Diagnosis and treatment of an acute reaction to a radiologic contrast agent

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INTRODUCTION

Contrast administration for imaging is associated with a low rate of adverse reactions. Most are mild and self-limited. However, a small proportion of reactions do require treatment and, if left untreated, could prove life-threatening.

The approach to the evaluation and management of a patient with an acute contrast reaction is described here and is based primarily on the evidence from iodinated contrast, used for computed tomography (CT) and angiography, and gadolinium-based contrast, used for magnetic resonance imaging (MRI). Management of an adverse reaction to gas-filled microbubble contrast agents used in ultrasound is similar, although these reactions are very uncommon and, as yet, not as well understood. (See "Contrast echocardiography: Contrast agents, safety, and imaging technique", section on 'Safety' and "Contrast-enhanced ultrasound for the evaluation of liver lesions", section on 'Safety'.)

Appropriate measures to **prevent** recurrent contrast reaction to iodinated or gadolinium-based contrast, contrast-induced nephropathy, or nephrogenic systemic fibrosis as well as the evaluation of patients with a history of a contrast reaction in the nonurgent setting are discussed separately in:

- (See "Patient evaluation prior to oral or iodinated intravenous contrast for computed tomography".)
- (See "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging".)
- (See "Prevention of contrast-associated acute kidney injury related to angiography".)
- (See "Allergy evaluation of immediate hypersensitivity reactions to radiocontrast media".)

EPIDEMIOLOGY

Intravascular contrast agents used for computed tomography (CT) are iodinated and are distinct from those used in magnetic resonance imaging (MRI), which are gadolinium-based. Hence, they do not demonstrate crossreactivity and a past reaction to one type (ie, iodinated or gadolinium-based) does not preclude future use of the other [1].

The frequency of acute adverse reactions to contrast varies with the contrast type (ie, iodinated versus gadolinium-based) and its molecular properties (eg, ionicity, osmolality, ligand structure) [1-7]. Contrast reactions have been observed with intra-arterial, intravenous (IV), enteral, and intraperitoneal administration. However, the vast majority of acute reactions are from intravascular administrations, which remain the basis for our understanding and approach to contrast reaction diagnosis and treatment. Cardiac adverse events are much more common during angiocardiography than intravenous contrast administration [1].

Incidence rates

Iodinated contrast — Iodinated contrast is given for CT and in fluoroscopic interventions such as angiography. A list of iodinated contrast agents on the market and their molecular properties can be found in Appendix A of the American College of Radiology Manual on Contrast Media [1].

The rate of acute adverse reactions from nonionic low- or iso-osmolar iodinated contrast is approximately 0.15 to 0.7 percent with >98 percent being mild and self-limited [8-11]. Fatality from iodinated contrast has been estimated at 2 to 9 per one million administrations [4,12].

The safety profile of the nonionic low- or iso-osmolar contrast currently in use is much better than the ionic high-osmolar agents of the past; consequently, the latter are no longer in use.

Gadolinium-based contrast — Gadolinium-based contrast agents (GBCAs) are classified according to ionicity (ionic or nonionic) and the chelating ligand (macrocyclic or linear). A list of GBCAs on the market and their molecular properties can be found in Appendix A of the American College of Radiology Manual on Contrast Media [1].

Rates of acute reactions to specific GBCAs range from 0.02 to 0.09 percent with >96 percent being mild and self-limited [13-17]. Severe, life-threatening reactions to GBCA, while extremely rare, have been reported [18]. Nonionic agents with a linear chelate are associated with 5- to 10-fold lower acute reaction rates than those that are ionic or with a macrocyclic chelate [17].

SIGNS AND SYMPTOMS

Acute reactions to contrast usually occur within 20 minutes of exposure but are generally defined as those occurring within an hour. They are classified as allergic-like or physiologic based upon the clinical presentation (table 1). Most life-threatening reactions occur within 20 minutes of contrast injection [1].

Allergic-like versus physiologic reaction — Allergic-like reactions are idiosyncratic, not related to dose, may occur in patients without prior exposure to the contrast agent, and do not predictably recur after each antigen exposure. The major risk factor is a history of a previous severe reaction to the same type of contrast agent [10,17,19].

Physiologic reactions are dose and concentration dependent and likely related to direct chemotoxicity, osmotoxicity, or binding of endogenous molecules [2,20,21]. Consequently, physiologic reactions are seen more often in angiography than with diagnostic imaging as the former are associated with higher doses of contrast and usually involve arterial administration directed at end organs.

Allergic-like reactions are characterized by [1]:

- Urticaria or pruritus
- Erythema
- Sneezing, conjunctivitis or rhinorrhea, or facial edema
- Hoarseness or stridor, with or without hypoxia (ie, upper airway compromise)
- Repetitive cough, wheezing, or chest tightness, with or without hypoxia (ie, bronchospasm)
- Anaphylactoid shock (ie, hypotension and tachycardia)

Physiologic reactions are characterized by [1]:

- Transient warmth (flushing) or chills
- Nausea or vomiting
- Hypertension
- Chest pain
- Pulmonary edema
- Arrhythmia
- Seizure
- Vasovagal reaction (ie, hypotension and bradycardia)

Reactions with mixed features — Reactions with both allergic-like and physiologic features or those where the categorization is ambiguous should be classified and treated as allergic-like. For example, cardiopulmonary arrest is a nonspecific result of either a severe allergic-like or physiologic reaction.

EVALUATION AND DIAGNOSIS

Onset of new symptoms following contrast administration should be presumptively evaluated and managed as a contrast reaction. However, definitive diagnosis does require that a complete history be obtained following the acute event to verify that the signs and symptoms were indeed new and temporally associated with exposure to contrast. (See "Allergy evaluation of immediate hypersensitivity reactions to radiocontrast media".)

Approach to the patient — A patient with a suspected contrast reaction should be

immediately evaluated because some reactions require urgent treatment.

The diagnostic assessment to classify a contrast reaction includes:

- Determination of responsiveness – Is the patient conscious? If not, resuscitation should be initiated. (See 'Unresponsive patient' below.)
- Assessment of signs or symptoms in patients who are responsive and verbal – The patient should be asked about symptoms associated with contrast reactions, which may include pruritus, nasal congestion, chest pain, palpitations, lightheadedness, and nausea or vomiting.
- Assessment of verbalization and phonation – Can the patient speak and, if so, is their voice normal? If not, this may be evidence of laryngeal or upper airway edema.
- Vital signs – The patient's heart and respiratory rate, blood pressure, and oxygen saturation should be measured. Continuous monitoring is initiated if any vital signs are abnormal.
- Skin examination of the face, torso, and extremities – The presence of urticaria, erythema, or edema indicate an allergic-like reaction.
- Chest auscultation – Patients with acute contrast reactions may develop bronchospasm or pulmonary edema. Bronchospasm may present as wheezing or repetitive dry cough.

Assessing severity — The American College of Radiology manual on contrast media describes signs/symptoms that are commonly seen in different severities of allergic-like and physiologic reactions [1]. In general terms, reaction severity is classified as:

- Mild – Reaction is self–limited, does not progress, and rarely requires treatment.
- Moderate – Reaction usually requires treatment and may progress to a severe reaction if untreated.
- Severe – Reaction is life-threatening and can cause significant morbidity.

Mild allergic-like — Mild reactions are usually self-limited [1]. Symptoms include one or

more of the following:

- Limited pruritus or urticaria, localized edema of the skin
- Limited itchy/scratchy throat
- Nasal congestion/rhinorrhea/sneezing, and/or conjunctivitis

Moderate/severe allergic-like — For allergic-type reactions, assessing the severity of the reaction is critical, as severe reactions should be treated with immediate epinephrine. Moderate reactions should be treated because they can progress to severe reactions, although epinephrine is not needed in all cases. Signs and symptoms include one or more of the following [1]:

- Widespread pruritus or urticaria, or diffuse skin erythema
- Facial edema (moderate - without dyspnea, severe - with dyspnea)
- Throat tightness or hoarseness (moderate - without dyspnea, severe - with dyspnea)
- Wheezing/bronchospasm/cough (moderate - minor or no hypoxia, severe - with hypoxia)
- Anaphylactic shock (hypotension plus tachycardia) in severe reactions

Mild physiologic — Signs/symptoms include one or more of the following:

- Transient flushing/warmth/chills
- Limited nausea/vomiting
- Headache/dizziness/anxiety
- Altered taste
- Mild hypertension
- Vasovagal reaction that resolves without treatment

Moderate/severe physiologic — Signs/symptoms include one or more of the following:

- Protracted nausea/vomiting
- Vasovagal reaction with symptoms (eg, hypotension with bradycardia, cyanosis, or altered mental status) (moderate - requires and responds to treatment, severe – refractory to treatment)
- Isolated chest pain or angina (moderate)
- Arrhythmia (severe)

- Convulsions, seizures (severe)
- Severe hypertension with symptoms of end organ injury (eg, encephalopathy, renal ischemia)

Examples of other rare but severe physiologic reactions include depressed myocardial contractility and cardiogenic pulmonary edema [1].

TREATMENT

Acute onset of symptoms that immediately follow contrast administration should presumptively be treated as a contrast reaction, unless there is an obvious alternative explanation. Contrast administration, if it is ongoing, should be immediately stopped. The appropriate treatment of a suspected contrast reaction is determined by the patient's signs and symptoms. Treatment is based upon type of reaction and severity.

Unresponsive patient — An unresponsive patient should be resuscitated according to advanced cardiac life support (ACLS) or pediatric advanced life support (PALS). (See "Advanced cardiac life support (ACLS) in adults" and "Pediatric advanced life support (PALS)".)

Once the ACLS or PALS pathways have been initiated, the patient should also be evaluated and treated for a presumed severe contrast reaction (see 'Moderate or severe reactions' below). Cardiopulmonary arrest can be a nonspecific result of either a severe allergic-like or physiologic reaction. If classification is unclear, an allergic-like reaction should be assumed.

Moderate or severe reactions — Moderate and severe reactions require immediate initiation of therapy. Following initiation of therapy, these patients should be triaged to the emergency department or to a specialized inpatient bed for continuous monitoring.

First steps for all moderate or severe contrast reactions are as follows:

- Call for help. This would involve calling emergency responders in the outpatient setting and the code team in the emergency department or hospital.
- Initiate oxygen 6 to 10 L/min by face mask. Oxygen flow should be titrated to the patient's hypoxia.

- Intravenous (IV) access should be obtained if it is not already in place.
- A continuous timed log of all interventions should be documented. This should include patient's vital signs, interventions, medications given, dose, and routs of administration.

Allergic-like — Treatment is equivalent to that for a classic anaphylactic reaction (see "Anaphylaxis: Emergency treatment"). The tables provide rapid overviews of the initial assessment and emergency management of anaphylaxis in adults (table 2) and in children (table 3).

Epinephrine administration — Epinephrine is given to patients with an allergic-like contrast reaction with symptoms affecting multiple organ systems (eg, airway compromise [repetitive cough, wheezing, hoarseness] plus cutaneous symptoms [urticaria]) or with anaphylactic shock (ie, hypotension with tachycardia). **There are no absolute contraindications to epinephrine in such settings.**

The dosing of epinephrine is different for intramuscular (IM) and IV administration, and the proper concentration for IV administration is 10-fold less than that of IM administration. Thus, it is critical to use the proper preparation.

Intramuscular (preferred) — Use of autoinjectors and IM administration avoids common dosing errors and is preferred over IV dosing because IM dosing is associated with fewer dosing errors and cardiovascular complications [22,23]. IM administration can be repeated in 5 to 15 minutes, and sooner if needed.

- In adults and adolescents weighing >25 kg, the dose 0.3 mg IM is given using an autoinjector (eg, EpiPen) or 0.3 mL IM of epinephrine drawn up at 1 mg/mL (ampule may be labeled 1:1000) [24,25].
- In infants and children weighing 10 to 25 kg, the dose is 0.15 mg IM using an autoinjector (eg, EpiPen Jr) and given as 0.15 mL IM of epinephrine drawn up at 1 mg/mL (1:1000).
- In infants weighing <10 kg, the dose is 0.1 mg IM using an infant autoinjector (eg, Auvi-q) or given as 0.1 mL IM of epinephrine drawn up at 1 mg/mL (1:1000).

Slow IV infusion — If the patient is unresponsive to two doses of IM epinephrine, a slow IV infusion of epinephrine is the preferred second-line option. However, IV epinephrine infusion requires continuous electronic hemodynamic monitoring and a health care provider with expertise in vasopressor infusion. Thus, this approach may be available in an interventional suite or in the operating room, but will rarely be an option for reactions that occur during diagnostic imaging examinations.

- In adults and adolescents weighing >25 kg, IV infusion is initiated at 0.1 mcg/kg/minute and increased every two to three minutes by 0.05 mcg/kg/minute until blood pressure and symptoms improve. The maximum dose is not known and will differ in each patient, but a patient will rarely require a dose exceeding 1 mcg/kg/minute (table 4).

- In infants and children weighing <25 kg, IV infusion is initiated at 0.1 to 1 mcg/kg/minute with use of an infusion pump, titrated to blood pressure with continuous cardiac monitoring (table 5 and table 6).

IV bolus (caution) — Epinephrine should be given as an IV bolus only if the IM bolus administration is not effective and the IV infusion option is not available. Epinephrine is also commonly given IV for anaphylaxis in certain settings, such as surgical or cardiac catheterization suites.

- In adults and adolescents weighing >25 kg, the dose is 50 to 100 mcg (0.05 to 0.1 mg) and IV bolus is given as a slow push. This is best administered as 0.5 to 1 mL of epinephrine drawn up at 0.1 mg/mL (ampule may be labeled 1:10,000).

- We avoid the use of IV boluses in infants and children because data are sparse on the efficacy or safety of this approach.

Systemic or airway symptoms

Hypotension and tachycardia — Hypotension and tachycardia indicate shock. Epinephrine should be given immediately and there are no contraindications to epinephrine in the setting of anaphylaxis (see 'Epinephrine administration' above). In addition, large volume fluid resuscitation should be initiated.

- Adults should immediately receive 1 to 2 liters of normal saline IV at the most rapid flow rate possible. Continuous rapid infusion may be necessary.

- Infants, children, and adolescents receive normal saline in boluses of 20 mL/kg each over 5 to 10 minutes, and repeated, as needed.

Laryngeal edema — Patients with hoarseness or inspiratory stridor should be treated with epinephrine (see 'Epinephrine administration' above). IV access should be maintained and vital signs should be monitored closely.

Bronchospasm — Patients with symptoms of lower airway compromise (ie, wheezing) in combination **accompanied by symptoms in any other organ system** (eg, urticaria) should be treated with epinephrine (see 'Epinephrine administration' above). In addition, inhaled beta-agonist bronchodilators (eg, albuterol) can be administered by metered dose inhaler (2 to 3 puffs) or as a nebulizer via a facemask. Note that bronchodilators should be considered adjunct to epinephrine as they do not prevent or treat the upper airway mucosal edema or hypotension associated with allergic-like contrast reactions. IV access should be preserved and vital signs should be monitored closely. Mild bronchospasm, without other signs or symptoms, may be treated with bronchodilators alone.

Diffuse skin symptoms — While focal urticaria is often seen in mild reactions to contrast, skin symptoms of urticaria, edema, or erythema that involves large areas or multiple anatomic locations indicate a moderate reaction. If systemic or airway manifestations are also present, the patient should be given epinephrine (see 'Epinephrine administration' above).

For the skin manifestations, an H1 antihistamine such as diphenhydramine 25 to 50 mg, administered IM or IV provides symptomatic relief of itching and hives. Note that H1 antihistamines are adjunctive to epinephrine, as they do not prevent or treat the upper airway mucosal edema or hypotension with allergic-like contrast reactions.

Mild reactions — Mild allergic-like reactions (eg, localized hives, urticaria, nasal congestion) can evolve into a moderate or severe reaction and do require observation. Patients should be observed for ≥30 minutes and until the symptoms have resolved. Treatment with an H1 antihistamine, such as diphenhydramine 25 to 50 mg PO, IM or IV, may be an option to provide symptomatic relief of itching and hives, but is usually unnecessary. Patients treated

with sedating H1 antihistamines will not be allowed to drive themselves home and they should be informed of this before initiating treatment.

Physiologic — Management of physiologic reactions is individualized based on the presenting symptoms. Clinical features of a moderate or severe physiologic reaction are:

Moderate or severe

Hypotension and bradycardia — Hypotension and bradycardia indicate a vasovagal reaction. This is thought to arise from increased vagal tone that depresses cardiac nodal activity and increases peripheral vasodilatation [2].

Patients should be laid supine with the legs elevated >60 degrees. If there are symptoms of end organ dysfunction (eg, altered mental status, cyanosis), large volume fluid resuscitation should be initiated.

- Adults should immediately receive 1 to 2 liters of normal saline IV at the most rapid flow rate possible. Continuous rapid infusion may be necessary.
- Children should receive normal saline in boluses of 20 mL/kg IV, each over 5 to 10 minutes, and repeated, as needed.

In patients who do not respond to the initial fluid bolus, an IV bolus of atropine is given. (See "Atropine (systemic): Drug information".)

- Adults should receive 0.6 to 1 mg IV every three to five minutes to a maximum dose of 3 mg.
- Infants, children, and adolescents: 0.02 mg/kg IV for a maximum single dose of 0.5 mg. This may be repeated once in three to five minutes for a maximum dose of 1 mg.

Hypertension — In most cases, hypertension associated with contrast administration is asymptomatic and detected because the patient is being monitored for other reasons, such as for angiography. It is usually self-limited and resolves as the contrast is cleared from the body. Management involves monitoring over several hours until the blood pressure normalizes and continued IV or oral hydration to facilitate urinary contrast clearance.

However, patients with symptoms of end organ injury (eg, encephalopathy, renal ischemia) should be treated for hypertensive emergency. (See "Overview of hypertension in adults", section on 'Hypertensive urgency and emergency' and "Evaluation and treatment of hypertensive emergencies in adults" and "Approach to hypertensive emergencies and urgencies in children".)

Cardiac symptoms — Adverse cardiac events are more frequent in patients with underlying cardiac disease. Management is determined by the presenting symptoms. Cardiac manifestations of a contrast reaction include:

- Chest pain (see "Overview of the acute management of non-ST-elevation acute coronary syndromes")
- Arrhythmia (see "Advanced cardiac life support (ACLS) in adults", section on 'Management of specific arrhythmias' and "Pediatric advanced life support (PALS)", section on 'AHA resuscitation guidelines')
- Pulmonary edema (see "Treatment of acute decompensated heart failure: Specific therapies")

Mild signs and symptoms — Mild physiologic reactions (eg, chills, nausea, metallic taste) usually are self-limited and do not require intervention. Most reactions can be managed with patient counseling and reassurance.

IMMEDIATELY FOLLOWING THE REACTION

Reaction classification — The contrast reaction should be classified based upon the severity (mild, moderate, or severe) and underlying physiology (allergic-like or physiologic) and these characteristics should be recorded in the patient's medical record [1] (see 'Allergic-like versus physiologic reaction' above). This classification is derived from the observed clinical manifestations of the adverse reaction and whether treatment was required.

Documentation — Any acute contrast reaction should be described in the patient's record. This guides decisions on the need for post-treatment allergy evaluation and on the need for

prophylaxis should future contrast administration be necessary. (See "Patient evaluation prior to oral or iodinated intravenous contrast for computed tomography", section on 'Patients with past reactions to contrast' and "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging", section on 'Patient with history of reaction to gadolinium contrast'.)

The medical record of the contrast reaction should include:

- Causative agent name, dose, and route of administration
- Reaction classification based on severity (mild, moderate, or severe) and pathophysiology (ie, allergic-like versus physiologic) (see 'Reaction classification' above)
- Clinical features of the reaction and their duration
- Treatment required

Serum tryptase testing — Measurement of serum tryptase can be helpful in patients with severe contrast reactions that were not easily categorized as allergic-like or physiologic (eg, hypotension with flushing). Tryptase is a protease that is released almost exclusively from mast cells and basophils, and an elevation in tryptase is strong evidence that a severe reaction was allergic in nature. Elevations in tryptase are not typically seen after cardiac or pulmonary events or severe physiologic reactions. Although the result does not provide information at the time of the reaction, it can help guide future management if the patient requires additional radiographic studies [26-30]. Several groups have reported elevated serum tryptase levels following severe or fatal immediate reactions to radiologic contrast material [26,28,31-33]. However, the diagnostic and prognostic utility of elevations in serum tryptase for the evaluation of contrast reactions specifically has not been studied [34].

Tryptase elevations are most often apparent after an allergic reaction involving hypotension. Elevations are transient and best detected if blood is collected between 15 minutes and 3 hours from the onset of symptoms. Instructions for accurate collection are provided (table 7). Serum total tryptase levels normally range from 1 to 11.4 ng/mL. Elevations during anaphylaxis can range from marginally elevated to levels >100 ng/mL. A normal tryptase level does not exclude anaphylaxis, because not all reactions result in tryptase

elevations, and mild reaction are rarely associated with tryptase elevations. (See "Laboratory tests to support the clinical diagnosis of anaphylaxis", section on 'Elevations in anaphylaxis'.)

CONTRAST READMINISTRATION

The approach to imaging examinations requiring readministration of the contrast agent that caused an adverse reaction varies with the severity of the index reaction and the clinical indication for the imaging examination. This is discussed separately. (See "Patient evaluation prior to oral or iodinated intravenous contrast for computed tomography", section on 'Patients with past reactions to contrast'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hypersensitivity to iodinated and gadolinium-based contrast agents".)

SUMMARY AND RECOMMENDATIONS

- The frequency of acute reactions to contrast varies with the contrast type (ie, iodinated versus gadolinium-based) and its molecular properties (eg, ionicity, osmolality, ligand structure). Contrast reactions have been observed with intra-arterial, intravenous (IV), enteral, and intraperitoneal administration, although serious allergic-like reactions are almost always encountered with intravascular administrations. (See 'Epidemiology' above.)

- Contrast administration for imaging is associated with a low rate of adverse reactions. Acute reactions usually occur within 20 minutes of exposure but are generally defined as those occurring within an hour. They are classified as allergic-like or physiologic based on the clinical presentation. (See 'Signs and symptoms' above.)

- A patient with a suspected contrast reaction should be immediately evaluated as some

will require urgent treatment. (See 'Evaluation and diagnosis' above.)

- Acute onset of symptoms that immediately follow contrast administration should presumptively be treated as a contrast reaction, unless there is an obvious alternative explanation. Contrast administration, if it is ongoing, should be immediately stopped. The appropriate treatment of a suspected contrast reaction is determined by the patient's signs and symptoms. (See 'Treatment' above.)

  - An unresponsive patient should be resuscitated according to advanced cardiac life support (ACLS) or pediatric advanced life support (PALS) (see "Advanced cardiac life support (ACLS) in adults" and "Pediatric advanced life support (PALS)"). Once the ACLS or PALS pathways have been initiated, the patient should also be evaluated and treated for a presumed severe contrast reaction. (See 'Unresponsive patient' above.)

  - Moderate or severe signs or symptoms require immediate initiation of therapy. Allergic-like reactions (ie, diffuse urticaria, cutaneous edema, or erythema, upper or lower airway compromise, or anaphylactoid shock) are treated with intramuscular (IM) epinephrine in most cases; treatment of physiologic reactions (ie, symptomatic vasovagal reaction, arrhythmia, angina, seizure, symptomatic hypertension, and intractable nausea and vomiting) are tailored to the specific symptoms. Following initiation of therapy, these patients should be triaged to the emergency department or be hospitalized for continued monitoring. (See 'Moderate or severe reactions' above.)

  - Mild reactions usually are self-limited and do not require intervention. Physiologic reactions (eg, chills, nausea, metallic taste) are transient and can be managed with patient counseling and reassurance. However, mild allergic-like reactions (eg, localized hives, urticaria, nasal congestion) can rarely evolve into a moderate or severe reaction and do require observation for ≥30 minutes or until the symptoms resolve. (See 'Mild signs and symptoms' above.)

- The contrast reaction should be classified based upon the severity (mild, moderate, or severe) and underlying physiology (allergic-like or physiologic). This classification is derived from the observed clinical manifestations of the adverse reaction and whether

treatment was required. (See 'Reaction classification' above.)

- Any acute contrast reaction should be described in the patient's record. This guides decisions on the need for post-treatment allergy evaluation and on the need for prophylaxis should future contrast administration be necessary. (See 'Immediately following the reaction' above.)

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