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## Assessment of medication use during pregnancy by Web-based questionnaires, pharmacy records and serum screening

Marleen M.H.J. van Gelder<sup>a,b,\*</sup>, Lutea A.A. de Jong<sup>c</sup>, Bernke te Winkel<sup>d</sup>, Erik J.H. Olyslager<sup>c</sup>, Saskia Vorstenbosch<sup>d</sup>, Eugène P. van Puijenbroek<sup>d,e</sup>, André L.M. Verbeek<sup>a</sup>, Nel Roeleveld<sup>a</sup>

<sup>a</sup> Department for Health Evidence, Radboud Institute for Health Sciences, Radboud University Medical Center, P.O. Box 9101, 6500 HB, Nijmegen, the Netherlands

<sup>b</sup> Radboud REshape Innovation Center, Radboud University Medical Center, P.O. Box 9101, 6500 HB, Nijmegen, the Netherlands

<sup>c</sup> Department of Pharmacy, Gelre Hospitals, P.O. Box 9014, 7300 DS, Apeldoorn, the Netherlands

<sup>d</sup> Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH, 's-Hertogenbosch, the Netherlands

<sup>e</sup> Pharmacotherapy, -Epidemiology and -Economics, Groningen Research Institute of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen, the Netherlands

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### ABSTRACT

**Objective:** To compare assessment of early pregnancy medication exposure using three methods of data collection.

**Methods:** Serum samples were obtained from 752 women participating in the PRIDe and Infant DEvelopment (PRIDE) Study before gestational week 17. For 52 women using medication at the date of blood sampling according to Web-based questionnaires or pharmacy records, we analysed serum samples using untargeted liquid chromatography time-of-flight spectrometry.

**Results:** Medication was detected in 18 serum samples (35%). Medications taken orally for chronic conditions reported in the questionnaire were detected in serum and vice versa. Pharmacy records did not identify additional exposed women, but missed exposure in 5 women mainly due to unavailability. We observed substantial discordance between the three methods for inhaled medication, dermatological preparations, and medications for short-term use, which went often undetected in serum.

**Conclusions:** It remains challenging to assess medication use in large-scale studies as no 'gold standard' is currently available.

### 1. Introduction

Medication use is very common during pregnancy, with prevalence estimates generally exceeding 65% and increasing over the years [1–7]. Pregnant women use a wide variety of both prescription and over-the-counter (OTC) medication, for both pregnancy-related conditions (e.g., nausea/vomiting, gastric reflux, hypertensive disorders) and conditions unrelated to pregnancy (e.g., asthma, migraine, hay fever). Paradoxically, insufficient data are currently available to completely characterize the foetal risks of many medications commonly used during pregnancy [8–10], hampering an evidence-based risk-benefit analysis in clinical practice. Therefore, more research into the safety of

medication use during pregnancy is urgently needed.

Because of the ethical concerns of including pregnant women into randomized controlled trials, we have to depend on post-marketing epidemiologic studies to get more insight into the benefits and risks of medication use during pregnancy. One of the major challenges of these studies is valid exposure assessment: each method of data collection comes with specific advantages and limitations. Many studies use self-reported questionnaires or maternal interviews to assess medication use during pregnancy. Although both prescription and OTC medication use may be assessed, validation studies showed that medication use, particularly medication for short-term use, is underreported using these methods of data collection [11–18]. Alternatively, routinely collected

**Abbreviations:** CI, confidence interval; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-TOF-MS, liquid chromatography time-of-flight spectrometry; OTC, over-the-counter; PRIDE, PRIDe and Infant DEvelopment

\* Corresponding author at: Department for Health Evidence, Radboud Institute for Health Sciences, Radboud University Medical Center, P.O. Box 9101, 6500 HB, Nijmegen, the Netherlands.

**E-mail addresses:** [marleen.vangelder@radboudumc.nl](mailto:marleen.vangelder@radboudumc.nl) (M.M.H.J. van Gelder), [l.van.gendt@gelre.nl](mailto:l.van.gendt@gelre.nl) (L.A.A. de Jong), [b.tewinkel@lareb.nl](mailto:b.tewinkel@lareb.nl) (B. te Winkel), [e.ollyslager@gelre.nl](mailto:e.ollyslager@gelre.nl) (E.J.H. Olyslager), [s.vorstenbosch@lareb.nl](mailto:s.vorstenbosch@lareb.nl) (S. Vorstenbosch), [e.vanpujenbroek@lareb.nl](mailto:e.vanpujenbroek@lareb.nl) (E.P. van Puijenbroek), [andre.verbeek@radboudumc.nl](mailto:andre.verbeek@radboudumc.nl) (A.L.M. Verbeek), [nel.roeleveld@radboudumc.nl](mailto:nel.roeleveld@radboudumc.nl) (N. Roeleveld).

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data on medication dispensing, for example prescription databases and administrative claims databases, do not suffer from recall problems [19]. These data sources, however, do not contain information on actual medication intake (i.e. adherence) and exact timing of medication use, and often lack data on OTC medication and inpatient medication exposures, leading to overreporting as well as underreporting of medication use during pregnancy.

Biological monitoring or screening on medication may overcome the potential for exposure misclassification associated with using self-reported information or routinely collected data [20]. Due to the constraints related to this method of data collection, such as high costs, increased potential for selection bias, and ethical and logistical challenges, this approach has rarely been used to assess medication use during pregnancy. In the German ‘Lifestyle and Newborn Allergy Risk’ (LiNA) cohort study, untargeted liquid chromatography-tandem mass spectrometry (LC-MS/MS) screening of urine samples collected in gestational week 36 was used, detecting medication in 24% of the samples [21,22]. Wolgast et al. used liquid chromatography with time-of-flight mass spectrometry (LC-TOF-MS) to screen plasma samples of 200 pregnant women for medication use and compared the results to self-reported data in the Swedish Medical Birth Registry [23]. Medication use was detected by screening among 23% of women, of whom 86% also self-reported the medication use. Of note, untargeted LC-MS/MS and LC-TOF-MS analyses provide only information concerning a limited time period after intake depending on the half-life of the medication and do not cover all compounds.

As a gold standard for assessing medication use in epidemiologic studies is unavailable, the aim of this study was to compare assessment of medication exposure in early pregnancy using three methods of data collection: self-administered Web-based questionnaires, pharmacy records, and screening of serum samples using untargeted LC-TOF-MS.

## 2. Methods

### 2.1. Study design and population

This study was embedded in the PRIDe and Infant Development (PRIDE) Study, an ongoing prospective cohort study among pregnant women in The Netherlands [24]. In short, pregnant women were invited for participation by their midwife or gynaecologist just before or during the first prenatal care visit (usually gestational weeks 8–10). After providing informed consent, participants completed three Web-based questionnaires during pregnancy (at baseline and in gestational weeks 17 and 34) and two questionnaires after giving birth (2 and 6 months after the estimated date of delivery), followed by biannual questionnaires during childhood. Paper-based questionnaires were available upon request.

In addition, participants recruited by midwives from the Nijmegen region were asked to donate 4 non-fasting 4.5 ml blood samples for genetic and biochemical analyses, which were collected during the routine blood sampling procedure in early pregnancy (preferably before gestational week 13). From 3 blood samples, serum and plasma was separated and subdivided into 7 units (4 serum, 2 plasma, and 1 erythrocytes). The fourth sample is whole blood for DNA extraction. All blood samples were processed as shortly after blood draw as possible, but in any case within 12 h, and stored at  $-80^{\circ}\text{C}$  until laboratory analyses. For this study, we selected all PRIDE Study participants enrolled between July 2011 and September 2015 for whom blood samples were available ( $n = 752$ ).

### 2.2. Web-based questionnaire

We used data from the first Web-based questionnaire that was completed after the blood draw, which could be either the baseline questionnaire or the second questionnaire at gestational week 17. In both questionnaires, medication use was assessed using a

comprehensive indication-oriented structure as recommended in the literature [25,26]. When pharmacological treatment for an indication was reported, closed-ended questionnaires were administered to collect information on the generic and brand name, exact timing and frequency of use, and dose taken. In addition, we assessed whether medications were used for conditions not included in the extensive list of indications using open-ended questions. This questionnaire was recently validated, with sensitivity ranging between 0.55 and 0.96 for medication for chronic conditions, between 0.30 and 0.70 for medication for occasional and short-term use, and between 0.60 and 0.89 for pregnancy-related medication groups [18].

### 2.3. Pharmacy records

In the informed consent form, permission was asked to obtain pharmacy records, which contained information on the name and amount of the medications dispensed, daily dose, and intended time period of use. The latter was derived from the date of dispensing and registered stop date. In case the stop date was missing from the pharmacy records, it was calculated from the amount dispensed and daily dose. Pharmacy records were retrieved for the time period starting 1 year before pregnancy until 6 months after the estimated date of delivery. In The Netherlands, pharmacy records are virtually complete as all pharmacies use computerized dispensing records and almost everyone is registered with a single pharmacy [27]. However, when a PRIDE Study participant reported to be registered at multiple pharmacies, records were requested from all pharmacies listed.

### 2.4. Inclusion and exclusion criteria

We selected all participants who reported any prescription or OTC medication use on the date of blood sampling in the Web-based questionnaire and/or were supposedly exposed to medication on the date of blood sampling according to the pharmacy records. For many women, the time period of medication use was not limited to the exact date of blood sampling, but also included the days before sampling. Medication that was taken as needed or with a frequency less than once per day was excluded. Furthermore, we excluded women who were only exposed to medication that cannot be detected in serum, including levothyroxine, ferrous fumarate, urea-containing cream, and artificial tears. These substances are either endogenous or undetectable by the analytical method. Of note, the time of day of medication use is not captured in the Web-based questionnaire nor in pharmacy records.

### 2.5. Serum analysis

The serum samples were pre-treated by protein precipitation and subsequently analysed qualitatively by LC-QTOF-MS (Waters® Xevo G2-S Quadrupole Time-of-Flight Mass Spectrometer), a high-resolution technique based on the exact mass of the molecule [21–23]. The results were compared with an in-house database of 1194 compounds (Supplemental Table 1). As an internal control, a 4-component test mixture (paracetamol, caffeine, verapamil, sulfadimethoxine) was used and accepted based on a retention time deviation of  $\pm 0.4$  min and a mass tolerance of  $\pm 20$  mDa in positive mode and a retention time deviation of  $\pm 0.2$  min and a mass tolerance of  $\pm 50$  mDa in negative mode, respectively. The drugs were identified when there was a match based on the same acceptance criteria as described above, on at least one unique daughter fragment and a height of more than 1000 counts. All positive samples identified had a mass tolerance of less than 10 mDa both in positive and negative mode.

### 2.6. Statistical analysis

For the women included in this study, exposure status based on the three methods of data collection was first examined manually on the

level of the individual medications. In an exploratory analysis, Kappa statistics with 95% confidence intervals (CIs) were calculated to quantify agreement between the methods of data collection for different groups of medications with at least 5 exposed women, including any medication use, any oral medication, medications taken orally for chronic conditions, antihistamines, meclizine with or without pyridoxine, inhalation medication, asthma medication, and dermatological preparations. Statistical analyses were conducted using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY, USA).

### 2.7. Ethical approval

The PRIDE Study was approved by the Committee on Research involving Human Subjects region Arnhem-Nijmegen (CMO 2009/305). Participation was voluntarily and all participants provided informed consent.

### 3. Results

Of the 752 women for whom blood samples were available, 52 women (6.9%) potentially exposed to medications included in the in-house database at the date of blood sampling were included in this study: 19 with reported use of these medications on the date of blood sampling in the questionnaire only (2.5%), 15 with medication exposure according to pharmacy records only (2.0%), and 18 with positive reports in both data sources (2.4%). For 9 women included based on the questionnaire data, pharmacy records were not available, because they did not provide consent to obtain records ( $n = 2$ ) or reported an unknown pharmacy ( $n = 3$ ), or because the pharmacy did not return the information requested ( $n = 4$ ). The mean age of the women included was 30.5 years (SD 2.8), it was the first pregnancy for 24 women (46%), and the mean gestational age at blood sampling was 11 weeks (SD 2.1). For 25 women (48%), questionnaire information was obtained from the baseline questionnaire (mean difference between blood sampling and questionnaire administration 12 days [SD 17]); for the remaining 27 women, data were obtained from the second questionnaire completed around gestational week 17 (mean difference between blood sampling and questionnaire administration 39 days [SD 15]).

In total, we detected 9 different medications in 18 out of 52 samples (35%): meclizine ( $n = 7$ ), mesalazine ( $n = 3$ ), paracetamol ( $n = 2$ ), desloratadine, fexofenadine, paroxetine, prednisolone, sulfasalazine, and venlafaxine. For 16 exposures, medication use was also self-reported in the questionnaire ( $n = 12$  [75%]) and/or abstracted from pharmacy records ( $n = 11$  [69%]; Table 1). Medications taken orally for chronic conditions detected in the serum samples (i.e. fexofenadine, mesalazine, paroxetine, sulfasalazine, and venlafaxine;  $n = 7$ ) were also reported in the questionnaire, but use would have been missed using pharmacy records only for 5 of these medications, mostly due to unavailability of pharmacy records ( $n = 4$ ). All 7 women who tested positive for meclizine in the serum sample filled a prescription for meclizine or the combination of meclizine and pyridoxine, mostly used for pregnancy-related nausea. However, only 5 of these women (71%) reported use of meclizine or meclizine/pyridoxine in the questionnaire while 1 woman reported use of an unspecified medication for a gastrointestinal problem. In addition, for the 2 samples in which desloratadine, a metabolite of loratadine, or prednisolone were detected, use was not reported in the questionnaire whereas the pharmacy records indicated use. For both samples with paracetamol, no reports of use were obtained from the questionnaires or the pharmacy records.

In Table 2, medications are shown that were reported in the questionnaire and/or abstracted from pharmacy records but were not detected by the LC-TOF-MS analysis in the serum samples. Inhaled medications and dermatological preparations were reported relatively frequently in the questionnaire ( $n = 15$ ), in pharmacy records ( $n = 10$ ), or both ( $n = 11$ ), but were not detected in the serum samples at all. Furthermore, reported use of oral antihistamines (questionnaire:  $n = 6$ ;

**Table 1**

Medication use detected by LC-TOF-MS screening of serum samples of pregnant women and medication use according to Web-based questionnaires and pharmacy records.

Subject ID	Detected in serum	Questionnaire	Pharmacy record
25	Desloratadine <sup>a</sup>	Not reported	Loratadine
45	Fexofenadine	Fexofenadine	Fexofenadine
7	Meclizine	Not reported	Meclizine
20	Meclizine	Unspecified medication for GI problem	Meclizine/pyridoxine
27	Meclizine	Meclizine/pyridoxine	Meclizine/pyridoxine
44	Meclizine	Meclizine/pyridoxine	Meclizine/pyridoxine
46	Meclizine	Meclizine	Meclizine
50	Meclizine	Meclizine/pyridoxine	Meclizine/pyridoxine
52	Meclizine	Meclizine/pyridoxine	Meclizine/pyridoxine
32	Mesalazine	Mesalazine	Not available
34	Mesalazine	Mesalazine	Not available
36	Mesalazine	Mesalazine	Not available
11	Paracetamol <sup>b</sup>	Not reported	Not registered
51	Paracetamol <sup>b</sup>	Not reported	Not registered
3	Paroxetine	Paroxetine	Not registered
16	Prednisolone	Not reported	Prednisolone
35	Sulfasalazine	Sulfasalazine	Not available
49	Venlafaxine	Venlafaxine	Venlafaxine

<sup>a</sup> Metabolite of loratadine.

<sup>b</sup> Available over-the-counter.

pharmacy record:  $n = 10$ ; both:  $n = 3$ ) often went undetected in the serum samples. Other medication exposures that were not detected in the LC-TOF-MS analysis but were reported in the questionnaire included paracetamol ( $n = 2$ ), amoxicilline/clavulanic acid, omeprazole, and prednisone, whereas use of amoxicillin ( $n = 2$ ) was obtained from pharmacy records only. Supplemental Table 2 shows the medication exposure information from the three methods of data collection for all women included in this study.

The Kappa statistics for agreement between the pairs of methods of data collection for the different medication groups are shown in Table 3. The Kappa statistics ranged between 0.00 (inhalation medication or dermatological preparation for questionnaire or pharmacy record versus serum screening) and 0.91 (95% CI 0.74–1.00; medication taken orally for chronic conditions for questionnaire versus serum screening). For medications taken orally, including the subgroups, agreement between the questionnaire and serum screening seemed to be higher compared to the other combinations of data collection methods.

### 4. Discussion

In this exploratory study, screening of 52 serum samples through untargeted LC-TOF-MS detected medications in only 35% of pregnant women who used medication on the date of sampling according to a Web-based questionnaire and/or pharmacy records. All medications detected in the serum samples were reported in the questionnaire and/or abstracted from the pharmacy records, with the exception of 2 women for whom additional exposure to paracetamol was detected. Medications taken orally for chronic conditions reported in the questionnaire were also detected in the serum samples, whereas pharmacy records did not yield additional exposures for these medications, but missed several truly exposed women mainly due to unavailability. Pregnancy-related medications detected in the serum samples were in accordance with pharmacy records, but were not correctly reported by 2 women. We observed substantial discordance between the three modes of data collection for inhaled medication, dermatological preparations, and medications for short-term use, which could often not be

**Table 2**

Medication exposure according to the Web-based questionnaires and/or pharmacy records undetected by LC-TOF-MS screening of serum samples of pregnant women (n = 52).

Questionnaire and pharmacy record		Questionnaire only				Pharmacy record only	
		Pharmacy record available		Pharmacy record unavailable			
Medication	n	Medication	n	Medication	n	Medication	n
Beclometasone	4	Beclometasone	3	Budesonide	3	Fluticasone	4 <sup>b</sup>
Clemastine	2	Aciclovir <sup>a</sup>	2	Paracetamol <sup>a</sup>	2	Levocetirizine	3 <sup>c</sup>
Salbutamol	2	Cetirizine <sup>a</sup>	2	Xylometazoline <sup>a</sup>	2	Loratadine <sup>a</sup>	3
Budesonide	1	Levocetirizine	2	Beclometasone	1	Amoxicillin	2
Clobetasone	1	Amoxicillin/clavulanic acid	1			Beclometasone	2
Fluticasone	1	Budesonide	1			Meclizine	2
Formoterol	1	Clemastine	1			Mometasone	2
Loratadine <sup>a</sup>	1	Formoterol/beclometasone	1			Budesonide	1
Mometasone	1	Levocabastine	1			Desloratadine	1
		Loratadine <sup>a</sup>	1			Hydrocortisone	1
		Omeprazole <sup>a</sup>	1			Meclizine/pyridoxine	1
		Prednisone	1				
		Salbutamol	1				
		Triamcinolone/salicylic acid	1				
Total n	14	Total n	19	Total n	8	Total n	22

<sup>a</sup> Available over-the-counter.

<sup>b</sup> 1 woman reported use of an unspecified respiratory medication in the questionnaire.

<sup>c</sup> 1 woman reported use of an unspecified anti-allergy medication in the questionnaire.

detected in serum samples with LC-TOF-MS.

Although biological monitoring or screening is often held in high regard for exposure assessment in medical studies, untargeted LC-TOF-MS analysis of a single serum sample seemed to miss the majority of medication exposures among women in early pregnancy. This analytical method might not be sufficiently sensitive to detect medications with low serum concentrations, including inhalation medication and dermatological preparations. However, these types of medications were included in the compound library (Supplemental Table 1) and may be detected with mass spectrometry [28–30]. Medications with a short half-life, such as amoxicilline (1–1.5 h), paracetamol (2.7 h), salbutamol (4 h), and meclizine (6 h), may not be detected by LC-TOF-MS analysis when the time span between intake and blood sampling is too long. We did not record the moment medication was taken and the time of blood sampling, however. Other matrices, such as urine and maternal hair [31], provide a broader detection time window for monitoring medication use, but are currently not available in the PRIDE Study. Furthermore, overestimation of medication intake due to non-adherence (pharmacy records) or irregular use (pharmacy records and questionnaires) may explain some of the discrepancies between the methods of data collection.

The prevalence of medication use in our population (6.9%) may seem low compared to other studies on first trimester medication use (> 30%) [1–4,6,7]. For the current study, however, we only determined medication use on the exact day of blood sampling instead of

in the first 13 weeks of pregnancy. Due to differences in the selection of samples for biological screening and possibly in the analytical approach, the prevalence of medication use among women included in this study (35%) was higher compared to the other two settings in which screening among pregnant women was applied (23–24%) [21–23]. In these studies, analgesics were often detected, whereas in our study, paracetamol was detected in only 2 samples. Meclizine, which is used to treat nausea and vomiting of pregnancy, was the most common medication detected in our serum samples collected in early pregnancy. Differences in gestational week of sampling and country may explain these differences, particularly for the studies conducted in the German LiNA cohort, in which urine was collected in gestational week 36.

The major strength of using PRIDE Study data to compare methods of data collection for assessing medication use during pregnancy is the availability of a validated Web-based questionnaire [18]. Although this questionnaire is prone to some underreporting of medication use, particularly for medication for short-term use, the sensitivity is higher compared to paper-based questionnaires. Through this questionnaire, the exact dates of medication use were gathered, which was often impossible in previous studies using more traditional modes of data collection. Whereas other studies evaluated only two methods of data collection, we were able to compare three different methods simultaneously, although pharmacy records were not available for all women included. Other limitations of this study include the relatively small

**Table 3**

Agreement between the three methods of data collection for medication use in early pregnancy among women participating in the PRIDE Study (n = 52).

Medication group	Kappa statistic (95% CI)		
	Questionnaire versus pharmacy record	Questionnaire versus serum screening	Pharmacy record versus serum screening
Any medication	NA <sup>a</sup>	0.24 (0.05–0.43)	0.10 (–0.09–0.29)
Any medication taken orally	0.14 (–0.14–0.42)	0.45 (0.21–0.69)	0.37 (0.13–0.61)
For chronic conditions	NA <sup>b</sup>	0.91 (0.74–1.00)	NA <sup>b</sup>
Antihistamines	0.34 (0.09–0.59)	0.54 (0.27–0.81)	0.43 (0.21–0.65)
Meclizine ± pyridoxine	0.61 (0.32–0.90)	0.81 (0.56–1.00)	0.78 (0.54–1.00)
Any inhalation medication	0.31 (0.00–0.62)	0.00	0.00
Asthma medication	0.63 (0.24–1.00)	0.00	0.00
Any dermatological preparation	0.45 (0.00–0.90)	0.00	0.00

<sup>a</sup> Not applicable: cannot be calculated due to the inclusion and exclusion criteria.

<sup>b</sup> Not applicable: less than 5 exposed subjects due to unavailability of pharmacy records.

sample size and the inability to determine serum concentrations for all medications. The latter may provide more insight into the pharmacokinetic characteristics among pregnant women, as well as into foetal exposure. Due to financial constraints, we could not analyse all serum samples, but the inclusion criteria (i.e. medication use reported in the questionnaire and/or recorded in the pharmacy record for the date of blood sampling), may have biased the estimated agreement between the methods of data collection. The inability to include women who did not use medication at all led to underestimation of the Kappa statistics, whereas the inability to include women who did not report medication use and did not use medication according to the pharmacy records, but would have been tested positive in the serum screening, may have led to overestimation of the kappa statistic. However, if medication cannot be detected in women who are likely to be exposed (i.e. the population included in this study), it is questionable whether analysing all women would yield a substantial number of additional exposures.

The results of this study confirm that currently no 'gold standard' is available for assessing medication use during pregnancy. It remains challenging if not impossible to determine the true exposure status in case of conflicting sources of information. Screening with LC-TOF-MS analysis using a single serum sample seemed unable to detect use of particular medications compared to the more traditional methods of self-reported questionnaires and pharmacy records, which are both prone to over- and underreporting. Novel methods of data collection, such as mobile applications to daily record medication intake, may improve exposure assessment of medication use during pregnancy [32].

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.reprotox.2019.01.002>.

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