GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT:

Preventing the Preventable: Bridging Gaps in Breast Cancer Screening for Veteran Women

- Do Antiseizure Medication(s) Cause Autism?
- Does Acetaminophen Really Cause Neurodevelopmental Disorders in Children?
- TBI for TBI: Does a Team-Based Intervention Improve Pain for Traumatic Brain Injury?
- Cystatin C for Better Estimation of GFR in Older Patients

Preventing the Preventable: Bridging Gaps in Breast Cancer Screening for Veteran Women

Automated Opt-Out vs Opt-In Patient Outreach Strategies for Breast Cancer Screening: A Randomized Clinical Trial

Marcotte LM, Deeds S, Wheat C, et al. Automated Opt-Out vs Opt-In Patient Outreach Strategies for Breast Cancer Screening: A Randomized Clinical Trial [published correction appears in JAMA Intern Med. 2024 Feb 1;184(2):228. doi: 10.1001/jamainternmed.2023.7148.]. *JAMA Intern Med*. 2023;183(11):1187-1194. doi:10.1001/jamainternmed.2023.4321

KEY TAKEAWAY: An opt-out referral strategy for breast cancer screening does not improve mammography completion rates in female veterans.

STUDY DESIGN: Randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Breast cancer screening has saved many lives. Yet female veterans, a historically underserved population, have faced significant barriers to accessing this care. This study aimed to evaluate the efficacy of an opt-out referral strategy for mammography in closing this preventive gap.

PATIENTS: Female veterans 45–75 years old eligible for breast cancer screening

INTERVENTION: Automatic mammography referral (opt-out)

CONTROL: Automated telephone call with option for mammography (opt-in)

PRIMARY OUTCOME: Mammography completion within 100 days

Secondary Outcome: Mammography completion or scheduling within 100 days, canceled referrals within 90 days

METHODS (BRIEF DESCRIPTION):

- Female veterans enrolled in primary care at a single Veterans Affairs (VA) medical center eligible for breast cancer screening per American Cancer Society guidelines but overdue for mammography (no screening in the past 2 years, depending on age) were included in the study.
    - The mean patient age was 59 years old, and 74% had a history of prior breast cancer screening.
    - Exclusion criteria included bilateral mastectomy, enrollment in hospice, recent death, or recent mammography
- Study participants were randomized 1:1 to either an opt-out automatic referral or an opt-in automated telephone call.
    - Opt-out group: Each patient was enrolled in mammography screening unless they specifically declined. The patient had to opt out manually. Medical records were reviewed by registered nursing staff for eligibility, and the nursing staff placed referrals for each patient.
    - Opt-in group: Automated telephone messages provided patients with three options: Request mammograms, discuss screening with a primary care provider, or decline screening. Screenings required active acceptance. Referrals were placed only for those patients who chose to opt in.
- Both groups followed standard scheduling and coordination procedures post-referral, with referrals remaining active for 90 days.
- The primary outcome measured the completion of mammography within 100 days, determined by electronic health record (EHR) data.
- The secondary outcomes assessed the number of participants who scheduled or completed mammography within 100 days and the number of canceled referrals within 90 days.
- Outcomes were binary (yes/no) and analyzed using intention-to-treat analysis. Statistics were adjusted for age, race, ethnicity, and prior screening history.

INTERVENTION (# IN THE GROUP): 441

COMPARISON (# IN THE GROUP): 442

FOLLOW-UP PERIOD: 100 days

RESULTS:

Primary Outcome –

- An opt-out automatic referral did not improve mammography completion compared to an opt-in automated telephone call (odds ratio [OR] 1.01; 95% CI, 0.69–1.5).

Secondary Outcome –

- An opt-out automatic referral did not improve mammography completion or scheduling compared to an opt-in automated telephone call.
- An opt-out automatic referral resulted in more canceled referrals within 90 days compared to an opt-in automated telephone call (24% vs 5.4%, respectively; *P*<.01).

LIMITATIONS:

- The study lacked adequate nursing staff to review records for veterans in the opt-in group who declined screening, potentially leading to a disproportionate exclusion of opt-out veterans.
- Veterans in the opt-out group did not receive prior messaging, which may have reduced engagement, as similar studies show increased participation with pre-notification.
- The opt-out strategy required extensive staff for medical record reviews and patient outreach, making it unsustainable in resource-limited settings.
- The absence of on-site mammography required external scheduling, adding logistical challenges that may have diminished the impact of the opt-out approach.
- The study was conducted at a single VA medical center with 883 patients, limiting its applicability to the broader female veteran population.

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Do Antiseizure Medication(s) Cause Autism?

Risk of Autism After Prenatal Topiramate, Valproate, or Lamotrigine Exposure

Hernández-Díaz S, Straub L, Bateman BT, et al. Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure. *N Engl J Med*. 2024;390(12):1069-1079. doi:10.1056/NEJMoa2309359

KEY TAKEAWAY: Prenatal exposure to valproate increases the risk for autism spectrum disorder (ASD). However, topiramate and lamotrigine do not after adjusting for confounders.

STUDY DESIGN: Retrospective, population-based cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Maternal use of valproate during pregnancy has been strongly linked to an increased risk of neurodevelopmental disorders, including ASD, while other antiseizure medications, such as lamotrigine, have not shown similar risks. However, data on the neurodevelopmental effects of prenatal topiramate exposure are limited and conflicting, with some studies suggesting an increased ASD risk. Given the growing use of topiramate for epilepsy, migraine, bipolar disorder, and weight management, understanding its potential impact on fetal brain development is crucial. This study aimed to investigate the association between prenatal topiramate exposure and the risk of ASD in children, using valproate as a positive control and lamotrigine as a negative control.

PATIENTS: Pregnant women and their children

INTERVENTION: Prenatal exposure to antiseizure medications

CONTROL: No exposure to prenatal antiseizure medication

PRIMARY OUTCOME: Clinical diagnoses of ASD

METHODS (BRIEF DESCRIPTION):

- Pregnant women and liveborn children from Medicaid Analytic eXtract-Transformed Medicaid Statistical Information System Analytic Files and Merative MarketScan Commercial Claims and Encounter Database from 2000 through 2020 were included in the study.
- The study was comprised of pregnant women with epilepsy who were 12–55 years old.
- The primary exposure group included pregnant women (gestation week 19 to delivery) with one dispensing for topiramate, valproate (positive control), and lamotrigine (negative control).
- Pregnant women without any prescription for antiseizure medications from 90 days before the last menstrual period through delivery acted as the unexposed (control) group.
- Subgroups were based on high or low doses of the medications to evaluate dose response.
    - A low daily dose was defined as <200 mg/day for topiramate, <1,000 mg/day for valproate, and <300 mg/day for lamotrigine.
- Early pregnancy exposure was defined as before 19 weeks' gestation, and late pregnancy exposure was defined as after 19 weeks.
- The primary outcome, ASD diagnosis, was made through the utilization of a validated claims-based algorithm requiring at least two visit claims with ASD diagnosis at or after one year.
- The propensity score weighting was used to adjust for measured baseline confounders for each medication compared to the control group.

INTERVENTION (# IN THE GROUP):

- Topiramate: 1,030
- Valproate: 800
- Lamotrigine: 4,205

COMPARISON (# IN THE GROUP): 8,815

FOLLOW-UP PERIOD: Eight years

RESULTS:

Primary Outcome –

- The use of prenatal valproate increased the risk of developing ASD in children after eight years (HR 2.7; 95% CI, 1.7–4.2).
- The use of prenatal topiramate did not increase the risk of developing ASD in children after eight years (hazard ratio [HR] 0.96; 95% CI, 0.56–1.7).
- The use of prenatal lamotrigine did not increase the risk of ASD in children after eight years (HR 1.0; 95% CI, 0.69–1.5).

LIMITATIONS:

- The study relied on claims-based data to define medication exposure, which may not accurately

reflect whether patients took the prescribed medications.

- There was a significant loss to follow-up after eight years, which could impact the generalizability of the findings.
- The use of diagnostic codes for ASD may have introduced misclassification, although the algorithm used had a high positive predictive value.
- Other confounding factors include maternal epilepsy type, maternal IQ, or detailed seizure frequency, which were not accounted for in the analyses.
- The study did not include long-term neurodevelopmental outcomes beyond ASD.

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Does Acetaminophen Really Cause Neurodevelopmental Disorders in Children?

Acetaminophen Use During Pregnancy and Children's Risk of Autism, ADHD, and Intellectual Disability

Ahlqvist VH, Sjöqvist H, Dalman C, et al. Acetaminophen Use During Pregnancy and Children's Risk of Autism, ADHD, and Intellectual Disability. *JAMA*. 2024;331(14):1205-1214. doi:10.1001/jama.2024.3172

KEY TAKEAWAY: Prenatal exposure to acetaminophen is associated with a slightly increased risk of autism and attention-deficit hyperactivity disorder (ADHD), however, this association is not observed when the outcome is controlled for sibling comparison. Acetaminophen exposure does not increase the risk of developing an intellectual disability.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Acetaminophen is one of the most used medications in the primary care setting, as it often bypasses many of the side effects of nonsteroidal anti-inflammatory drugs, is cost-effective, can be found over the counter, and does not lead to dependency. While this medication is generally considered safe, a 2021 consensus statement in *Nature Reviews Endocrinology* recently reported that the children who were exposed to acetaminophen in utero carry an increased risk of developing autism, ADHD, or other developmental disorders. The studies included were either limited in power or had other confounding factors that led them to this conclusion. As acetaminophen is considered a first-line treatment for many conditions in pregnancy, a study considering confounding factors, and a large sample size is necessary for optimizing the care of the pregnant population.

PATIENTS: Swedish children

INTERVENTION: Acetaminophen use in mothers during the prenatal period

CONTROL: Mothers who did not use acetaminophen during the prenatal period and sibling control

PRIMARY OUTCOME: Neurodevelopmental conditions

METHODS (BRIEF DESCRIPTION):

- All live-born children born from July 1, 1995, to December 31, 2019, in Sweden were examined.
- Patients were excluded if there was any missing information relating to missing maternal demographics, region, or income.
- Children were divided based upon exposure to acetaminophen while in the womb via a Medical Birth Register and Prescribed Drug Register Data.
- Children were further categorized if they had ADHD, autism, or other developmental delays (based on International Classification of Disease [ICD] codes in their charts).
- The primary outcome measured neurodevelopmental conditions such as autism, ADHD, or any intellectual disability, which were identified using the ICD codes from the National Patient Register and the Prescribed Drug Register to identify the dispersion of ADHD medication.
- Covariates and sibling analysis were also examined to account for genetic and environmental confounding variables.
- Statistical analysis via Cox proportional hazard models was finally used to approximate the risk of developing a neurodevelopmental condition.

INTERVENTION (# IN THE GROUP): 185,909

COMPARISON (# IN THE GROUP): 2,294,888

FOLLOW-UP PERIOD: Median 13 years

RESULTS:

Primary Outcome –

- Acetaminophen exposure in children during the prenatal period resulted in a slightly increased risk of developing autism and ADHD compared to children not exposed:
  - Autism (hazard ratio [HR] 1.1; 95% CI, 1.02–1.1)
  - ADHD (HR 1.1; 95% CI, 1.05–1.1)
- Acetaminophen exposure in children during the prenatal period did not result in an increased risk of developing an intellectual disability compared to children not exposed (HR 1.1; 95% CI, 1.0–1.1)
- There was no increased risk in children exposed to acetaminophen compared to those not exposed when controlled for siblings:
  - Autism (HR 0.98; 95% CI, 0.93–1.0)
  - ADHD (HR 0.98; 95% CI, 0.94–1.0)
  - Intellectual disability (HR 1.0; 95% CI, 0.92–1.1)

Secondary Analysis –

- There was no dose-related response pattern seen with increasing dose of acetaminophen when sibling-controlled in the diagnoses of autism, ADHD, and intellectual disability compared to placebo.

LIMITATIONS:

- Exposure assessment has imperfections (difficulty in identifying over-the-counter use of acetaminophen)
- The median age of diagnosis of neurodevelopmental disorders was older than that of prior studies.
- Lower rates of acetaminophen are used in birthing parents compared to other studies.
- Self-reporting of acetaminophen use may be subject to under-reporting.
- May be difficult to generalize as all children were from Sweden.

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TBI for TBI: Does a Team-Based Intervention Improve Pain for Traumatic Brain Injury?

Collaborative Care for Chronic Pain After Traumatic Brain Injury: A Randomized Clinical Trial

Hoffman JM, Curran M, Barber J, Lucas S, Fann JR, Zumsteg JM. Collaborative Care for Chronic Pain After Traumatic Brain Injury: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(6):e2413459. Published 2024 Jun 3. doi:10.1001/jamanetworkopen.2024.13459

KEY TAKEAWAY: In patients with chronic pain after a diagnosed traumatic brain injury (TBI), an initial 12 weeks of treatment using the collaborative care (CC) framework significantly improves pain interference over four months, with persistent effects after eight months, compared to usual care (UC).

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to incomplete blinding and small sample size)

BRIEF BACKGROUND INFORMATION: Chronic pain after a TBI affects a significant proportion of TBI patients, is often multimodal, and can be debilitating. Treatment can be effective, but factors intrinsic and extrinsic to TBI can interfere with receiving care. CC is a multi-focused approach initially developed to coordinate physical and behavioral health care through the integration of care managers and behavioral health care providers.

PATIENTS: Adults with TBI

INTERVENTION: CC

CONTROL: UC

PRIMARY OUTCOME: Pain interference

Secondary Outcome: Pain intensity, anxiety, depression, sleep

METHODS (BRIEF DESCRIPTION):

- In this randomized controlled trial with blinded outcomes assessors, patients with TBI ≥18 years old were recruited from two academic hospital-based rehabilitation clinics in Seattle.
- Patients had a mean age of 47 years, most were female (58%), identified as White (79%), and had mild TBI severity (65%).
- Participants were those who were seen by a TBI clinician in the past 12 months and had pain rated ≥4 on a 0–10 scale for at least six months.
- Patients were excluded for diagnoses of bipolar disorder with psychotic features, terminal illness, anticipated major surgery, or cognitive impairment by the Six-Item Screener.
- Patients were assigned by an unblinded researcher via computer algorithm to CC or UC.
- The CC arm had a care manager (CM) who reached out to the patients to initiate the intervention, including cognitive behavioral treatment, care coordination, and support in collaborative care.
    - A maximum of 12 sessions over 16 weeks were held in person (or via telephone or video during the COVID-19 pandemic), covering flexible tailored modules of education and home self-management practice skills.
    - Workbooks and relaxation recordings were provided.
    - The care manager consulted weekly with a team of TBI specialists to discuss patients further.
- The UC arm was provided with standard resources for TBI care.
- Baseline pain experience and TBI severity were collected after randomization by blinded researchers for both arms of the study.
- All outcome assessments were conducted by blinded researchers at baseline, four months, and eight months via structured telephone interviews.
- The primary outcome measured pain interference.
    - At every visit with the CM, pain severity and interference in daily life were assessed by a blinded researcher using the Pain Interference Scale (PIS) of the Brief Pain Inventory (BPI). Scores range from 0–10, with higher scores indicating greater interference.
- The following were measured as the secondary outcomes:
    - Sleep was assessed using the Pittsburgh Sleep Quality Index. Scores range from 0–21, with higher scores indicating worse sleep.
    - Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9). Scores range from 0–27, with higher scores indicating more severe depression

    - Anxiety was assessed using the Generalized Anxiety Disorder-7 (GAD-7). Scores range from 0–21, with higher scores indicating more severe anxiety.
    - At four months and eight months post-treatment, pain intensity was measured using the Brief Pain Intensity-4 subscale from the BPI, which assesses current, worse, average, and least pain levels over the past seven days. Scores range from 0–10, with higher scores indicating worse pain.
- A medium effect size of 0.5 (Cohen *d*=.50) was considered significant.

INTERVENTION (# IN THE GROUP): 79

COMPARISON (# IN THE GROUP): 79

FOLLOW-UP PERIOD: Eight months

RESULTS:

Primary Outcome –

- At four months, CC improved pain interference compared to UC (mean score 3.5 vs 5.0, respectively; effect size –1.3; 95% CI, −1.9 to −0.59).

Secondary Outcome –

- At four months, CC improved the following compared to UC:
    - Pain severity (3.6 vs 4.9, respectively; effect size –0.85; 95% CI, −1.3 to −0.37)
    - Depressive symptoms (8.1 vs 11, respectively; effect size –1.9; 95% CI, −3.7 to −0.14)
    - Anxiety symptoms (6.2 vs 9.6, respectively; effect size –1.8; 95% CI, −3.7 to −0.14)
- At eight months, CC improvement persisted compared to UC for the following:
    - Pain interference (3.6 vs 4.7, respectively; effect size –0.71; 95% CI, −1.4 to −0.03)
    - Depressive symptoms (7.7 vs 11, respectively; effect size –1.7; 95% CI, –3.5 to –0.02)

LIMITATIONS:

- The study participants and care managers administering the treatment were unable to be blinded, which may have introduced performance bias.
- Collaborative care is a combination of different interventions, so it is unclear which aspect of the intervention most influenced the outcomes.
- The impact of in-person vs virtual sessions conducted due to the COVID-19 pandemic is not known.
- Generalizability is limited by:
    - The majority of patients were female, identified as White, and had completed secondary education.
    - Most subjects had mild TBI.
    - All patients were recruited from a specialty clinic population.

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Cystatin C for Better Estimation of GFR in Older Patients

Association of Low Glomerular Filtration Rate with Adverse Outcomes at Older Age in a Large Population with Routinely Measured Cystatin C

Fu EL, Carrero JJ, Sang Y, et al. Association of Low Glomerular Filtration Rate With Adverse Outcomes at Older Age in a Large Population With Routinely Measured Cystatin C. *Ann Intern Med*. 2024;177(3):269-279. doi:10.7326/M23-1138

KEY TAKEAWAY: The use of both serum cystatin C level and serum creatinine level in calculation of estimated glomerular filtration rate (eGFR) appears to lead to more accurate eGFR for older persons, compared to the eGFR based on the serum creatinine level alone.

STUDY DESIGN: Population-based cohort

LEVEL OF EVIDENCE: STEP 4 (downgraded due to extensive limitations of the study)

BRIEF BACKGROUND INFORMATION: Chronic kidney disease (CKD) is associated with higher adverse outcomes. This association is weaker in older persons, as older persons may have less muscle mass, which may lead to overestimation of their GFR. In contrast to the serum creatinine, cystatin C is minimally affected by muscle mass. This study compared the risks associated with estimated GFR based on serum creatinine level vs estimated GFR based on serum creatinine level and serum cystatin C level.

PATIENTS: Older adults

INTERVENTION: eGFRcr-cys

CONTROL: eGFRcr

PRIMARY OUTCOME: All-cause mortality, cardiovascular mortality, kidney failure with replacement therapy (KFRT), heart failure, acute kidney injury (AKI), all-cause hospitalizations, myocardial infarction (MI) or stroke, and hospitalization with infection

METHODS (BRIEF DESCRIPTION):

- 82,154 patients ≥65 years old in Stockholm, Sweden, from 2010–2019, who had routine outpatient serum creatinine and serum cystatin C levels drawn on the same day were included in the study.
- Individuals with a history of kidney failure with replacement therapy were excluded from the study.
- With the Chronic Kidney Epidemiology Collaboration (CKD-EPI) 2021 equations, the participants' estimated GFR was measured, using serum creatinine levels only (eGFRcr); and by using the combination of the serum creatinine levels and serum cystatin C levels (eGFRcr-cys).
- Patients were followed from their first concurrent creatinine and cystatin C after 65 years old through either 2019 or an outcome of death, whichever occurred first.
- The primary outcomes measured all-cause mortality, cardiovascular mortality, KFRT, all-cause hospitalization, hospitalization with infection, MI or stroke, heart failure, or AKI via national registries and patient medical records.

INTERVENTION (# IN THE GROUP): 82,154

COMPARISON (# IN THE GROUP): The same 82,154 patients

FOLLOW-UP PERIOD: Median 3.9 years

RESULTS:

Primary Outcome –

- eGFRcr-cys and eGFRcys were more associated with the primary outcomes than eGFRcr (results presented via figure).
- Compared to healthy patients (GFR 80 mL/min/1.73 m^2), patients with CKD assessed through eGFRcr-cys were associated with an increased risk of:
  - All-cause mortality (adjusted hazard ratio [aHR] 1.2; 95% CI, 1.1–1.3)
  - Cardiovascular mortality (aHR 1.3; 95% CI, 1.2–1.4)
  - KFRT (aHR 2.6; 95% CI, 1.2–5.8)
  - Infections (aHR 1.3; 95% CI, 1.2–1.4)
  - MI/stroke (aHR 1.2; 95% CI, 1.1–1.4)
  - Heart failure (aHR 1.5; 95% CI, 1.4–1.7)
  - AKI (aHR 2.3; 95% CI, 2.0–2.6)
- Compared to healthy patients (GFR 80 mL/min/1.73 m^2), patients with CKD assessed through eGFRcr-cys were not at an increased risk of hospitalization (aHR 1.1; 95% CI, 1.0–1.1).
- Compared to healthy patients (GFR 80 mL/min/1.73 m^2), patients with CKD assessed through eGFRcys were associated with an increased risk of:
  - All-cause mortality (aHR 1.3; 95% CI, 1.2–1.4)

- Cardiovascular mortality (aHR 1.4; 95% CI, 1.2–1.6)
- Hospitalization (aHR 1.1; 95% CI, 1.1–1.2)
- Infections (aHR 1.4; 95% CI, 1.3–1.5)
- MI/stroke (aHR 1.2; 95% CI, 1.1–1.4)
- Heart failure (aHR 1.7; 95% CI, 1.6–1.9)
- AKI (aHR 2.3; 95% CI, 1.9–2.7)

- Compared to healthy patients (GFR 80 mL/min/1.73 m^2), patients with CKD assessed through eGFRcys were not at an increased risk of KFRT (aHR 1.5; 95% CI, 0.6–3.9)
- Compared to healthy patients (GFR 80 mL/min/1.73 m^2), patients with CKD assessed through eGFRcr were associated with an increased risk of:
  - Heart failure (aHR 1.2; 95% CI, 1.1–1.4)
  - AKI (aHR 1.6; 95% CI, 1.4–1.9)
- Compared to healthy patients (GFR 80 mL/min/1.73 m^2), patients with CKD assessed through eGFRcr were not associated with an increased risk of:
  - All-cause mortality (aHR 1.0; 95% CI, 0.9–1.0)
  - Cardiovascular mortality (aHR 1.0; 95% CI, 0.9–1.1)
  - KFRT (aHR 1.4; 95% CI, 0.7–2.8)
  - Hospitalization (aHR 1.0; 95% CI, 1.0–1.1)
  - Infections (aHR 1.1; 95% CI, 1.0–1.1)
  - MI/stroke (aHR 1.1; 95% CI, 0.9–1.2)

LIMITATIONS:

- The study did not measure GFR.
- The study data were not adjusted for all non-GFR determinants that may influence creatinine and cystatin C levels (muscle mass, inflammation, smoking, body mass index or obesity status, and diet).
- The study data did not include race.
- The outcomes were based on diagnosis codes, which have low sensitivity and high specificity.
- The measurement of eGFRcr-cys may have affected the subsequent treatment course.
- Higher prevalence of diabetes and cardiovascular disease; and older age were noted in this study population, compared to the rest of the population who did not have the same-day serum creatinine and serum cystatin C level.

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