart standards.[9]

The patients were categorized according to treatment outcomes: success or failure. Treatment success was defined as clinical response to medical management, such as resolution of presenting signs and symptoms (e.g., fever) and/or no significant urine culture after treatment. Treatment failure was defined as persistence of clinical presentation of UTI, or persistent significant XDR or multi-drug-resistance (MDR) gram-negative growth on subsequent urine culture, and/or death.

To summarize the demographic and clinical characteristics of the patients in the overall and between treatment groups, descriptive statistics were used. This includes, count and percent, as well as median and interquartile range (IQR). Univariate analysis was used to assess statistical differences between the two groups of treatment outcomes. Specifically, Fisher-exact test and Mann-Whitney U test were used for categorical and continuous variables, respectively. To determine the variables that were predictive of poor patient response, the multivariate logistic regression tool was used. Odds ratio (OR) and corresponding 95% confidence interval (CI) were generated. The statistically significant level was set at $p<0.05$. All statistical analyses were performed using SPSS v 21.0.

Results

A total of 4571 gram-negative isolates were collected from January 2014 to June 2017. Among these gram-negative isolates, 151 XDR isolates were identified. There were 29 (19.2%) XDR gram-negative cultures from urine specimens. The most common XDR isolates from urine cultures were *Klebsiella* (51.7%), *Acinetobacter* (24.1%), and *Pseudomonas* (10.3%). Approximately 51.7% of isolates were sensitive to colistin only, followed by sensitivity to colistin and aminoglycosides (34.5%).

Table 1 summarizes the demographic and clinical characteristics of all patients included in the study. The median hospital stay prior to development of XDR was approximately 19 days (IQR 1.5–38). Interestingly, all patients with XDR UTI had at least one comorbidity. Most of the XDR cases were hospital-acquired, and the majority of patients had previous or current antibiotic treatment, either as monotherapy or combination therapy. However, it should be noted that none of the patients in the study was on a prophylatctic dose of antibiotics.

No between-group differences were noted for sex, age, hospital stay, days to XDR infection, overall nutritional status, number of comorbidities, surgical procedures, hospital- or community-acquired patients, isolates, sensitivity to antibiotics, or prior antibiotic treatment. In the poor treatment outcome group (Table 1), there was a significantly higher proportion of patients who had indwelling Foley catheters (40.9% vs. 85.7%, p=0.08) and who received immunosuppressants (22.7% vs. 71.4%, p=0.03), when compared to the good treatment outcome group.

Treatment outcome of XDR gram-negative UTI patients showed that combination therapy with colistin had the highest success rate (40.9%), followed by non-colistin (36.4%) and combination therapy without colistin (22.7%). However, univariate analysis showed no significant difference among the different treatment groups (p=0.65) (Table 2).

Multivariate logistic regression analysis confirmed that immunosuppressant and indwelling catheter were independent predictors for poor treatment outcome of XDR, with OR 19.44, 95% CI 1.50–251.4, p=0.023 and OR 20.78, 95% CI 1.16–371.28, p=0.039; respectively (Table 3).

Discussion

Worldwide, there has been an increasing prevalence of extended spectrum beta-lactamase-producing enteric bacteria and an increasing resistance of antibiotics of primarily preferred empiric treatment.[4,5,6,10] In our study, a total of 29 cases with gram-negative XDR pediatric UTI were identified

Table 1. Patient demographic and clinical characteristics with comparison between treatment success and treatment failure groups

Variable	Overall (n=29)	Success (n=22)	Failure (n=7)	p
	n (%)	n (%)	n (%)	Fisher-exact test
Gender				
Male	17 (58.6%)	13 (59.1%)	4 (57.1%)	1.00
Female	12 (41.4%)	9 (40.9%)	3 (42.9%)	
Nutrition status				
Severely wasted	8 (27.6%)	5 (22.7%)	3 (42.9%)	0.21
Wasted	1 (3.4%)	1 (4.5%)	0 (0%)	
Normal	19 (65.5%)	16 (72.7%)	3 (42.9%)	
Overweight	1(3.4%)	0 (0%)	1 (14.3%)	
Number of comorbidities				
1	21 (72.4%)	14 (63.6%)	7 (100%)	0.25
2	6 (20.7%)	6 (27.3%)	0 (0%)	
3	2 (6.9%)	2 (9.1%)	0 (0%)	
Surgical procedure				
No surgery	26 (89.7%)	20 (90.9%)	6 (85.7%)	1.00
With urological surgery	3 (10.3%)	2 (9.1%)	1 (14.3%)	
Indwelling Foley catheter				
No	14 (48.3%)	13 (59.1%)	1 (14.3%)	0.08
Yes	15 (51.7%)	9 (40.9%)	6 (85.7%)	
Manner of infection				
Hospital-acquired	19 (65.5%)	13 (59.1%)	6 (85.7%)	0.37
Community-acquired	10 (34.5%)	9 (40.9%)	1 (14.3%)	
Prior antibiotics				
None	3 (10.3%)	3 (13.6%)	0 (0%)	0.52
Monotherapy	18 (62.1%)	14 (63.6%)	4 (57.1%)	
Duo therapy (w/ colistin)	6 (20.7%)	4 (18.2%)	2 (28.6%)	
Duo therapy (w/o colistin)	2 (6.9%)	1 (4.5%)	1 (14.3%)	
Immunosuppressant				
No	19 (65.5%)	17 (77.3%)	2 (28.6%)	0.03
Yes	10 (34.5%)	5 (22.7%)	5 (71.4%)	
Bacterial isolate				
Acinetobacter	7 (24.1%)	4 (18.2%)	3 (42.9%)	0.75
Citrobacter	1 (3.4%)	1 (4.5%)	0 (0%)	
Enterobacter cloacae	2 (6.9%)	2 (9.1%)	0 (0%)	
E. coli	1 (3.4%)	1 (4.5%)	0 (0%)	
Klebsiella	15 (51.7%)	11 (50%)	4 (57.1%)	
Pseudomonas	3 (10.3%)	3 (13.6%)	0 (0%)	
Sensitivity to colistin only				
No	14 (48.3%)	11 (50%)	3 (42.9%)	1.00
Yes	15 (51.7%)	11 (50%)	4 (57.1%)	
Sensitivity only to non-colistin				
No	28 (96.6%)	21 (95.5%)	7 (100%)	1.00
Yes	1 (3.4%)	1 (4.5%)	0 (0%)	
Sensitivity to colistin and fluoroquinolones				
No	27 (93.1%)	21 (95.5%)	6 (85.7%)	0.43
Yes	2 (6.9%)	1 (4.5%)	1 (14.3%)	
Sensitivity to colistin and carabapenems				
No	28 (96.6%)	21 (95.5%)	7 (100%)	1.00
Yes	1 (3.4%)	1 (4.5%)	0 (0%)	
Sensitivity to colistin and aminoglycosides				
No	19 (65.5%)	14 (63.6%)	5 (71.4%)	1.00
Yes	10 (34.5%)	8 (36.4%)	2 (28.6%)	
Variable	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**p**
Age in years	3.71 (1.21–13.12)	2.9 (1.17–13.1)	9.79 (1.21–18)	0.40
Total hospital days	32 (12–81)	22 (11.75–56)	36 (32–277)	0.18
Hospital days prior to EDR	19 (1.5–38)	9.5 (1–35.5)	28 (24–42)	0.14
Clinical response	–	4 (3–5)	–	

EDR: emergency department registration; IQR: interquartile range.

within a 42-month period from January 2014 to June 2017 in a single tertiary pediatric institution.

Klebsiella, *Acinetobacter,* and *Pseudomonas* were the most common resistant bacterial uropathogens isolated among children with UTIs in this institution. Our study showed a consistent finding that *Klebsiella* is one of the most common uropathogens with an increasing trend of antibiotic resistance.[4,11] Compared to other international reports on pediatric UTIs, the typical uropathogens *E. coli* and *Enterococcus sp.* constituted only a small proportion of our XDR isolates.[4,6,10] Furthermore, what is concerning about our finding is that *Acinetobacter* and *Pseudomonas* isolates, according to other reports, were rare uropathogens in children, and their presence implies difficult clinical management.[8,12-14] Our local antimicrobial resistance surveillance program also reported an increase in *Acinetobacter* XDR rate from 48% to 50%, while the *Pseudomonas* XDR rates decreased from 21% to 16% for the year 2016.[11] The increases in antibiotic resistances among these organisms were usually preceded by prior broad-spectrum antibiotic usage.[12-14] In this study, 89.7% of the patients received at least one antibiotic within 30 days prior to infection (Table 1). Furthermore, almost half of the XDR gram-negative isolates were sensitive to colistin only, which implies limited

Table 2. Treatment outcome of XDR gram-negative UTI patients

Variable	Overall (n=30)	Success (n=22)	Failure (n=7)	p
	n (%)	n (%)	n (%)	Fisher-exact test
Non-colistin (carbapenem/fluoroquinolone)	10 (33%)	8 (36.4%)	2 (28.6%)	0.65
Combination therapy with colistin (carbapenem/fluoroquinolone + colistin)	11 (36.7%)	9 (40.9%)	2 (28.6%)	
Combination without colistin (carbapenem/fluoroquinolone + aminoglycosides)	8 (27%)	5 (22.7%)	3 (42.9%)	

XDR: extensively drug-resistant; UTI: urinary tract infection.

medical agents were available to treat these infections. The findings illustrate an increased trend of rare uropathogens becoming more XDR and should raise awareness among clinicians: inappropriate broad-spectrum empiric or prophylactic antibiotic usage needs to be monitored and halted to prevent further increase in the prevalence of XDR among pediatric UTI. Likewise, efforts should be made to improve appropriate antibiotic prescribing practices in the community, as well as in emergency settings.[15]

In this study, although combination therapy with colistin had the highest success rate (40.9%), followed by non-colistin (36.4%) and combination therapy without colistin (22.7%), univariate analysis showed no significant difference among the different treatment groups (p=0.65). However, these findings can still be clinically significant because when clinicians decide which therapeutic option to start, the best treatment outcome is always the goal. Previous studies on the use of intravenous colistin in the pediatric population showed a favorable outcome in 65–89% of patients treated for all types of infections.[8] In the previous study by Batalla et al, the treatment success of XDR infections was significantly higher in the colistin group (70.3%) than in the non-colistin group (46.5%, p=0.014). This study covered laboratory confirmed XDR bloodstream, urinary tract, central nervous system, wound/surgical site infections, and pneumonia.[8]

There is a paucity of similar studies focusing on treatment outcome of colistin, particularly in pediatric XDR UTI. In a prospective, single-center study by Carrilho et al, which included 51 adult patients with carbapenem-resistant UTI, 21% of patients that received monotherapy died compared with 26% of patients that received combination therapy, and the overall mortality of patients with UTI was 24%. There was no statistically significant difference in infection-related mortality comparing colistin-susceptible and colistin-resistant UTI (p=0.41).[16] Likewise, Sorli et al found no significant difference in terms of microbiological clearance between patients who received colistin monotherapy and those who received combination therapy (76.9% vs. 90%, p=1) in the treatment of XDR *Pseudomonas aeruginosa* UTI in 33 adults.[17]

In our results, children with a poor treatment outcome consisted of a higher proportion of patients who have received immunosuppressants (cases of malignancy or hematopoietic disease), and with patients who had indwelling Foley catheter (71.4% and 85.7%, respectively). On multivariate logistic regression, they are independent predictors of poor clinical response among pediatric patients with XDR gram-negative UTI (OR 19.43, 95% CI 1.5–251.44, p=0.023 and OR 20.78, 95% CI 1.16–371.28, p=0.039; respectively). Both identified factors were previously described as risk factors for development of urosepsis.[18] The lack of early signs and symptoms accompanied by the substantial increase of microbial load among immunocompromised patients can lead to delayed detection and management of UTI, which leads to poor treatment outcome.[19] While an indwelling Foley catheter, as a foreign body, provides an ideal environment for bacterial colonization with biofilm formation and eventual development of MDR,[20,21] a study by Bardoloi showed that biofilm-producing properties were present in isolates from both community-acquired and catheter-associated UTI. However, the overall percentage of strains with MDR was significantly higher in catheter-associated UTI (83.33%) than in community-acquired UTI (64.76%) (χ^2=8.317; p=0.0039).[22] This suggests that urethral catheterization might influence the growth of MDR. In a catheterized patient, there is stasis of urine, which contributes to bacterial overgrowth.[22-24] We strongly propose the timely identification of immunosuppressant use and the presence of an indwelling Foley catheter in pediatric XDR UTIs, as they have been identified as independent predictors for poor treatment outcome in our study. Proper identification of these patient factors, combined with an avoidance or early removal of an indwelling catheter, could lead to early detection of UTI and improve future management and treatment outcome of pediatric UTI with XDR gram-negative infections.[19,21,25]

Since this retrospective study was done in a single medical center, the small sample size for analysis and other variables,

Table 3. Multivariate logistic regression analysis determined OR and 95% CI

Predictors	p	OR	95% CI	
			Lower	Upper
Immunosuppressant	0.023	19.438	1.503	251.436
Indwelling Foley catheter	0.039	20.778	1.163	371.277

CI: confidence interval; OR: odds ratio.

such as different treatment regimens, the differences in the dose, and the differences in the time lapse before treatment was initiated, limit us from drawing a fair conclusion. An example of this was some of the patients did not have a repeat urine culture. This was either due to financial constraints or the infectious diseases specialist's decision to base improvement on clincal response, and a repeat urinalysis was requested instead. As a pragmatic approach in the clinical setting, clinical response is a surrogate that the source of infection has been treated. Also, we strongly believe that the significant insight derived from our study is raising awareness and urgency to address the increasing trend of pediatric UTI with XDR organisms. Likewise, to our knowledge, this is the first descriptive study to identify clinical characteristics and patient factors that are associated with poor treatment outcome in pediatric XDR UTI, which could be useful to improve management strategies in the future.

Conclusions

XDR gram-negative UTI comprised 19.2% of the total culture-proven XDR gram-negative infections in a 42-month period, with treatment success ranging from 22.7–36.4%. This study is not an intention-to-treat analysis, as some of the subjects dropped out due to premature discharge or death, which were excluded from our analysis. Our findings emphasize the need to implement antibiotic stewardship programs to prevent further increase in XDR UTIs. Likewise, we have identified that immunosuppressant use and indwelling Foley catheters are associated with poor treatment outcome. We recommend early identification of these clinical characteristics to provide appropriate and timely management. Future prospective studies are recommended to develop suitable management strategies to improve treatment outcome of pediatric XDR gram-negative UTI.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

References

1. Desai DJ, Gilbert B, Mcbride CA. Paediatric urinary tract infections: Diagnosis and treatment. *AustFam Physician* 2016;45:558-63.
2. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Dis Mon* 2003;49:71-82. https://doi.org/10.1067/mda.2003.8
3. Kutasy B, Coyle D, Fossum M. Urinary tract infection in children: Management in the era of antibiotic resistance — a pediatric urologist's view. *Eur Urol Focus* 2017;3:207-11. https://doi.org/10.1016/j.euf.2017.09.013
4. Koçak M, Büyükkaragöz B, Çelebi Tayfur A, et al. Causative pathogens and antibiotic resistance in children hospitalized for urinary tract infection. *Pediatr Int* 2016;58:467-71. https://doi.org/10.1111/ped.12842
5. Wang J, He L, Sha J, et al. Etiology and antimicrobial resistance patterns in pediatrics with urinary tract infections. *Pediatr Int* 2018;60:418-22. https://doi.org/10.1111/ped.13526
6. Parajuli NP, Maharjan P, Parajuli H, et al. High rates of multidrug resistance among uropathogenic *Escherichia coli* in children and analyses of ESBL producers from Nepal. *Antimicrob Resist Infect Control* 2017;6:9. https://doi.org/10.1186/s13756-016-0168-6
7. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant, and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268-81. https://doi.org/10.1111/j.1469-0691.2011.03570.x
8. Batalla CP, Paje-Villar E. A retrospective study on the outcome of children with extensively drug-resistant gram-negative infection treated with colistin vs. other antimicrobials. *Ped Infect Dis Soc Philippines J* 2018;19:54-65.
9. World Health Organization. (2009) WHO child growth standards and the identification of severe acute malnutrition in infants and children: Joint statement by the World Health Organization and the United Nations Children's Fund. Available at: https://apps.who.int/iris/bitstream/handle/10665/44129/9789241598163_eng.pdf. Accessed Aug. 8. 2020.
10. Edlin RS, Shapiro DJ, Hersh AL, et al. Antibiotic resistance patterns of outpatient pediatric urinary tract infections. *J Urol* 2013;190:222-7. https://doi.org/10.1016/j.juro.2013.01.069
11. Antimicrobial Resistance Surveillance Program — Philippines Annual Report 2016:34-45.
12. Pobiega M, Maciag J, Pomorska-Wesolowska M, et al. Urinary tract infections caused by *Pseudomonas aeruginosa* among children in Southern Poland: Virulence factors and antibiotic resistance. *J Pediatr Urol* 2016;12:36.e1-6. https://doi.org/10.1016/j.jpurol.2015.05.034
13. Chan MC, Chiu SK, Hsueh PR, et al. Risk factors for healthcare-associated extensively drug-resistant *Acinetobacter baumannii* infections: A case-control study. *PLoS One* 2014;9:e85973. https://doi.org/10.1371/journal.pone.0085973
14. Marcus N, Ashkenazi S, Samra Z, et al. Community-acquired *Pseudomonas aeruginosa* urinary tract infections in children hospitalized in a tertiary center: Relative frequency, risk factors, antimicrobial resistance, and treatment. *Infection 316* 2008;36:421-6. https://doi.org/10.1007/s15010-008-7328-4
15. Poole NM, Kronman MP, Rutman L, et al. Improving antibiotic prescribing for children with urinary tract infection in emergency and urgent care settings. *Pediatr Emerg Care* 2020;36:e332-9. https://doi.org/10.1097/PEC.0000000000001342
16. De Maio Carrilho, CMD, de Oliveira LM, et al. A prospective study of treatment of carbapenem-resistant *Enterobacteriaceae* infections and risk factors associated with outcome. *BMC Infect Dis* 2016;16:629. https://doi.org/10.1186/s12879-016-1979-z
17. Sorli L, Luque S, Li J, et al. Colistin for the treatment of urinary tract infections caused by extremely drug-resistant *Pseudomonas aeruginosa*: Dose is critical. *J Infect* 2019;79:253-61. https://doi.org/10.1016/j.jinf.2019.06.011
18. Parasuraman R, Julian K; AST Infectious Disease Community of Practice. Urinary tract infections in solid organ transplantation. *Am J Transplant* 2013;13Suppl4:327-36. https://doi.org/10.1111/ajt.12124
19. Sabir N, Ikram A, Zaman G, et al. Bacterial biofilm-based catheter-associated urinary tract infections: Causative pathogens and antibiotic resistance. *Am J Infect Control* 2017;45:1101-5. https://doi.org/10.1016/j.ajic.2017.05.009
20. Pradeep Kumar SS, Easwer HV, Maya Nandkumar A. Multiple drug-resistant bacterial biofilms on implanted catheters — a reservoir of infection. *J Assoc Physicians India* 2013;61:702-7.
21. Edlin RS, Copp HL. Antibiotic resistance in pediatric urology. *Ther Adv Urol* 2014;6:54-61. https://doi.org/10.1177/1756287213511508
22. Bardoloi V, Yogeesha Babu KV. Comparative study of isolates from community-acquired and catheter-associated urinary tract infections with reference to biofilm-producing property, antibiotic sensitivity, and multi-drug resistance. *J Med Microbiol* 2017;66:927-36. https://doi.org/10.1099/jmm.0.000525
23. KolarM, UrbanekK, Latal T. Antibiotic selective pressure and development of bacterial resistance. *Int J Antimicrob Agents* 2001;17:357-63. https://doi.org/10.1016/S0924-8579(01)00317-X
24. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerg Infect Dis* 2004;10:514-7. https://doi.org/10.3201/eid1003.030252
25. Alexander BT, Marschall J, Tibbetts RJ, et al. Treatment and clinical outcomes of urinary tract infections caused by KPC-producing *Enterobacteriaceae* in a retrospective cohort. *Clin Ther* 2012;34:1314-23. https://doi.org/10.1016/j.clinthera.2012.05.002

Correspondence: Dr. Michael E. Chua, Division of Urology, The Hospital for Sick Children, Department of Surgery, University of Toronto, Toronto, ON, Canada; michael.chua@sickkids.ca