Supplemental Online Content

Supplemental Table 1. Cephalosporin indications

Antibiotic	Indication
Cefprozil[1,2] **(Brand names: Apo-Cefprozil; Auro-Cefprozil; Ava-Cefprozil; Cefzil; RAN-Cefprozil; Sandoz-Cefprozil)**	Acute otitis media Sinusitis Uncomplicated urinary tract infection Acute bacterial exacerbation of chronic bronchitis Pharyngitis/tonsillitis Skin and skin-structure infections,
Cephalexin[3,4] **(Brand names: Daxbia,Keflex,Apo-Cephalex;Dom-Cephalexin; PMS-Cephalexin;Teva-Cephalexin)**	Impetigo Skin and skin structure infections Streptococcal pharyngitis Uncomplicated cystitis Group A streptococcal pharyngitis Acute Osteomyelitis Diabetic foot infection
Cefuroxime[5–7] **(Brand names: Ceftin;Zinacef; Apo-Cefuroxime; Auro-Cefuroxime; Ceftin; PRO-Cefuroxime; ratio-Cefuroxime)**	Acute bacterial maxillary sinusitis Acute bacterial exacerbations of chronic bronchitis Lyme disease (early) Pharyngitis/tonsillitis Pneumonia Skin/skin structure infection, uncomplicated Urinary tract infection, uncomplicated

Supplemental Table 2. Literature search for cephalosporin dosing and dose related adverse effects

Database: Ovid MEDLINE®

1946 to March, 2018

1 Cephalexin/ or (cephalexin$ or cephalexin$ or ceporexine$ or palitrex$).mp. (3393)

2 (Cefprozil$ or cefproxil or Cefzil or Cefproz).mp. (316)

3 Cefuroxime/ or (Zinacef or cefuroxime$ or cephuroxime$ or ketocef$).mp. (4570)

4 exp cephalosporins/ or cefamandole/ or cefazolin/ or cefonicid/ or cefsulodin/ or cephacetrile/ or cephalexin/ or cephaloridine/ or cephamycins/ (39951)

5 (cephalosporin$ or (cephalosporanic$ adj3 acid$)).tw,kw. (20362)

6 or/1-5 (52178)

7 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ab. /freq=2 (103772)

8 (adrs or (allergy adj to) or anaphylax$ or (safe or safety or side effect* or undesirable effect*or treatment emergent or tolerability or toxicity)).ti. or (adrs or (allergy adj to) or anaphylax$ or safe or safety or side effect* or undesirable effect*or treatment emergent or tolerability or toxicity).ab. /freq=2 (518380)

9 or/7-8 (593211)

10 6 and 9 (2549)

11 *Cephalexin/ae or *Cefuroxime/ae or exp *Cephalosporins/ae [Adverse Effects] (1526)

12 10 or 11 (3814)

13 (cephalosporin$ or (cephalosporanic$ adj3 acid$) or (cephalexin$ or cephalexin$ or ceporexine$ or palitrex$) or (Cefprozil$ or cefproxil or Cefzil or Cefproz) or (cephalosporin$ or (cephalosporanic$ adj3 acid$))).ti. (6428)

14 (ae or co or de).fs. or (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs).ab,ti. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ab,ti. or exp Drug Hypersensitivity/ or ci.fs. (6518507)

15 13 and 14 (3663)

16 12 or 15 (7014)

17 ((course$ adj of) or (per$ adj course$) or exposure$).tw,kw. or use-of.ti. or Dose-Response Relationship, Drug/ or exp Drug Administration Schedule/ or therapeutic equivalency/ or (dose$1 or

dosin$ or dosage$ or ((dose$ adj3 regimen$) or (dose$ adj3 schedule$))).mp. or concentrat$.tw. or exp *administration, oral/ or ad.fs. or bl.fs. [Blood] (6131901)

18 *Cephalexin/ad or *Cefuroxime/ad or exp *Cephalosporins/ad [Administration & Dosage] (2240)

19 or/17-18 (6131901)

20 exp administration, oral/ or oral$3.mp. (672864)

21 16 and 19 and 20 (769)

22 exp Renal Dialysis/ or exp Renal Insufficiency/ or Kidney Diseases/ or (renal$ or kidney$ or nephro$ or renovas$ or renoscleros$ or glomerul$ or nephri$ or anti-glomerul$ or pyelonephrit$ or pyelitis$ or pyelocystit$ or hydronephros$ or pyonephros$ or tubulonephros$ or proteinuria or anuria or ESRD or CKD or ESRF or uremia or uremic or prerenal$ or pre-renal$ or tubular-necrosis or creatinine or predialy$ or pre-dialy$ or pre-esrf or pre-esrd or GFR or osteodystrophy or azotaemia or azotemia or hyperazotemia or hyperuremia or uraemia or dialy$ or microdialy$ or hemodial$ or haemodial$ or cvvhd or cavh or cvvh or cavhd or hemodiafiltrat$ or hemofiltrat$ or haemodiafiltrat$ or haemofiltrat$ or cvvhdf or renograph$ or renogram$ or radionephrograp$ or radiorenograp$ or vesicouret$ or vesico-ureter$ or CAPD).mp. (1217481)

23 21 and 22 (97)

24 (pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or neonat$).ti. (1213704)

25 23 not 24 (83)

26 limit 25 to "all adult (19 plus years)" (48)

27 limit 25 to "all child (0 to 18 years)" (13)

28 25 not (27 not (26 and 27)) (82)

29 limit 28 to english language (69)

Supplemental Table 3. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement[8]

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
INTRODUCTION				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses.		Introduction
METHODS				
Study design	4	Present key elements of study design early in the paper.		Methods: Study Design and Setting
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods: Study Design and Setting, Patient Selection and Cephalosporin Dosing, Outcomes
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods: Data Sources, Patients and Cephalosporin Dosing
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be	Methods: Patients and Cephalosporin Dosing,

			provided. If these cannot be reported, an explanation should be provided.	Outcomes; Supplemental Table 4, 5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Methods: Data Sources
Bias	9	Describe any efforts to address potential sources of bias.		Methods: Statistical analyses
Study size	10	Explain how the study size was arrived at.		Methods: Patients and Cephalosporin Dosing; Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods: Statistical Analyses
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		Methods: Data Sources, Statistical Analyses
Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	Methods: Data Sources, Patients and Cephalosporin Dosing
Linkage		N/A	(12.3) State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods: Data Sources
RESULTS				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	(13.1) Describe in detail the selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results: Baseline Characteristics; Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		Results: Baseline Characteristics; Table 2; Supplemental Table 8

Outcome data	15	Report numbers of outcome events or summary measures over time.		Results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		Results: Primary Outcome, Secondary Outcome; Table 3, 4
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		N/A
Key results	18	Summarize key results with reference to study objectives.		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion: Strengths and Limitations of Study
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion; Conclusion
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion: Strengths and Limitations of Study
OTHER INFORMATION				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		Acknowledge-ments
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Methods: Data Sources

Supplemental Table 4. Coding definitions for baseline characteristics

Characteristic	Database	Codes / Details
DEMOGRAPHICS (at index date)		
Age	RPDB	
Sex	RPDB	
Year of cohort entry	ODB	
Long-term care residence	ODB	
Neighbourhood income quintile	Statistics Canada	
Local Health Integration Network	RPDB	
PRESCRIBER INFORMATION (at index date)		
Prescribing physician	IPDB	General practitioner, Internal medicine, Other/missing
COMORBIDITIES (5 years prior to index date)		
Anemia	CIHI-DAD	**ICD-10:** D46, D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64, D69, D70, D71, D72
	OHIP	**Diagnostic:** 28
Chronic kidney disease	CIHI-DAD	**ICD-10:** E102, E112, E132, E142, I12, I13, N00, N01, N02, N03, N04, N05, N06, N07, N08, N10, N11, N12, N13, N14, N15, N16, N17, N18, N19, N20, N21, N22, N23
	OHIP	**Diagnostic:** 403, 585
Chronic liver disease	CIHI-DAD	**ICD-10:** B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77
	OHIP	**Diagnostic:** 571, 573, 070 **Fee:** Z551, Z554
Chronic lung disease	CIHI-DAD	**ICD-10:** I272, I278, I279, J40, J41, J42, J43,J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J701, J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99
	OHIP	**Diagnostic:** 491, 492, 493, 494, 496, 501, 502, 515, 518, 519 **Fee:** J889, J689
Coronary artery disease (excluding angina)	CIHI-DAD	**ICD-10:** I21, I22, Z955, T822
	CCI	1IJ50, 1IJ76
	CCP	4801, 4802, 4803, 4804, 4805, 481, 482, 483
	OHIP	**Diagnostic:** 410, 412 **Fee:** R741, R742, R743, G298, E646, E651, E652, E654, E655, Z434, Z448
Dementia	CIHI-DAD	**ICD-10:** F065, F066, F068, F069, F09, F00, F01, F02, F03, F051, G30, G31, R54
	OHIP	**Diagnostic:** 290,331, 797
Diabetes	CIHI-DAD	**ICD-10:** E10, E11, E13, E14
	OHIP	**Fee:** K045, K046, K029, K030, Q040
Heart failure	CIHI-DAD	**ICD-10:** I500, I501, I509, I255, J81

	CCI	1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR
	CCP	4961, 4962, 4963, 4964
	OHIP	**Diagnostic:** 428 **Fee:** R701, R702, Z429
Other infections	CIHI-DAD	**ICD-10:** A49
	OHIP	**Diagnostic:** 785, 136, 040, 039
Peripheral vascular disease	CIHI-DAD	**ICD-10:** I700, I702, I708, I709, I731, I738, I739, K551
	CCP	5125, 5129, 5014, 5016, 5018, 5028, 5038, 5126, 5159
	CCI	1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76MI, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87, 1KA87LA, 1KE57
	OHIP	**Fee:** R787, R780, R797, R804, R809, R875, R815, R936, R783, R784,R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649
Prosthetic joint infection	CIHI-DAD	**ICD-10:** T845
	OHIP	**Diagnostic:** 739
Respiratory infection	CIHI-DAD	**ICD-10:** J22, J02, J98, H66, J03, H65, J20, J18, J42, J06, J35, J01, J44
	OHIP	**Diagnostic:** 519, 460, 382, 463, 381, 466, 486, 491, 474, 461, 496, 034
Skin and soft tissue infection	CIHI-DAD	**ICD-10:** L08, L03, T01, L01, T814, A46
	OHIP	**Diagnostic:** 709, 686, 698, 682, 998, 879, 894, 884, 684, 250
Stroke/ Transient ischemic attack	CIHI-DAD	**ICD-10:** I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340
Urinary incontinence	CIHI-DAD	**ICD-10:** N393, N394, R32
Urinary retention	CIHI-DAD	**ICD-10:** R33
Urinary tract infection	CIHI-DAD	**ICD-10:** N10, N11, N12, n136, N151, N159, N160, N300, N308, N309, N340, N390, N410, N411, N412, N413, N431, N45, T835
MEDICATION USE (120 days prior to index date)	ODB	
HEALTHCARE USE (1 year prior to index date)		
Family physician visits	IPDB	
Nephrologist visits	IPDB	
Neurologist visits	IPDB	
Number of hospitalizations	CIHI-DAD	
Number of emergency department visits	NACRS	
LABORATORY TESTS (1 year prior to index date; and 7 days prior to index date for select tests, denoted by *)		
At-home physician service*	OHIP	**Fee:** A901, B960, B961, B962, B963, B964, B966, B990, B992, B993, B994, B996, B997, B998
Bone mineral density test	OHIP	**Fee:** J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888

Cardiac catheterization	CCI	4995, 4996, 4997, 4892, , 4893, 4894, 4895, 4896, 4897, 4898
	CCP	3IJ30GP, 3HZ30GP, 2HZ24GPKJ, 2HZ24GPKL, 2HZ24GPKM, 2HZ24GPXJ, 2HZ28GPPL, 2HZ71GP, 3IP10, 3IS10
	OHIP	**Fee:** G296, G297, G299, G300, G301, G304, G305, G306, G297, G509
Cardiac stress test	CCI	2HZ08, 3IP70
	CCP	0341, 0342, 0343, 0344, 0605
	OHIP	**Fee:** G315, G174, G111, G112, G319, G582, G583, G584, J607, J608, J807, J808, J809, J866, J609, J666
Carotid ultrasound	CCI	3JE30, 3JG30
	CCP	0281
	OHIP	**Fee:** J201, J501, J190, J191, J490, J491, J492
Cervical cancer screening	OHIP	**Fee:** E430, G365, G394, L713, L812
Chest x-ray*	OHIP	**Fee:** X090, X091, X092, X195
Colorectal cancer screening	OHIP	**Fee:** G004, L179, L181, Q043, Q152, X112, X113, Z535, Z536, Z555, Z580
Coronary revascularization	CCI	1IJ50, 1IJ26, IIJ27, 1IJ57, 1IJ76, 1IJ57GQ, 1IJ54GQAZ
	CCP	481, 482, 483, 480
	OHIP	**Fee:** R741, R742, R743, E651, E652, E654, E646, G298, Z434, G262
CT abdomen*	OHIP	**Fee:** X126, X409, X410
CT extremities*	OHIP	**Fee:** X127, X412, X413
CT head	OHIP	**Fee:** X188, X400, X401, X402, X405, X408
CT neck	OHIP	**Fee:** X124, X403, X404
CT pelvis	OHIP	**Fee:** X231, X232, X233
CT spine	OHIP	**Fee:** X128, X415, X416
CT thorax*	OHIP	**Fee:** X125, X406, X407
Coronary angiogram	CCI	3IP10, 3IS10
	CCP	4892, 4893, 4894, 4895, 4896, 4897, 4898
	OHIP	**Fee:** G297, G509
Cystoscopy*	OHIP	**Fee:** Z606, Z607, Z628, Z632, Z633, Z634
Echocardiography	CCI	3IP30
	CCP	0282
	OHIP	**Fee:** G560, G561, G562, G566, G567, G568, G570, G571, G572, G574, G575, G576, G577, G578, G581
eGFR values	OLIS	
Electrocardiography	CCI	2HZ24JAKE
	OHIP	**Fee:** G310, G313
Electroencephalo-cardiography	OHIP	**Fee:** G414, G415, G416, G417, G418, G540, G542, G544, G545, G546, G554, G555
Hearing test	OHIP	**Fee:** G153, G154, G440, G441, G442, G443, G448, G450, G451, G452, G525, G526, G529, G530, G533, G815, G816

Holter monitoring	CCI	2HZ24JAKH
	CCP	0354
	OHIP	**Fee:** G311, G320, G647, G648, G649, G650, G651, G652, G653, G654, G655, G656, G657, G658, G659, G660, G661, G682, G683, G684, G685, G686, G687, G688, G689, G690, G692, G693
Influenza vaccination	OHIP	**Fee:** G590, G591
Mammography	OHIP	**Fee:** X172, X178, X184, X185, X201
Nasal swab	OHIP	**Fee:** L715
Prostate-specific antigen test	OHIP	**Fee:** Q005, Q118, Q119, Q120, Q121, Q122, Q123, Q133
Serum creatinine values*	OLIS	
Sputum*	OHIP	**Fee:** L629
Transurethral resection of the prostate	CCI	1QT59BAAD, 1QT59BAAG, 1QT59BAAW, 1QT59BAAZ, 1QT59BACG, 1QT59BAGX, 1QT87BA, 1QT87BAAG, 1QT87BAAK
	CCP	721
	OHIP	**Fee:** S655
Urinalysis*	OHIP	**Fee:** L253, L254, L255, L633, L634, L641, G009, G010
Vaginal smear*	OHIP	**Fee:** L625
Wound swab*	OHIP	**Fee:** L628

Abbreviations: CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI-DAD, Canadian Institutes for Health Information Discharge Abstract Database; CT, computed tomography; eGFR, estimated glomerular filtration rate; ICD-10, International Statistical Classification of Diseases, Tenth Revision; IPDB: Institute for Clinical Evaluative Sciences Physicians Database; NACRS, National Ambulatory Care Reporting System; ODB: Ontario Drug Database; OHIP, Ontario Health Insurance Plan; OLIS, Ontario Laboratory Information System; RPDB, Registered Persons Database

* Assessed in the 7 days and 365 days prior to index date

Supplemental Table 5. Coding definitions for adverse effects

Adverse effect[1]	ICD-10 code
GASTROINTESTINAL	
Diarrhea [2]	R19, R197
Enterocolitis due to Clostridium difficile [2]	A047
Epigastic pain [2]	R101
Flatulence [2]	R14, R143
Gastritis and duodenitis [2]	K29
Generalized abdominal pain [2]	R108
Nausea [2]	R110
Vomiting [2]	R111
GENITOURINARY	
Acute vaginitis	N760
Other urogenital candidiasis	B374
HEMATOLOGIC	
Acquired haemolytic anaemia, unspecified [3]	D599
Eosinophilia	D721
Other agranulocytosis [3]	D708
Other anemias	D64
Other coagulation defects	D68
Neutropenia	D700
Secondary thrombocytopenia	D695
Thrombocytopenia, unspecified	D696
Thrombophlebitis	I80
HEPATIC	
Abnormal levels of other serum enzymes [2]	R74
Toxic liver disease with acute hepatitis [2]	K712
Toxic liver disease with cholestasis [2]	K710
Toxic liver disease with hepatitis, not elsewhere classified [2]	K716
Toxic liver disease, unspecified [2]	K719
Unspecified jaundice [2]	R17
HYPERSENSITIVITY	
Anaphylactic shock, unspecified [3]	T782
Angioneurotic oedema [3]	T783
NEUROLOGIC	
Dystonia	G24
Encephalopathy, unspecified	G934
Seizure	G40, G41
RENAL	
Acute kidney failure, unspecified	N179
Acute tubular necrosis	N170
Tubulo-interstitial nephritis, not specified as acute or chronic [3]	N12
SKIN AND SOFT TISSUE	
Allergic urticaria [3]	L500
Erythema multiforme [3]	L51
Idiopathic urticaria [3]	L501
Rash and other nonspecific skin eruption [3]	R21
Stevens-Johnson syndrome [3]	L511
Toxic epidermal necrolysis [3]	L512

OTHER		
	Disorientation, unspecified	R410
	Dizziness	R42
	Drowsiness	R400
	Hallcuinations, unspecified	R443
	Headache	R51
	Fever, unspecified	R509
	Insomnia	G470
	Other and unspecified arthropathy	M12
	Other malaise and fatigue	R53, R538
	Pain in joint	M255
	Restlessness and agitation	R451
UNSPECIFIED		
	Adverse effect, unspecified	T789
	Allergy, unspecified [3]	T784
	Other serum reactions [3]	T806
	Poisoning by cephalosporins and other beta-lactam antibiotics [3]	T361

Abbreviations: ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

[1] All adverse effects listed were included as "possible cephalosporin-related side effect" in analysis

[2] Included as "Gastrointestinal-related issue" in analysis

[3] Included as "Allergic-specific reaction" in analysis

Supplemental Table 6. Study cephalosporin antibiotic doses and prescription details

	CEFUROXIME	CEPHALEXIN	CEFPROZIL
N (%)	1547 (16%)	6453 (70%)	1347 (14%)
Median daily dose (IQR)	1000 mg (500, 1000)	2000 mg (1000, 2000)	1000 mg (500, 1000)
Median days supply (IQR)	10 days (7, 10)	7 days (7, 10)	10 days (7, 10)

Abbreviations: IQR, interquartile range

Supplemental Table 7. Full table of baseline characteristics

	Dose-Reduced (n=3,094)	Higher Dose (n=6,253)	Standardized Difference [1]
Study Medications			
Cefuroxime	541 (18%)	1006 (16%)	4%
Cephalexin	2090 (68%)	4363 (70%)	5%
Cefprozil	463 (15%)	884 (14%)	3%
Days supply			
Mean ± SD	8 ± 2	8 ± 2	16%
Median (IQR)	7 (7, 10)	7 (7, 10)	--
Demographics			
Age, years			
Mean ± SD	83.6 ± 7.9	81.7 ± 8.0	23%
Median (IQR)	84 (78, 89)	82 (76, 88)	--
66-70 years	167 (5%)	564 (9%)	14%
71-75 years	282 (9%)	756 (12%)	10%
76-80 years	478 (15%)	1070 (17%)	5%
81-85 years	660 (21%)	1376 (22%)	2%
86-90 years	736 (24%)	1348 (22%)	5%
>90	771 (25%)	1139 (18%)	16%
Sex, Women	2024 (65%)	3571 (57%)	17%
Long-term care resident	545 (0.2%)	653 (0.1%)	21%
Patient location [2]			
Urban	2679 (87%)	5451 (87%)	2%
Rural	415 (13%)	802 (13%)	2%
Year of cohort entry			
2007	6 (0%)	15 (0%)	0%
2008	182 (6%)	314 (5%)	4%
2009	322 (10%)	653 (10%)	0%
2010	348 (11%)	750 (12%)	2%
2011	388 (13%)	809 (13%)	1%
2012	415 (13%)	844 (14%)	0%
2013	438 (14%)	881 (14%)	0%
2014	442 (14%)	921 (15%)	1%
2015	494 (16%)	943 (15%)	2%
2016	59 (2%)	123 (2%)	1%
Income based socioeconomic status [3]			
1 (lowest)	669 (22%)	1314 (21%)	1%
2	633 (21%)	1403 (22%)	5%
3	650 (21%)	1301 (21%)	0%
4	602 (20%)	1230 (20%)	1%

5 (highest)	524 (17%)	984 (16%)	3%
Local Health Integration Network (LHIN) [4]			
Erie St. Clair	121 (4%)	318 (5%)	6%
South West	323 (10%)	652 (10%)	0%
Waterloo Wellington	176 (6%)	299 (5%)	4%
Hamilton Niagara Haldimand Brant	385 (12%)	932 (15%)	7%
Central West	128 (4%)	296 (5%)	3%
Mississauga Halton	191 (6%)	412 (7%)	2%
Toronto Central	193 (6%)	393 (6%)	0%
Central	379 (12%)	718 (12%)	2%
Central East	461 (15%)	898 (14%)	1%
South East	149 (5%)	284 (5%)	1%
Champlain	291 (9%)	500 (8%)	5%
North Simcoe Muskoka	123 (4%)	203 (3%)	4%
North East	132 (4%)	267 (4%)	0%
North West	42 (1%)	81 (1%)	1%
Prescriber specialty [3]			
General practitioner	2452 (79%)	4921 (79%)	1%
Internal medicine	21 (1%)	46 (1%)	0%
Other	251 (8%)	582 (9%)	4%
Comorbidities [4]			
Anemia	1430 (46%)	2841 (45%)	2%
Dementia	938 (30%)	1415 (23%)	18%
Chronic liver disease	144 (5%)	271 (4%)	2%
Chronic lung disease	1022 (33%)	2172 (35%)	4%
Coronary artery disease	1288 (42%)	2715 (43%)	4%
Diabetes	1301 (42%)	2813 (45%)	6%
Heart failure	1298 (42%)	2526 (40%)	3%
Peripheral vascular disease	103 (3%)	240 (4%)	3%
Stroke/transient ischemic attack	173 (6%)	309 (5%)	3%
Urinary incontinence	61 (2%)	106 (2%)	2%
Urinary retention	121 (4%)	267 (4%)	2%
Urinary tract infections	586 (19%)	923 (15%)	11%
Respiratory infection	2141 (69%)	4390 (70%)	2%
Skin and soft tissue infection	2310 (75%)	4830 (77%)	6%
Prosthetic joint infection	406 (13%)	914 (15%)	4%
Infections, other	1211 (39%)	2638 (42%)	6%
Charlson Comorbidity Index [5]			
Mean ± SD	1.7 ± 2	1.7 ± 2.1	2%
Median (IQR)	1 (0, 3)	1 (0, 3)	--

Medication use [6]			
ACE inhibitors	1004 (32%)	2114 (34%)	3%
Angiotensin receptor blockers	776 (25%)	1731 (28%)	6%
Beta blockers	1618 (52%)	3219 (52%)	2%
Calcium channel blockers	1544 (50%)	2966 (47%)	5%
Diabetes	1030 (33%)	2373 (38%)	10%
Gastric acid suppressants	1600 (52%)	3117 (50%)	4%
Immunosuppressive agents [7]	204 (7%)	454 (7%)	3%
Loop diuretics	1659 (54%)	3292 (53%)	2%
Potassium sparing diuretics	354 (11%)	705 (11%)	0%
Thiazide diuretics	591 (19%)	1326 (21%)	5%
NSAIDs	250 (8%)	644 (10%)	8%
Statins	1842 (60%)	3892 (62%)	6%
Overactive bladder medications	123 (4%)	256 (4%)	1%
Inhaler – acetylcholine	328 (11%)	679 (11%)	1%
Inhaler – beta agonist	323 (10%)	683 (11%)	2%
Inhaler – corticosteroid	185 (6%)	359 (6%)	1%
Bronchodilators	265 (9%)	620 (10%)	4%
Warfarin	604 (20%)	1215 (19%)	0%
Number of unique drug names			
Mean ± SD	9.9 ± 4.3	9.8 ± 4.3	2%
Median (IQR)	10 (7, 12)	9 (7, 12)	--
Healthcare use [8]			
General practitioner visits			
Mean ± SD	15 ± 13	14 ± 13	9%
Median (IQR)	12 (6, 18)	10 (6, 17)	--
Neurologist visits			
Mean ± SD	14.79 ± 13.47	13.62 ± 12.61	9%
Median (IQR)	12 (6, 18)	10 (6, 17)	--
Nephrologist visits			
Mean ± SD	3.12 ± 2.78	2.98 ± 2.61	5%
Median (IQR)	2 (2, 4)	2 (2, 4)	--
Number of any hospitalizations			
Mean ± SD	0.7 ± 1.2	0.7 ± 1.1	0%
Median (IQR)	0 (0, 1)	0 (0, 1)	--
Number of any emergency department visits			
Mean ± SD	1.1 ± 1.7	1.1 ± 1.6	5%
Median (IQR)	1 (0, 2)	0 (0, 2)	--
Number of serum creatinine tests			
Mean ± SD	4.9 ± 4.5	4.3 ± 3.8	14%
Median (IQR)	4 (2, 6)	3 (2, 6)	--

CT abdomen	310 (10%)	677 (11%)	3%
CT extremities	29 (1%)	67 (11%)	2%
CT head	440 (14%)	820 (11%)	3%
CT neck	31 (1%)	54 (6%)	1%
CT pelvis	297 (10%)	630 (10%)	2%
CT spine	61 (2%)	124 (2%)	0%
CT thorax	223 (7%)	486 (8%)	2%
Carotid ultrasound	179 (6%)	431 (7%)	5%
Cardiac catheterization	59 (2%)	145 (2%)	3%
Coronary angiogram	59 (2%)	140 (2%)	2%
Echocardiography	866 (28%)	1895 (30%)	5%
Electroencephalography	1870 (60%)	3731 (60%)	1%
Holter monitoring	294 (10%)	591 (10%)	0%
Cardiac stress test	289 (9%)	652 (10%)	4%
Coronary revascularization	24 (1%)	64 (1%)	2%
Electrocardiography	21 (1%)	34 (1%)	3%
Colorectal cancer screening	335 (11%)	789 (13%)	6%
Cervical cancer screening	33 (1%)	83 (1%)	2%
Prostate-specific antigen test	40 (1%)	122 (2%)	5%
Mammography	120 (4%)	317 (5%)	6%
Influenza vaccination	1463 (47%)	3268 (52%)	10%
Bone mineral density test	166 (5%)	347 (6%)	0%
Hearing test	133 (4%)	246 (4%)	2%
Cystoscopy	147 (5%)	332 (5%)	2%
Transurethral resection of the prostate	13 (0%)	33 (1%)	1%
Chest x-ray	1612 (52%)	3088 (49%)	5%
At-home physician service	307 (10%)	482 (8%)	8%
Urinalysis	2096 (68%)	3937 (63%)	10%
Sputum	16 (1%)	25 (0%)	1%
Vaginal smear	23 (1%)	29 (1%)	3%
Wound swab	368 (12%)	490 (8%)	14%
Recent laboratory tests [9]			
Serum creatinine tests	433 (14%)	618 (10%)	13%
CT abdomen	8 (0%)	11 (0%)	2%
CT thorax	9 (0%)	12 (0%)	2%
Cystoscopy	7 (0%)	6 (0%)	3%
Chest x-ray	112 (4%)	176 (3%)	5%
At-home physician service	54 (2%)	96 (2%)	2%
Urinalysis	370 (12%)	379 (6%)	21%
Wound swab	41 (1%)	66 (1%)	2%
Laboratory values [10]			

Estimated glomerular filtration rate, ml/min per 1.73m^2 (eGFR) [11]			
Mean ± SD	23 ± 5	24 ± 5	19%
Median (IQR)	24 (19, 27)	25 (21, 28)	--
Serum creatinine, mg/dL			
Mean ± SD	2.3 ± 0.8	2.3 ± 0.7	6%
Median (IQR)	2.1 (1.8, 2.5)	2.1(1.8, 2.5)	--
Serum creatinine in women , mg/dL			
Mean ± SD	2.8 ± 0.8	2.6 ± 0.7	13%
Median (IQR)	2.5 (2.2, 3.0)	2.4 (2.2, 2.8)	--
Serum creatinine in men, mg/dL			
Mean ± SD	2.8 ± 0.8	2.6 ± 0.7	18%
Median (IQR)	2.5 (2.2, 3.0)	2.4 (2.2, 2.8)	--

Abbreviations: ACE, angiotensin-converting enzyme; CT, computed tomography; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LHIN, local health integration network; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation

Note: In accordance with ICES privacy policies, cell sizes less than or equal to 5 cannot be reported.

[1] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between the groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference between the groups. [9]
[2] Rural location was defined as a population < 10,000 individuals. Patients with missing location (<0.5%) were included as urban.
[3] LHIN refers to health authorities responsible for regional administration of public healthcare services in Ontario. LHIN was not missing for any patients.
[4] Income was categorized into fifths of average neighbourhood income on the index date. Income was not available for 37 (0.4%) patients with a prescription for a study drug.
[5] Prescriber specialty was not available for 370 (12%) patients taking a low dose study drug and 704 (11%) patients taking a high dose study drug.
[6] Comorbidities in the 5 years preceding the index date were considered.
[7] Charlson Comorbidity index was calculated using 3 years of hospital admission data. "No hospital admissions" received a score of 0. [10,11]
[8] Baseline medication use was assessed in the prior 120 days.
[9] Healthcare use was assessed in the prior 1 year.
[10] Select laboratory tests were assessed in the prior 7 days.
[11] Assessed in the prior 7-365 days.
[12] eGFR was calculated using the CKD-EPI equation[12]: 141 × min([serum creatinine concentration in µmol/L/88.4]/κ, 1)α × max([serum creatinine concentration in µmol/L/88.4]/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if African-American]; κ=0.7 if female and 0.9 if male; α=-0.329 if femal and -0.411 if male; min=the minimum of serum creatinine concentration/κ or 1; max=the maximum of serum creatinine concentration/κ or 1.[13] Information on race was not available in our data sources and all patients were assumed not to be of African-Canadian race; African-Canadians represented less than 5% of the population of Ontario in 2006.[12]

Supplemental Table 8. Event rates for 30-day hospital encounter with a possible cephalosporin-related side effect, stratified by type of cephalosporin

Type of Cephalosporin	Number of patients		Number (%) of events		Adjusted* Odds Ratio (95% confidence interval)	Interaction P-value
	Dose-Reduced	Higher Dose	Dose-Reduced (Referent)	Higher Dose		
Cefuroxime	541	1006	49 (9.1%)	68 (6.8%)	0.73 (0.50, 1.07)	0.31
Cephalexin	2090	4363	124 (5.9%)	265 (6.1%)	1.03 (0.82, 1.28)	
Cefprozil	463	884	26 (5.6%)	50 (5.7%)	1.01 (0.62, 1.64)	

*Adjusted for age, sex, income quintile, living in a long-term care residence, the duration of dispensed cephalosporin, as well as baseline evidence of dementia. After reviewing the baseline table for characteristics with clinically meaningful differences between groups (standardized differences ≥10%), we added 8 other potential confounders to our models: receipt of a wound swab, urinalysis, or influenza vaccination, evidence of urinary tract infection, baseline eGFR, the number of prior serum creatinine measurements, and number of primary care physician visits.

References

1 Cefprozil: Drug information - UpToDate. https://www.uptodate.com/contents/cefprozil-drug-information?source=history_widget (accessed 17 Feb 2018).

2 Cefzil. https://www-myrxtx-ca.proxy1.lib.uwo.ca/search (accessed 17 Feb 2018).

3 Cephalexin (CPhA Monograph). https://www-myrxtx-ca.proxy1.lib.uwo.ca/search (accessed 17 Feb 2018).

4 Cephalexin: Drug information - UpToDate. https://www.uptodate.com/contents/cephalexin-drug-information?search=cephalexin&source=search_result&selectedTitle=1~92&usage_type=default&display_rank=1 (accessed 17 Feb 2018).

5 Aronoff GR, Bennett WM BJ. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*. 5th ed. Philidelphia, PA: : American College of Physicians 2007.

6 Auro-Cefuroxime. https://www-myrxtx-ca.proxy1.lib.uwo.ca/search (accessed 17 Feb 2018).

7 Cefuroxime: Drug information - UpToDate. https://www.uptodate.com/contents/cefuroxime-drug-information?search=cefuroxime&source=search_result&selectedTitle=1~70&usage_type=default&display_rank=1#F148270 (accessed 16 Feb 2018).

8 Benchimol EI, Smeeth L, Guttmann A, *et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med* 2015;**12**. doi:10.1371/journal.pmed.1001885

9 Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;**38**:1228–34. doi:10.1080/03610910902859574

10 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83. doi:10.1016/0021-9681(87)90171-8

11 Quan H, Sundararajan V, Halfon P, *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;**43**:1130–9. doi:10.1097/01.mlr.0000182534.19832.83

12 Statistics Canada. Population by selected ethnic origins, by province and territory (2006 Census). 2006 Census. 2006.http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo26f-eng.htm

13 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. doi:10.7326/0003-4819-150-9-200905050-00006