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Healthcare Resource Utilization and Cost of Invasive Meningococcal Disease in Ontario, Canada

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Background: Invasive meningococcal disease (IMD) is associated with significant morbidity and mortality, thus remaining a concern for healthcare providers and the public. Evidence of the longitudinal burden of IMD and associated costs are scarce. Here we have evaluated the healthcare utilization and cost associated with hospitalized IMD cases in Ontario, Canada.

Methods: Observational cohort study utilizing the Ontario provincial claims databases, comprising: (1) individuals hospitalized with IMD between January 1995 and June 2012 and (2) age-, gender- and area-matched non-IMD controls (1:20 ratio). IMD cases were identified through diagnostic codes from hospitalization data and medical services claims. Costs are presented in Canadian dollars.

Results: Nine-hundred twelve IMD cases and 18,221 non-IMD controls were included. Over 5 years of follow-up, 27% of IMD cases (excluding initial hospitalization and 30-day acute phase) versus 15% of non-IMD controls ($P < 0.001$) were hospitalized. Compared with controls, IMD cases were more likely to receive alternative level of care (6.7% vs. 1.1%; $P < 0.001$) or visit the intensive care unit (49.2% vs. 2.4%; $P < 0.001$), and were associated with significantly higher mean hospitalization cost per case ($40,075 vs. $2827; $P < 0.001$). The hospitalization cost per case remained significantly higher when excluding the initial hospitalization and acute phase ($9867 vs. $3312; $P < 0.001$). The mean total cost per IMD case, including medications, hospitalization and medical services, was $45,768–$52,631 ($13,520–$23,789 excluding initial hospitalization and acute phase), for an overall cost (all cases during total follow-up) of $41,740,142–$47,999,289.

Conclusions: In addition to its clinical burden, IMD is associated with significant economic burden to the public health system.

Key Words: invasive meningococcal disease; meningitis; healthcare utilization; economic burden; observational

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Meningococcal disease is a serious illness caused by the bacterium *Neisseria meningitidis* (or meningococcus), which is currently classified into 12 different serogroups based on the structure of the polysaccharide capsule. In Canada, almost all cases of invasive meningococcal disease (IMD) are caused by 5 of these serogroups, specifically serogroups A, B, C, W and Y,[1] the most common being serogroup B followed by serogroup Y.[2]

Before the introduction of vaccine programs, the annual incidence of IMD in Canada ranged between 0.4 and 1.6 cases per 100,000 persons.[2] Although the annual rates of all IMD in Ontario decreased following the introduction of a routine vaccine program against serogroup C, the annual incidence of serogroup B infections remained relatively stable and, therefore, with control of other serogroups via vaccination programs, serogroup B gradually accounted for a higher proportion of IMD cases.[3,4] In Ontario, infants had the highest rates of serogroup B infection, followed by those 1–4 years of age.[3] In severe cases, IMD can result in death. The average case fatality ratio between 2006 and 2011 in Canada was 8.1%, accounting for a total of 94 deaths during this period[5]; in Ontario, the case fatality ratio for serogroup Y and serogroup C IMD cases was 8.3% and 17.4%, respectively.[6]

Although the incidence of IMD is relatively low, long-term sequelae, which are often serious, occur frequently among IMD survivors,[7–10] with reports suggesting rates of 11%–19% in Canada.[11] In a recent systematic review of studies assessing sequelae and quality of life among IMD patients, sequelae including hearing loss, cognitive impairment, psychologic problems, motor deficits, amputation and disability (physical and communication) were reported.[12] In Canada, sequelae after infection with serogroup B occur at a rate of 19%, the most common including hearing loss, skin scarring and amputations.[13]

There are currently limited cost data in Canada concerning the long-term sequelae of IMD. The aim of this study is to describe the healthcare resource utilization and associated costs among patients hospitalized with IMD in Ontario. The results will in turn provide local policy makers with evidence regarding the burden of IMD on the Canadian healthcare system that could be used to populate health economic models and cost-effectiveness analyses of interventions.

METHODS

Study Design

This was a population-based retrospective administrative data analysis using data from the following provincial health insurance claims databases of the Ontario Ministry of Health and Long-Term Care databases. In Ontario, the publicly funded healthcare system provides universal coverage for medically necessary health care services. However, patients may pay privately for some drugs and other services.

The Ontario Registered Persons Database, which contains demographic information, vital status information and eligibility for Ontario Health Insurance Plan (OHIP) coverage over time for anyone who has ever received an Ontario Health card number.

The Ontario Drug Benefit (ODB) program database, providing pharmacy claim data for all individuals covered under this plan,

which includes individuals over the age of 65 years, residents of long-term facilities, residents of homes for special care, individuals receiving professional services under the "Home Care Program" and those that are "Trillium Drug Program" recipients. In addition, the "Trillium" program (available to all Ontario residents regardless of their income level and age) and the Exceptional Access Program were also included. Prescription drug use not covered by provincial drug benefit plans was not assessed.

The Discharge Abstract Database is a national database on all separations from acute care institutions, including discharges, deaths, sign-outs and transfers.

The OHIP database, containing information on all fee-for-service physician claims for all residents of Ontario regardless of age and income that are covered under OHIP.

Unique encrypted identifier numbers were used to link individual patients across all databases. The study was approved by an Independent Ethics Review Board (Institutional Review Board Services, Aurora, Ontario, Canada).

Study Population

The study population comprised 2 groups: (1) individuals hospitalized with IMD between January 1, 1995, and June 30, 2012, and (2) non-IMD controls matched using a random stratified sampling algorithm in a 20:1 ratio to each IMD case by age, gender, postal code and duration of follow-up. IMD cases were identified through International Classification of Diseases, 9th revision (036); International Classification of Diseases, 10th revision (A39: "meningococcal infection") primary and secondary diagnostic codes from hospitalization data (Discharge Abstract Database) and medical services claims (OHIP).

Data Collection

All patients were followed from the index date until the date of data extraction without any limitations placed on the duration of follow-up. The index date was defined as the date of IMD diagnosis during hospitalization for the IMD cohort and, for the non-IMD cohort, as the index date of the matched IMD individual. Furthermore, all the pharmaceutical and medical claims, and hospitalization records were extracted for a period of 2 years preceding the index date to ascertain the medical and pharmaceutical history.

The following outcomes were assessed: hospitalization including hospital-based acute inpatient care, alternative level of care (non-acute hospital care), intensive care unit visits and emergency room (ER) visits; medical services including visits to the general practitioner's (GP) office (including clinics), visits to a specialist and all procedures/tests performed in an outpatient setting out of hospital; and utilization of prescribed medications. Healthcare resource utilization costs from the government's perspective related to hospitalization data, medical and pharmaceutical claims and medication acquisition costs were directly used from the provincial health insurance claims databases and adjusted to 2012 cost as per inflation rates reported by the Consumer Price Indexes for Canada.

Statistical Analysis

All analyses were conducted for the 5-year follow-up duration as well as stratified by follow-up period, namely the acute phase from admission to 30-days post-discharge from the hospital (the last hospital was used in the case of referrals), 1–6 months, 6–12 months, 12–60 months and the total 5-year period with and without the acute phase. Summary statistics including the mean and standard deviations (median and interquartile range also provided for costs because of the skewness of these data) for continuous variables and counts and proportions for categorical variables, were produced for patient demographics, baseline characteristics and all outcomes. Comparisons between groups in patient demographics and baseline characteristics were conducted using the independent-samples t test for continuous variables and the χ^2 test for categorical variables. Comparisons of healthcare resource utilization were conducted using multivariate logistic regression and adjusting for potential differences in the use of respective resource within the 2-year look-back period and for duration of follow-up (for overall follow-up period, 12–60 months and 1–60 months). Statistical analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Demographics and Claims History

A total of 912 IMD cases and 18,221 non-IMD matched controls were included in the study. Demographics are shown in (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D374).

Within the 2-year period preceding the index date, IMD patients were more likely to have been hospitalized compared with the control group as well as to have received all types of hospital services, including acute inpatient care, alternative care, visits to the intensive care unit and ER visits. Furthermore, visits to the GP's office or a specialist were also more common among IMD cases.

Healthcare Resource Utilization During Follow-Up

Table 1 summarizes the healthcare resource utilization among patients with IMD and the matched controls during the 5-year follow-up period as well as broken down for the acute phase of the disease (0–30 days), 1–6 months, 6–12 months, 12–60 months and 30 days to 60 months.

During the 5-year follow-up period, 15% (n = 2725) of non-IMD cases were hospitalized. Hospitalization was significantly higher among IMD cases even excluding the initial hospitalization for the IMD infection and the 0–30 day period, specifically for 1–6 months (11.2% vs. 2.5%; $P < 0.001$), 6–12 months (13.8% vs. 6.8%; $P < 0.001$), 12–60 months (16.4% vs. 10.9%; $P < 0.001$) and the overall period between 30 days and 60 months (27% vs. 14.3%; $P < 0.001$). Acute inpatient care and visits to the intensive care unit and the ER were also significantly higher in the IMD group irrespective of follow-up period examined while alternative care was only different between groups in the first 6 months of the IMD infection.

In terms of out of hospital outpatient care, visits to the GP's office and to a specialist were more frequent among IMD cases compared with controls, particularly during the acute phase (GP's office: 81.7% vs. 28.7%, $P < 0.001$; specialist: 97.9% vs. 21.3%; $P < 0.001$) and 1–6 months (GP's office: 72.0% vs. 61.8%, $P < 0.001$; specialist: 72.1% vs. 48.4%; $P < 0.001$). However, no remarkable differences were observed for the remaining periods or the overall period between 30 days and 60 months.

Medication use was more frequent among IMD cases compared with non-IMD controls, particularly during the acute phase of the disease (4.6% vs. 2.3%; $P < 0.001$) but also between 30 days and 60 months (6.8% vs. 5.2%; $P = 0.036$).

Healthcare Costs During Follow-Up

IMD was associated with a significantly higher cost for medication claims (particularly during the acute disease phase), hospitalization and medical services, with hospitalization being the main cost driver (Table 2). Specifically, the mean hospitalization cost per case was $40,075 (median: $16,927) for IMD cases compared with $2827 (median: $0) for controls ($P < 0.001$) during the

Table 1. Healthcare Resource Utilization during Follow-Up

Parameter Period*	IMD, n = 912	Control, n = 18,221	*P*
Patient with at least 1 medication claim, %			
0–30 d (acute phase)	4.6	2.3	<0.001
1–6 mo	4.7	3.5	0.059
6–12 mo	5.4	4.1	0.072†
12–60 mo	5.5	4.9	0.430†
30 d to 60 mo	6.8	5.2	0.036†
0–60 mo	8.4	5.2	<0.001†
Hospitalization‡, %			
0–30 d (acute phase)	100.0	1.0	NA
1–6 mo	11.2	2.5	<0.001
6–12 mo	13.8	6.8	<0.001†
12–60 mo	16.4	10.9	<0.001†
30 d to 60 mo	27.0	14.3	<0.001†
0–60 mo	100.0	15.0	NA
Hospital-based acute inpatient care, %			
0–30 d (acute phase)	98.6	1.0	NA
1–6 mo	10.4	2.5	<0.001
6–12 mo	13.7	6.8	<0.001†
12–60 mo	16.4	10.9	<0.001†
30 d to 60 mo	26.4	14.3	<0.001†
0–60 mo	99.5	14.9	NA
Alternative level of care, %			
0–30 d (acute phase)	4.9	0.0	<0.001
1–6 mo	1.4	0.1	<0.001
6–12 mo	0.5	0.4	0.571†
12–60 mo	1.0	0.8	0.739†
30 d to 60 mo	2.7	1.1	<0.001†
0–60 mo	6.7	1.1	<0.001†
Intensive care unit, %			
0–30 d (acute phase)	47.1	0.1	<0.001
1–6 mo	2.2	0.4	<0.001
6–12 mo	1.8	0.9	0.007†
12–60 mo	2.5	1.6	0.115†
30 d to 60 mo	5.2	2.3	<0.001†
0–60 mo	49.2	2.4	<0.001†
ER visits, %			
0–30 d (acute phase)	79.9	0.4	NA
1–6 mo	5.7	1.6	<0.001
6–12 mo	9.6	4.1	<0.001†
12–60 mo	16.4	10.9	<0.001†
30 d to 60 mo	22.7	13.0	<0.001†
0–60 mo	100.0	15.0	NA
Visit to the GP's office, %			
0–30 d (acute phase)	81.7	28.7	<0.001
1–6 mo	72.0	61.8	<0.001
6–12 mo	80.8	80.6	0.002†
12–60 mo	81.4	84.7	<0.001†
30 d to 60 mo	88.5	89.5	<0.001†
0–60 mo	95.8	91.2	0.058†
Visit to a specialist, %			
0–30 d (acute phase)	97.9	21.3	<0.001
1–6 mo	72.1	48.4	<0.001
6–12 mo	75.3	71.9	0.983†
12–60 mo	80.0	80.9	0.003†
30 d to 60 mo	89.5	85.5	0.246†
0–60 mo	99.8	87.7	<0.001†

*Among the 912 IMD cases, all had 1–6 months of follow-up, 902 had 6–12 months of follow-up and 885 had 12–60 months of follow-up. Controls were matched to IMD cases in terms of follow-up duration.

†Adjusted for duration of follow-up and differences in historical use.

‡Hospitalization includes hospital-based acute inpatient care, alternative level of care and intensive care unit visits.

NA indicates not applicable since initial hospitalization was a selection criterion for IMD cases.

5-year follow-up period. The mean hospitalization cost remained significantly higher when excluding the initial 30-day period for the IMD group ($9867 vs. $3312; $P < 0.001$), when focusing on cases with at least 1 hospitalization ($40,075 vs. $18,904; $P < 0.001$), or when both scenarios were considered ($31,024 vs. $18,904; $P < 0.001$).

Overall, the mean total cost per case during the overall follow-up period was estimated to range between $45,768 and $52,631 for IMD cases (median: between $20,593 and $27,462) and between $5414 and $11,650 for non-IMD controls (median: between $1135 and $7646) based on conservative (assuming persons not included in ODB incurred no cost for medication claims) versus nonconservative (assuming persons not included in ODB and those included incurred the same cost for medication claims) estimates of medication claims cost incurred by individuals not eligible for the ODB. These differences were consistent for the acute phase, 1–6 months, 6–12 months, 12–60 months and the overall period between 30 days and 60 months. Based on these mean cost estimates, the overall cost for all IMD cases during the study period is estimated at $41,740,142–$47,999,289 ($18,780,907–$25,044,979 based on median estimates).

DISCUSSION

This study was conducted to evaluate the healthcare resource utilization and associated costs among patients hospitalized with IMD (any serogroup) in Ontario by evaluating hospitalization records and medical and pharmaceutical claims. The number of cases identified was in line with what was reported in the provincial surveillance report.[14] We demonstrated that significant long-term healthcare and economic burden can be attributed to IMD in Ontario.

IMD patients had significantly higher rates of hospitalization, ER visits and outpatient visits in the preceding 2-year period as compared with controls which might be because of several reasons including, but not limited to, prodrome symptoms and differences in underlying medical conditions. Upon adjusting for these historical differences in healthcare resource utilization, IMD patients used a significantly higher amount of healthcare resources compared with non-IMD patients, including hospitalizations and inpatient care, medication claims, alternative level of care, intensive care unit and ER visits, GP's office visits and visits to a specialist. The United States reported similar healthcare resource utilization for overall IMD during a follow-up period of 12 months,[15] which included complicated IMD (presence of sequelae) and non-complicated IMD (no sequelae), specifically in regard to the rate of doctor's office visits which was 95.4% compared with 95.8% in our study for the entire duration of the follow-up. Although only 38.2% of patients visited the ER in the United States, in our study, 100% visited the ER during the entire follow-up period which could be explained by our inclusion criteria, namely the selection of IMD patients who were hospitalized. The explanation of this difference in the reported rates of ER use is supported by the fact that, when evaluating the visits to the ER after the acute phase of IMD, the proportion of patients in our study that visited the ER was 22.7%. The United States also reported that 82.1% of IMD patients had at least 1 medication claim compared with 8.4% of IMD patients in our study, explained in part by our inclusion of medical claims from public health insurance only, indicating we may have underestimated the medication claims by not capturing claims from private insurers.

Healthcare costs were significantly higher among IMD patients compared with the matched controls. The main driver of costs was hospitalization, which was a total of $40,075 per patient (median: $16,927) for the entire 5-year follow-up period among IMD patients versus $2827 for the control patients (median: $0). The initial hospitalization during the acute phase of IMD was $31,707 per patient (median: $14,213), accounting

Table 2. Healthcare Costs During Follow-Up

Parameter Period*	IMD, n = 912	Control, n = 18,221	*P*
Medication claims, CAD, mean/median (IQR) per person			
0–30 d (acute phase)			
Patients with ≥1 claim†	808.1/392.2 (774.7)	251.4/169.1 (275.2)	<0.001
All patients‡	37.2/0.0 (0.0)	5.9/0.0 (0.0)	<0.001
1–6 mo			
Patients with ≥1 claim†	1178.1/691.3 (1343.5)	808.2/524.8 (913.6)	0.020
All patients‡	55.5/0.0 (0.0)	28.5/0.0 (0.0)	<0.001
6–12 mo			
Patients with ≥1 claim†	4125.7/1869.9 (3568.0)	2550.2/1656.3 (3108.5)	<0.001
All patients‡	221.7/0.0 (0.0)	105.8/0.0 (0.0)	<0.001
12–60 mo			
Patients with ≥1 claim†	8606.0/3317.7 (8034.2)	5608.0/3061.1 (6985.0)	0.042
All patients‡	471.8/0.0 (0.0)	275.5/0.0 (0.0)	0.025
30 d to 60 mo			
Patients with ≥1 claim†	11018.0/3508.0 (10771.9)	7842.4/4101.7 (10337.0)	0.111
All patients‡	749.0/0.0 (0.0)	409.7/0.0 (0.0)	0.007
0–60 mo			
Patients with ≥1 claim†	7494.8/1793.4 (7840.0)	6580.6/3436.9 (8334.1)	0.674
All patients‡	632.8/0.0 (0.0)	345.0/0.0 (0.0)	0.006
Hospitalization, CAD, mean/median (IQR) per person			
0–30 d (acute phase)	31706.6/14212.8 (26101.9)	122.4/0.0 (0.0)	<0.001
1–6 mo	2815.4/0.0 (0.0)	428.7/0.0 (0.0)	<0.001
6–12 mo	3420.7/0.0 (0.0)	964.1/0.0 (0.0)	<0.001
12–60 mo	3630.8/0.0 (0.0)	1918.7/0.0 (0.0	<0.001
30 d to 60 mo	9866.9/0.0 (1292.1)	3311.5/0.0 (0.0)	<0.001
0–60 mo	40075.0/16927.2 (32283.3)	2827.1/0.0 (0.0)	<0.001
Medical services¶, CAD, mean/median (IQR) per person			
0–30 d (acute phase)	1681.7/931.0 (1328.2)	46.2/0.0 (37.5)	<0.001
1–6 mo	732.8/225.0 (579.7)	221.1/72.5 (224.8)	<0.001
6–12 mo	1142.6/435.6 (1110.3)	738.1/303.1 (735.7)	0.034
12–60 mo	2171.2/884.0 (2132.1)	1715.9/734.5 (1792.5)	<0.001
30 d to 60 mo	2904.1/1344.4 (2976.5)	1937.0/889.3 (1988.7)	<0.001
0–60 mo	5060.0/2917.3 (4695.9)	2242.0/1079.0 (2295.9)	<0.001
Total cost—conservative‡, CAD, mean/median (IQR) per person			
0–30 d (acute phase)	33425.50/15059.0 (25819.8)	174.5/0.0 (38.8)	<0.001
1–6 mo	3603.7/237.1 (713.6)	678.3/73.4 (234.7)	<0.001
6–12 mo	4785.0/458.9 (1434.0)	1808.0/308.6 (802.6)	<0.001
12–60 mo	6273.8/963.0 (3143.0)	3910.1/760.5 (2112.4)	0.002
30 d to 60 mo	13520.0/1650.6 (6410.9)	5658.3/939.6 (2597.3)	<0.001
0–60 mo	45767.7/20593.1 (36480.0)	5414.0/1135.3 (2925.4)	<0.001
Total cost—least conservative§, CAD, mean/median (IQR) per person			
0–30 d (acute phase)	34196.4/15819.7 (25824.8)	420.0/251.4 (37.3)	<0.001
1–6 mo	4726.3/1402.3 (671.1)	1458.1/877.3 (219.0)	<0.001
6–12 mo	8689.0/4521.9 (1265.8)	4252.4/2841.3 (754.7)	<0.001
12–60 mo	14408.0/9472.6 (2722.7)	9242.6/6316.6 (1955.6)	<0.001
30 d to 60 mo	23789.0/12519.5 (5488.1)	13091.0/8723.5 (2393.7)	<0.001
0–60 mo	52630.8/27461.6 (36011.4)	11649.6/7645.8 (2705.9)	<0.001

*Among the 912 IMD cases, all had 1–6 months of follow-up, 902 had 6–12 months of follow-up and 885 had 12–60 months of follow-up.

†IMD: n = 42, n = 43, n = 49, n = 50, n = 63 and n = 77 at 0–30 days, 1–6 months, 6–12 months, 12–60 months, 30 days to 60 months and 0–60 months, respectively; control: n = 426, n = 642, n = 756, n = 895, n = 952 and n = 955 at 0–30 days, 1–6 months, 6–12 months, 12–60 months, 30 days to 60 months and 0–60 months, respectively.

‡Assuming persons not included in ODB incurred no cost for medication claims.

§Assuming persons not included in ODB and those included incurred the same cost for medication claims.

¶Medical services include visits to the GP's office, visits to a specialist and all procedures/tests performed in an outpatient setting out of hospital.

IQR indicates interquartile range.

for the majority of the overall hospitalization cost. In Australia, the inpatient costs during the acute hospitalization period ranged between 12,311.5 Australian dollars (AU$) and AU$21,338.6 per patient in (2011 AUDAU$), [equivalent to $12,572.8–$21,791.4 (in 2011 $) Canadian dollar (CAD)].[16,17] The Australian data support our results when we consider that in Canada, the average length of hospital stay for IMD hospitalizations is 11.2 days[13] compared with the 7.2–9.6 days reported by Wang et al.[17] in Australia. In the United States, hospitalizations were estimated at 23,294 US dollars (US$) per patient (in 2003 USD US$), [equivalent to $32,624 (in 2003 CAD$)],[18] which is in line with what we report.

The mean overall cost per case during our study for the complete follow-up period was $45,768–$52,631 for IMD cases (median: between $20,593 and $27,462) compared with $5414–$11,650 for non-IMD controls (median: between $1135 and $7646). In line with our results, a simulation study done by Tu et al.[19] evaluating the economic impact of a potential meningococcal serogroup B childhood vaccination in Ontario, also showed a substantial cost burden associated with IMD; specifically, the total life-time cost for 23 IMD cases was estimated at $631,522 (in 2012 CAD$), corresponding to $27,457 per IMD case. Older studies from the province of Quebec have also shown costs of up to $22,953.75 (in 1993 CAD$) per IMD case from 1992 to 1993.[20]

The results of our study should be interpreted considering its retrospective design and use of administrative databases for data extraction. Possible data entry errors cannot be excluded; however, it could be argued that erroneous data entries are more likely random and therefore there is low probability of systematic or directional bias. Given the average age of the IMD cases (and the non-IMD controls) in our study and the fact that the ODB plan covers predominantly individuals over the age of 65 years it is likely that the estimated cost for medication use in IMD has been underestimated in our primary analysis which, however, we have tried to address in our least conservative sensitivity analysis. The burden of illness presented by IMD is manifested not only through increased use of hospital and medical services, and medications but also through revenue and productivity loss, professional and family caregiving, as well as the use of special education requirements and assistive devices which are not covered by the public health system, none of which were not considered in our study; this may have also contributed to the underestimation of the economic burden of IMD. Further measurements of these parameters as well as on patient quality of life in long-term prospective studies are required to provide a comprehensive evaluation of the impact of IMD.

CONCLUSIONS

In addition to its clinical burden on patients, IMD is associated with a significant burden to the public health system. These data can be used in health economic evaluations of IMD vaccines and the impact of implementing a national immunization program in Canada (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/D375).

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