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Narrative Review

Angioedema and emergency medicine: From pathophysiology to diagnosis and treatment

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ABSTRACT

Angioedema is a self-limiting edema of the subcutaneous or submucosal tissues due to localised increase of microvascular permeability whose mediator may be histamine or bradykinin. Patients present to emergency department when angioedema involves oral cavity and larynx (life-threatening conditions) or gut (mimicking an acute abdomen).

After initial evaluation of consciousness and vital signs to manage breathing and to support circulation if necessary, a simple approach can be applied for a correct diagnosis and treatment. Forms of edema such as anasarca, myxedema, superior vena cava syndrome and acute dermatitis should be ruled out. Then, effort should be done to differentiate histaminergic from non-histaminergic angioedema. Concomitant urticaria and pruritus suggest a histaminergic origin. Exposure to allergens and drugs (mainly ACE inhibitors and non steroidal anti-inflammatory drugs) should be investigated as well as a family history of similar symptoms. Allergic histaminergic angioedema has a rapid course (minutes) whereas non histaminergic angioedema is slower (hours). Since frequently the intervention needs to be immediate, the initial diagnosis is only clinical. However, laboratory tests can be subsequently confirmatory.

Allergic angioedema is sensitive to standard therapies such as epinephrine, glucocorticoids and antihistamines whereas non histaminergic angioedema is often resistant to these drugs. Therapeutic options for angioedema due C1-inhibitor deficiencies are C1-inhibitor concentrates, icatibant and ecallantide. If these drugs are not available, fresh frozen plasma can be considered. All these medications have been used also in ACE inhibitor-induced angioedema with variable results thus they are not currently recommended whereas experts agree on the discontinuation of the causative drug.

1. Introduction

Angioedema is a circumscribed non-pitting edema of the subcutaneous tissues involving lips, face, neck and extremities and/or submucosal tissues affecting oral cavity, larynx and gut. Larynx involvement may be life-threatening whereas intestinal angioedema can be very painful and can mimick an acute abdomen. Angioedema derives from bouts of localised increase of microvascular permeability and usually lasts several hours to one or two days [1–3].

The disorder may be acquired or hereditary (Fig. 1). Acquired forms may be of allergic origin (histaminergic angioedema), generally associated with other manifestations of anaphylaxis, or non-allergic (non-histaminergic angioedema), presenting isolated or in combination with urticaria. Other forms of acquired angioedema may be drug-induced (mainly by angiotensin converting enzyme inhibitors and non steroidal anti-inflammatory drugs) or complement-mediated (due to an acquired deficiency of C1-inhibitor). However, in several cases, a specific cause of angioedema can not be defined and thus they remain idiopathic. Two types of idiopathic angioedema have been described: one responsive and one not responsive to H1 antihistamines [4–6]. Hereditary forms are due to genetic mutations in C1-inhibitor gene leading to C1-inhibitor deficiency and complement activation. The hereditary deficiency of C1-inhibitor, affecting 1 every 50.000 individuals, comprises two forms: type 1 and type 2 hereditary angioedema. In type 1, the antigenic and functional levels of C1-inhibitor are decreased, whereas in type 2, C1-inhibitor levels are normal but there is a functional impairment [3,7]. Another form of hereditary angioedema, previously called type 3, is characterised by normal C1-inhibitor levels and in some

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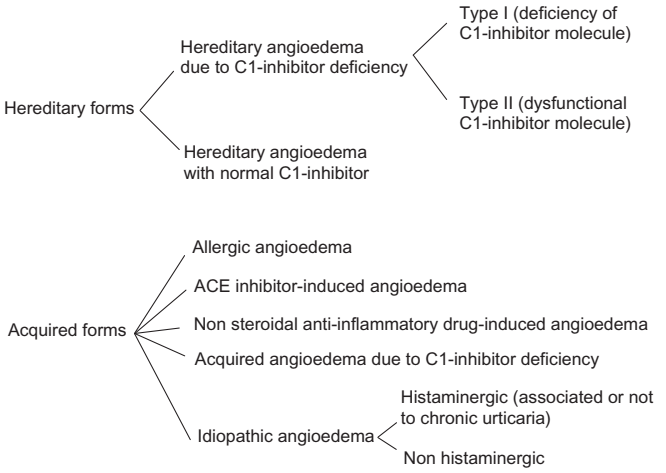

Fig. 1. Classification of angioedema.

cases mutations of the factor XII gene have been described [8]. However, not all the forms of angioedema with normal C1-inhibitor are due to factor XII mutations and may differ in several aspects including gender distribution, genetics, symptoms, and estrogen impact [9]. Recently two other mutations have been described in genes encoding for angiopoietin-1 and plasminogen [10,11].

In different forms of angioedema different mechanisms may contribute to the pathogenesis of angioedema, and two main mediators of increased vascular permeability, i.e. histamine and bradykinin, have been shown to be involved. Other mediators like leukotrienes, prostaglandins, cytokines and chemokines, although probably implicated, still need sound data to be included [12]. The clinical response to specific antagonists can provide a good evidence for a particular mediator. Histamine, which can be blocked by anti-histamines, is the best identified mediator [13] along with bradykinin, whose effects can be blocked by icatibant [14]. A direct demonstration of increased bradykinin levels in circulating blood has been provided in angioedema due to C1-inhibitor deficiency and in angioedema due to ACE inhibitors treatment [15–17].

Many physicians may not be aware of all the forms of angioedema and of the underlying pathogenetic mechanisms [18–20]; for this reason, recognition and differentiation of the various aetiologies and pathogenesis of angioedema are essential for carrying out a prompt effective treatment, especially in emergency room. In this review, we will focus on the pathophysiology of angioedema and the related clinical entities, trying to provide a simple approach for diagnosis and therapy in an emergency context.

2. Pathophysiology and clinical manifestations of angioedema

Knowing the underlying pathogenetic mechanisms and distinguishing the various forms of angioedema is pivotal because the therapeutic strategy is markedly different. Family history, clinical presentation and the time of symptoms onset may help in the diagnosis and the choice of treatment.

1) Histamine-mediated angioedema is the most common and it is secondary to mast-cell and basophil activation. It can be acute or chronic and with or without urticaria; other symptoms, as flushing, pruritus, bronchospasm, abdominal pain and vomiting may be present. Symptoms typically develop within 60 min after allergen exposure (food intake, environmental allergens, drugs or insect venom) and last about 24 to 48 h. In addition, angioedema may occur in the context of spontaneous and inducible chronic urticaria, the former now recognized as an autoimmune/autoreactive disorder and the latter as a condition due to specific and reproducible triggers, mainly physical stimuli [12]. Histaminergic angioedema responds to antihistamines and in the allergic acute forms also corticosteroids and epinephrine are indicated.
2) Bradykinin-mediated angioedema comprises hereditary angioedema (associated or not with C1-inhibitor deficiency), acquired C1-inhibitor deficiency and ACE inhibitor-associated angioedema. These forms are not triggered by an allergic reaction nor associated with hives. C1-inhibitor is a regulator of complement and contact system. When C1-inhibitor is deficient or dysfunctional, the contact system is inappropriately activated with a consequent uncontrolled production of kallikrein leading to proteolysis of high molecular-weight kininogen and production of the nonapeptide bradykinin. Bradykinin is a vasoactive peptide inducing vasodilation and increase in vascular permeability which eventually result in edema formation [21].

The deficiency of C1-inhibitor may be inherited (hereditary angioedema) or acquired (in this case association with lymphoproliferative disorders, autoimmune, neoplastic or infectious diseases have been reported). Hereditary angioedema (HAE) is an autosomal dominant disease caused by mutations in the gene encoding for C1-inhibitor leading to its deficiency or dysfunction and consequent excessive generation of bradykinin. In type I HAE plasma levels of C1-inhibitor are reduced whereas in type II HAE the protein is functionally impaired but quantitatively normal.

Another rarer form of HAE is characterised by normal C1-inhibitor levels and comprises HAE associated to mutations of factor XII, angiopoietin-1 or plasminogen genes. Lastly, some patients have HAE due to unknown mutations [3].

Acquired C1-inhibitor deficiency is characterised by low C1-inhibitor antigen and function and low C1q. The association of this condition with lymphoproliferative, autoimmune, neoplastic and infectious has been reported and frequently autoantibodies against C1-inhibitor are detectable [22,23]. The differentiation between acquired C1-inhibitor angioedema and type 1 or type 2 HAE could be facilitated by a negative family history and onset of disorder after 40 years of age [3].

Patients with bradykinin-mediated angioedema can present with non pitting subcutaneous edema involving face and oral cavity (tongue, palate and uvula), extremities and genitals. Usually edema is not itchy but can be painful. When larynx is involved, angioedema can be life-threatening because of partial or complete airway obstruction, while bowel edema can cause intense abdominal pain and diarrhea. Symptoms develop progressively over several hours, they last up to 48–72 h and are usually self-limiting.

As C1-inhibitor deficiency angioedema, ACE inhibitor-associated angioedema is a form of bradykinin-mediated angioedema but, while the former is due to an excessive production of bradykinin, the latter may be attributable to a decreased degradation of bradykinin, a peptide that causes vasodilation and fluid extravasation into tissues [24,25]. Black people have an increased risk for ACE inhibitor-associated angioedema [26] and other potential risk factors may be female sex, chronic heart failure, coronary heart disease and smoking [27,28]. Angioedema can occur at any time during the therapy with ACE inhibitors but the greatest risk is in the first weeks to months of assumption [25] and it typically involves lips, tongue, face and sometimes bowel. ACE inhibitor-associated angioedema is characterised by normal C1-inhibitor antigen and function and normal C1q. Treatment consists in drug discontinuation and airway management. Bradykinin-mediated angioedema is often resistant to standard therapies such as epinephrine, glucocorticoids or antihistamines.

3) Non steroidal anti-inflammatory drugs-associated angioedema is another form frequently observed. The pathogenetic mechanism underlying this form of angioedema may be due to the cyclooxygenase-1 inhibition producing an imbalance in arachidonic acid

metabolism or altered leukotriene/prostaglandin binding to receptors or, more rarely, may be linked to IgE-mediated type I hypersensitivity [24] Cyclooxygenase-1 inhibition shunts arachidonic acid away from the production of anti-inflammatory prostaglandin D2 and E2, increasing the production of leukotrienes C4 and D4 which cause vasodilation, plasma leakage and angioedema [24]. Discontinuation of the involved drugs is mandatory.

4) Idiopathic angioedema can be hereditary (HAE of unknown origin) or acquired (histaminergic or non-histaminergic). The two idiopathic acquired forms can be distinguished on the basis of response to antihistamines; thus the lack of response to antihistamines defines acquired idiopathic non histaminergic angioedema [5,29,30]. In these forms a bradykinin involvement has been demonstrated both by the response to bradykinin inhibitor icatibant [31,32] and by direct measurement of bradykinin during acute attacks [6].

3. Patient evaluation

3.1. Initial evaluation

Initial evaluation starts with the assessment of the level of consciousness and vital signs, i.e. blood pressure, heart rate, oxygen saturation and peripheral perfusion. Skin examination may detect the presence of edema and/or urticaria. Most patients with acute angioedema have normal hemodynamic parameters, whereas several patients may be critically ill. Both histaminergic and non histaminergic angioedema can potentially cause hypovolemic shock due to the shift of fluids in various site of the body and/or acute respiratory failure secondary to airway edema [33].

3.2. Head, neck and respiratory function evaluation

A meticulous oropharyngeal examination is essential in patients with angioedema. Physicians should look for edema involving lips, tongue, soft palate and larynx. Indirect laryngoscopy is the optimal method for evaluating the upper airway but, if this cannot be performed, the site of airway involvement may be predicted by clinical signs such as dyspnea, hoarseness and stridor. Oropharyngeal involvement can occur in any form of angioedema; however, ACE inhibitor-induced angioedema has a predilection for the head and neck and most frequently involves the tongue and lips [34].

3.3. Abdomen

Gastrointestinal symptoms may occur in bradykinin- or histamine-mediated angioedema. Vomit and intense abdominal pain associated to signs of acute abdomen like severe tenderness, guarding and rebound tenderness, can mislead physicians being interpreted as an acute surgical disease. Gastrointestinal symptoms are more frequently observed in hereditary angioedema patients [35].

4. Diagnostic approach

When a patient presents with a new-onset angioedema in the Emergency Department, after initial evaluation of level of consciousness and vital signs, a simple three-step approach could be applied to make the correct diagnosis.

1. True angioedema should be distinguished from other forms of false angioedema such as anasarca syndromes (due to hepatic, renal, cardiac or bowel diseases), hypothyroidism (myxedema), superior vena cava syndrome, acute dermatitis (dermatomyositis, drug rash with eosinophilia and systemic symptoms [DRESS]) and systemic capillary leak syndrome (Clarkson's disease). Identifying these forms is essential because conventional angioedema treatment is generally ineffective [36].
2. Once established that the patient has a true angioedema, effort should be done to differentiate histaminergic from non-histaminergic angioedema. The presence of urticaria strongly suggests a histaminergic origin whereas bradykinin-mediated angioedema does not manifest with hives or urticaria but, if anything, with erythema marginatum especially in the hereditary forms [37]. Other symptoms like intense pruritus, flushing, bronchospasm, vomiting and abdominal pain should be sought because they are suggestive of allergic reaction. Histamine-mediated angioedema has a rapid course with symptoms developing quickly, even within minutes, and it can evolve to anaphylaxis which can be life-threatening. Finally, patients with symptoms of allergic reaction should be asked about a recent exposure to an allergen (specific foods, insect venom, drugs and environmental allergens).
3. Compared to histamine-mediated angioedema, symptoms of non histaminergic angioedema have a slower onset and develop over several hours, lasting up to 48–72 h. Episodes of recurrent swelling and/or abdominal pain, if associated to a family history of similar symptoms, suggest hereditary angioedema [19,38]. If symptoms are not associated to family history, they suggest acquired angioedema although de novo cases of hereditary angioedema should be considered [19]. Both hereditary and acquired forms can be associated to C1-inhibitor deficiency but they may also present with normal levels of C1-inhibitor. The patient should be asked about exposure to potential triggers, such as dental and surgical procedures, stress or trauma, menses, drugs (mainly ACE inhibitors, non steroidal anti-inflammatory drugs and estrogens), possibility of pregnancy and infections. Furthermore, the evaluation of comorbidities is important, in particular, previous diagnosis of malignancies, haematological and autoimmune diseases. The main clinical features of histaminergic and non histaminergic angioedema are summarised in Table 1.
4. Lastly, the response to treatment can help for diagnosis. Allergic angioedema is very sensitive to standard therapies such as epinephrine, glucocorticoids or antihistamines whereas bradykinin-mediated angioedema is often resistant to these drugs.

5. Laboratory tests

Unfortunately, laboratory tests for a correct diagnosis of angioedema need time to be performed whereas in several cases the intervention should be immediate. For this reason, at the beginning, the diagnosis relies only on clinical data. Once the initial treatment has been started, confirmatory tests on blood samples can be performed.

Table 1
Clinical and therapeutic differences between histaminergic and non-histaminergic angioedema.

	Type of angioedema	
Clinical features	Histaminergic angioedema (Allergic and idiopathic)	Non histaminergic angioedema (Angioedema due to C1-inhibitor deficiencies, ACE inhibitor angioedema and angioedema with normal C1–inhibitor)
Onset	Rapid (minutes)	Slow (hours)
Duration	12–24 h	48–72 h or more
Urticaria	Frequent	No
Laryngeal edema	Possible	Possible
Bronchospasm	Frequent	Rare
Abdominal pain	Possible	Frequent (HAE)
Hypotension	Frequent	Rare
Therapy with H1 antihistamines, corticosteroids and epinephrine	Effective	Not effective

Table 2
Classification and laboratory abnormalities in the different types of angioedema.

Types of angioedema	Laboratory tests				
	C4	C1-inhibitor Ag	C1-inhibitor function	C1q	C1-inhibitor antibodies
Histaminergic angioedema	N	N	N	N	negative
Hereditary angioedema Type 1	↓	↓	↓	N	negative
Hereditary angioedemaType 2	↓	N	↓	N	negative
Hereditary angioedema with normal C1– inhibitor	N	N	N	N	negative
Acquired angioedema	↓	↓	↓	↓	may be detectable
Drug-induced angioedema	N	N	N	N	negative
Idiopathic angioedema	N	N	N	N	negative

N = normal, ↓ = low level.

The measurement of C4 plasma levels allows to identify the deficiencies of C1-inhibitor in which C4 is consumed. Antigenic and functional plasma levels of C1-inhibitor allow to differentiate a quantitative from a qualitative deficiency of C1-inhibitor. Usually in acquired C1-inhibitor deficiencies, C1q levels are very low, anti-C1-inhibitor antibodies are frequently detected and a monoclonal component may be present on serum protein electrophoresis. In histaminergic angioedema and in ACE inhibitor-associated angioedema complement levels as well as C1-inhibitor antigen and function are normal. A summary of the main alteration in haematic tests is reported in Table 2.

6. Therapeutic options

6.1. Airway management

Angioedema may involve several sites of the body, and patients not always refer to the emergency department because edema of extremities or other cutaneous sites are not considered at risk. The situation is completely different when lips, oral cavity, larynx and bowel are involved because laryngeal angioedema may be life-threatening.

The first step in managing any patient in the emergency department is to manage airway and breathing and to support circulation function if necessary. Physician should evaluate if the airway is safe or not. If airway obstruction is imminent or manifest, acute airway management takes immediate precedence and the local anaphylaxis protocol should be followed [19], e.g. epinephrine 500 μg i.m., clorphenamine 10 mg i.m. or iv slowly and hydrocortisone i.m. or iv slowly. If the patient with oral cavity or upper airway angioedema is not critical on presentation, efforts should be done to define the site of airway compromise. The identification of the site of airway obstruction is useful to triage patients appropriately and to prepare the emergency staff for possible airway intervention. In 1999 Ishoo et al. proposed a staging system which considered the anatomic site of airway obstruction on presentation: facial or lips edema (stage I); soft palate edema (stage II); tongue edema (stage III); laryngeal edema (stage IV). Complete head and neck examination with indirect laryngoscopy is the optimal method of evaluating the upper airway but, if this cannot be performed, the site of airway involvement may be predicted by clinical signs. Dyspnea can be present in soft palate, tongue and larynx edema, whereas hoarseness and stridor indicate laryngeal involvement. Facial, lips and soft palate edema generally do not represent dangerous situations, whereas laryngeal angioedema needs immediate airway intervention. Lingual angioedema is not always life threatening and anatomic distinction must be made between edema of anterior and lateral tongue angioedema from diffuse lingual angioedema. Inability to visualize the soft palate suggests a dangerous airway [39].

Neck X-rays or computed tomography cannot replace physical examination of the obstructed airway because they could delay diagnostic and therapeutic approach [33,39].

Intubation needs to be considered early because disease can progress quickly and intubation could become difficult or fail requiring emergent tracheostomy or cricothyroidotomy [33].

6.2. Therapies for acute angioedema

When a patient presents with histaminergic angioedema or with angioedema of unknown etiology a rational first-line treatment comprises H1 antihistamines, corticosteroids and epinephrine (see above). In the absence of anaphylaxis, epinephrine is not indicated for non life-threatening symptoms that do not involve the airway. On the contrary, when a patient manifests airway swelling or hypotension the local anaphylaxis protocol should be followed (see above).

When ACE inhibitor-induced angioedema is suspected, the offending drug must be discontinued. There are no specific therapies for ACE inhibitor-induced angioedema so that standard treatment comprises H1 antihistamines, glucocorticoids and epinephrine. However, these medications may not be effective [25,40]. As this form of angioedema is not histamine-mediated, the role of antihistamines is not clear and response to these medications is minimal or absent [41]. Glucocorticoids have been shown to induce the expression of ACE and could theoretically accelerate bradykinin metabolism and alleviate angioedema [42].

Several therapies approved for the treatment of hereditary angioedema have been tested for ACE inhibitor-induced angioedema with variable results. In particular, fresh frozen plasma has been used successfully in few patients with ACE inhibitor-induced angioedema refractory to standard treatment with steroids, antihistamines and epinephrine [43–45]. However, in another case report a worsening of angioedema syptoms after administration of fresh frozen plasma was reported [46]. The efficacy of the selective bradykinin B2 receptor antagonist icatibant was demonstrated by Bas et al. [40]; however these results were not confirmed by other two studies [47,48]. Currently, icatibant is not approved for this indication [24]. Similarly, the kallikrein inhibitor ecallantide approved for the treatment of hereditary angioedema has not showed to be effective in ACE inhibitor-induced angioedema [49,50]. Few case reports have shown positive results after administration of C1-inhibitor concentrate for ACE inhibitor-induced angioedema [51–54]. Although evident support regarding the efficacy of C1-inhibitor concentrate and icatibant in ACE inhibitor associated angioedema is lacking these therapies are frequently used obtaining sometimes good responses.

Symptoms at presentation and patient history along with a lack of response to antihistamines indicate non histaminergic angioedema. For hereditary angioedema due to C1 inhibitor deficiency, C1-inhibitor concentrates, the bradykinin-receptor antagonist icatibant and the plasma kallikrein inhibitor ecallantide are registered. Early administration is recommended because it provides a better treatment response than late treatment with a shorter time to resolution of symptoms [3]. If C1-inhibitor concentrates, ecallantide or icatibant are not available, acute angioedema should be treated with solvent detergent-treated plasma or fresh frozen plasma. Treatment with C1-inhibitor concentrates replace the deficient or dysfunctional C1-inhibitor in patients

with hereditary angioedema type 1 and 2. At present, two C1-inhibitor plasma-derived concentrates (Cynrize® ViroPharma [Europe only] and Berinert® CSL Behring) and one recombinant (Ruconest® Pharming Group NV [Europe only]). All the three concentrates are administered intravenously at different dosages: Berinert 20 U/kg, Cynrize 1000 U and Ruconest 50 U/kg. The kallikrein inhibitor ecallantide is available only in the United States for the on-demand treatment of acute attacks in patients with hereditary angioedema at the dose of 30 mg subcutaneously. Ecallantide inhibits kallikrein activity which in turn inhibits the cleavage of high-molecular-weight kininogen to bradykinin. This drug can potentially induce serious hypersensitivity reactions, including anaphylaxis [55]. Icatibant is a selective competitive antagonist of the bradykinin B2 receptor which prevents binding of bradykinin to its receptor. The safety and tolerability of icatibant are good, although transient local injection site reactions (erythema, wheal, pruritus and burning sensation) occur whereas allergic reactions have not been reported [3]. The drug is administrated at the dose of 30 mg as subcutaneous injection.

6.3. Observation period and discharge

According to expert guidelines, patients experiencing an angioedema attack for the first time and those without a clear diagnosis [18] and those with edema involving face or lips [19] should remain under observation for at least 6 h after treatment administration and then, when symptoms start improving, they can be discharged with specific therapy. Discharge is not recommended when angioedema progression is observed despite treatment, in case of permanent clinical instability, or when the diagnosis remains uncertain [18]. When a C1 inhibitor deficiency is suspected the patient should be referred to a specialized centre for appropriate treatment and follow-up. Patient whose angioedema has been responsive to H1 antihistamines and corticosteroids treatment can continue H1 antihistamines therapy for seven days and taper off corticosteroids, i.e. oral prednisone 25 mg for three days, and 5 mg for three days. ACE inhibitors should be discontinued and substituted with an antihypertensive of another class in all cases of ACE inhibitor-induced angioedema [18,19].

7. Learning points

- Angioedema is a self-limiting edema of the subcutaneous or submucosal tissues due to localised increase of microvascular permeability whose mediators are mainly histamine or bradykinin.
- Angioedema can be hereditary or acquired. The most frequent forms are allergic (histaminergic), less frequent forms are drug-induced (mainly by ACE inhibitors and NSAIDs) or complement-mediated (deficiencies of C1-inhibitor). Angioedema of unknown origin is termed idiopathic.
- Angioedema may involve several sites of the body such as lips, face, extremities and genitals. The most dangerous forms involve larynx or tongue (life-threatening) and bowel (very painful and mimicking an acute abdomen); they are usually managed in emergency department.
- After initial evaluation and management of breathing and circulation, false angioedema (e.g. myxedema, anasarca and acute dermatitis) should be ruled out; response to first line therapy (i.e. H1 antihistamines, corticosteroids and epinephrine) indicates a histaminergic form.
- If first line therapy is not effective, second line therapy with C1-inhibitor concentrates, ecallantide, icatibant or fresh frozen plasma should be considered; for ACE-I induced angioedema the discontinuation of the offending drug is mandatory.
- A minimum of 6 h observation should be warranted and discharge can be done only after stabilisation or regression of symptoms.

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