

Angiotensin-converting Enzyme Inhibitor and Other Drug-associated Angioedema



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KEYWORDS

- Angioedema • ACE inhibitor • Bradykinin • NSAID • Leukotriene • Drug • Medication

KEY POINTS

- Drug-induced angioedema should be characterized as being either allergic (histamine mediated) or nonallergic mechanism based, because this guides therapeutic decision making.
- Nonsteroidal antiinflammatory drugs can cause angioedema in a susceptible host via shifts in the synthesis of prostaglandins and leukotrienes.
- A growing number of drugs cause angioedema by inhibiting pathways involved in the degradation of bradykinin and substance P.
- B₂ receptor antagonism and kallikrein inhibition have not been as successful in the treatment of drug-induced bradykinin-mediated angioedema as in hereditary angioedema.

INTRODUCTION

Angioedema is characterized by localized deep dermal, subcutaneous, and/or mucosal edema resulting from increased vasodilatation and vascular permeability. Nonsteroidal antiinflammatory drugs (NSAIDs), β -lactam antibiotics, non- β lactam antibiotics, and angiotensin-converting enzyme (ACE) inhibitors are the most common classes of drugs that cause angioedema.^{1–3} Drug-induced angioedema is best categorized as allergic or nonallergic. The most common form of allergic angioedema is caused by immunoglobulin (Ig)-E-mediated degranulation of mast cells and release of histamine (type I hypersensitivity) in response to a drug and this is the most common

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cause of angioedema caused by β -lactam and other antibiotics.¹ Nonallergic forms of angioedema result as a consequence of the underlying mechanism of the drug. NSAIDs may cause hypersensitivity reactions but angioedema results more commonly because of the diversion of arachidonic acid metabolism from the cyclooxygenase (COX) pathway to the leukotriene pathway. ACE inhibitor-associated angioedema results from decreased degradation of kinins and other vasoactive peptides; there is a growing list of drugs that affect these pathways.

Clinically it is important to distinguish between allergic and nonallergic forms of drug-induced angioedema because the response to therapy differs dramatically. Allergic forms of drug-induced angioedema respond to antihistamines, glucocorticosteroids, and epinephrine, whereas nonallergic forms do not. The presence of pruritus or urticaria in a patient without a prior history of urticaria suggests an allergic form of drug-induced angioedema. For completeness, **Table 1** provides a list of drugs that cause histamine-mediated angioedema (see Busse PJ, Smith T: [Histaminergic Angioedema](#), in this issue). This article focuses primarily on nonallergic forms of drug-induced angioedema.

ANGIOEDEMA ASSOCIATED WITH NONSTEROIDAL ANTIINFLAMMATORY DRUG USE

The European Academy of Allergy and Clinical Immunology Task Force on NSAID Hypersensitivity proposed classifying immediate-type NSAID reactions into 5 categories, 3 of which can present with angioedema.⁴

Table 1 Drugs that cause histamine-mediated angioedema and their reported mechanisms of mast cell degranulation		
IgE Mediated	Direct Mast Cell Degranulation, Via G-Protein-coupled Receptors or Other Means	Drug Causes Histamine-mediated Angioedema Only Rarely, or Mechanism is Not Understood
Antimicrobials: Penicillins, ⁵¹ cephalosporins, ⁵² Carbapenems, ⁵¹ fluoroquinolones, ⁵³ sulfonamides, ⁵⁴ vancomycin, ⁵⁵ macrolides ⁵⁶ Chemotherapeutics: Platinum-based agents, ⁵⁷ paclitaxel, ⁵⁸ cetuximab (via galactose- α -1, 3-galactose allergy) ⁵⁹ Procedural medications: Radiographic contrast, ⁶⁰ opiates, ⁶¹ neuromuscular blocking agents, ⁶² NSAIDs ⁶³ Gastrointestinal medications: Proton pump inhibitors, ⁶⁴ polyethylene glycol ⁶⁵	Antimicrobials: Fluoroquinolones, ⁶⁶ sulfonamides ⁶⁷ (especially in patients with human immunodeficiency virus), vancomycin ^a (associated with worsening of angioedema only) ^{3,55} Chemotherapeutics: Paclitaxel ^{a,68} Procedural medications: Radiographic contrast, ^{a,69} opiates, ^{a,70} neuromuscular blocking agents ^{a,66}	Antimicrobials: Daptomycin, ⁷¹ clindamycin, ⁷² chloramphenicol ⁷³ Antituberculosis agents: Rifampicin, ⁷⁴ streptomycin, ⁷⁵ ethambutol, ⁷⁶ isoniazid ⁷⁷ Immune suppressants: Tacrolimus, ⁷⁸ sirolimus ⁷⁹ Psychiatric medications: selective serotonin reuptake inhibitors ⁸⁰ Procedural medications: Hyaluronidase ⁸¹

^a For medications with more than 1 reported mechanism, what seems to be the most common mechanism for reactions is indicated when that information is available.

The most straightforward category is single NSAID-induced urticaria/angioedema or anaphylaxis in a patient with no underlying urticaria/angioedema disease. The patient presents with angioedema while using a particular NSAID, or NSAIDs that are structurally related, and has no symptoms when using NSAIDs of different structural categories. The mechanism for these structure-specific reactions is generally thought to be IgE-mediated type I hypersensitivity, and IgEs specific for pyrazolone NSAIDs have been detected in patients who developed angioedema or urticaria while taking these agents.⁵ Identification of IgEs specific for other families of NSAIDs has not been reported. Treatment involves the discontinuation and avoidance of NSAIDs structurally related to the NSAID that caused symptoms.

The second category is NSAID-induced urticaria/angioedema (NIUA). These reactions occur in patients without an underlying tendency to chronic urticaria/angioedema in response to the ingestion of structurally dissimilar NSAIDs. The mechanism underlying this class effect is thought to involve an imbalance in arachidonic acid metabolism or altered leukotriene/prostaglandin binding to receptors. Angioedema results when COX-1 inhibition shunts arachidonic acid away from the production of antiinflammatory prostaglandin D₂ and E₂ and toward increases in production of leukotriene B₄, C₄, and D₄, which cause vasodilation, plasma leakage, and angioedema. Genetic variants in the genes encoding *ALOX5*, *ALOX15*, *PTGDR*, *PTGER1*, and *CYSLTR1* have been reported to predispose patients to this condition.^{6–8} Typically, acetaminophen is safe for use in this group of patients, and selective COX-2 inhibitors have also been used safely.

The third category of NSAID-induced angioedema occurs in patients with underlying chronic urticaria and/or angioedema, and is called NSAID-exacerbated cutaneous disease. The mechanism seems to be similar to NIUA, whereby alterations in the balance between prostaglandin and leukotriene production leads to angioedema in patients with an underlying predisposition to angioedema or urticaria. For this reason, NSAID desensitization is not effective in this type of patient.⁹ Treatment should emphasize control of underlying chronic angioedema/urticaria.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR-ASSOCIATED ANGIOEDEMA

Clinical Features of Angiotensin-converting Enzyme Inhibitor-associated Angioedema

ACE inhibitor-associated angioedema typically involves the lips, tongue, or face. Angioedema may also involve the bowel; in this case, the patient may present with abdominal pain and symptoms of obstruction and the diagnosis can be made by identification of bowel edema on computed tomography scan with resolution of symptoms after discontinuation of the ACE inhibitor. The risk of ACE inhibitor-associated angioedema is greatest during the first week to month of exposure, but angioedema can occur at any time,^{10–12} suggesting that an additional inciting factor may contribute to the pathogenesis of ACE inhibitor-associated angioedema (discussed later). Angioedema may remit spontaneously, but, if ACE inhibitor use is continued, angioedema typically recurs.¹¹ Many patients with ACE inhibitor-associated angioedema do not present for acute care. However, among those presenting for emergency treatment, up to 16% require intubation and 1% require tracheostomy.¹³ Rapid evolution of symptoms; involvement of the tongue, soft palate or larynx; and symptoms of drooling or respiratory distress are associated with a higher risk of intubation.¹³

Epidemiology of and Risk Factors for Angiotensin-converting Enzyme Inhibitor-associated Angioedema

The reported incidence of ACE inhibitor-associated angioedema ranges from 0.1% to 0.7% in retrospective studies to as high as 2.8% to 6% in prospective clinical

trials.^{14–17} The incidence of ACE inhibitor–associated angioedema is 4.5-fold to 5-fold higher in patients of African descent compared with white people.^{12,18–20} ACE inhibitor–associated angioedema is uncommon in Asian patients. A history of seasonal allergies, antihistamine use, or corticosteroid use is associated with an increased risk of ACE inhibitor–associated angioedema.^{10,20} At least 1 group has reported that there is seasonal variation in presentation of ACE inhibitor–associated angioedema, with increased presentations occurring during months with high pollen counts, especially in patients with allergic sensitization.²¹ Smokers and former smokers are at increased risk of ACE inhibitor–associated angioedema, whereas patients with type 2 diabetes mellitus are at decreased risk.^{10,12,20} Immunosuppressant use, rheumatoid arthritis, and history of transplant have been associated with an increased risk of ACE inhibitor–associated angioedema.^{10,22,23}

Pathophysiology of Angiotensin-converting Enzyme Inhibitor–associated Angioedema

Like hereditary angioedema, ACE inhibitor–associated angioedema is thought to result from excess bradykinin. Hereditary angioedema results from increased production of kinins²⁴; however, ACE inhibitor–associated angioedema results from decreased degradation of bradykinin and other vasoactive ACE substrates, such as substance P (Fig. 1). Bradykinin increases vascular permeability through its B₂ receptor and via sensitization of the transient potential vanilloid receptor I (TRPV1).²⁵

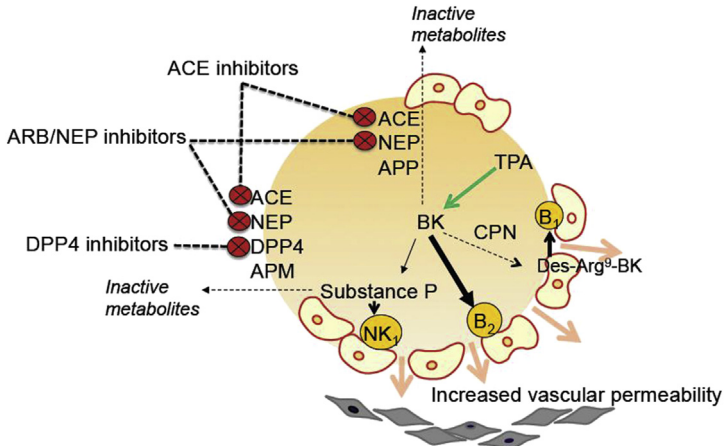


Fig. 1. Hypothesized mechanism of drug-induced angioedema mediated by bradykinin and substance P. Activation of kallikrein-kinin system results in the generation of bradykinin (BK). TPA can also increase BK through formation of plasmin and the contact system. BK activates the B₂ and transient potential vanilloid receptor I (TRPV1; not shown) receptors to cause vasodilation and vascular permeability, and stimulates the release of substance P. Substance P increases vascular permeability via the neurokinin 1 (NK₁) receptor. BK is inactivated primarily by ACE, aminopeptidase P (APP), and neutral endopeptidase (NEP), whereas substance P is inactivated by ACE, NEP, and dipeptidyl peptidase 4 (DPP4). Inhibition of these enzymes by drugs in a susceptible patient can lead to accumulation of BK and/or substance P and angioedema. Des-Arg⁹-BK, a metabolite of BK by carboxypeptidase N (CPN), may also cause angioedema via the B₁ receptor. ARB, angiotensin receptor blocker; APM, aminopeptidase M; TPA, tissue plasminogen activator. (Modified from Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 2010;30(Suppl 1):46; with permission.)

Bradykinin also stimulates the release of substance P from nerve terminals; substance P increases vascular permeability by activating the NK₁ receptor.^{26,27} Treatment with a bradykinin B₂ receptor antagonist, a TRPV1 antagonist, or a substance P NK₁ receptor antagonist decreases ACE inhibitor-associated angioedema in rodent models.^{25–28}

ACE degrades both bradykinin and substance P. When ACE is inhibited, other enzymes, such as neprilysin (neutral endopeptidase [NEP]), carboxypeptidase N, and aminopeptidase P (APP), degrade and inactivate bradykinin. Likewise, during ACE inhibition, dipeptidyl peptidase 4 (DPP4) and NEP inactivate substance P. Genetic or environmental factors that decrease the activity of these non-ACE enzyme pathways in the degradation of bradykinin and substance P would be expected to increase the risk of angioedema.

Genetics of Angiotensin-converting Enzyme Inhibitor-associated Angioedema

Sturrock and colleagues²⁹ reported that a 9-base-pair deletion variant in the bradykinin B₂ receptor, leading to increased transcription and increased sensitivity to bradykinin, is associated with ACE inhibitor-associated angioedema in black and mixed-race South Africans.³⁰ The investigators did not find an association between an ACE insertion/deletion polymorphism and ACE inhibitor-associated angioedema, but reported that ACE activity was significantly decreased in patients with angioedema compared with ACE inhibitor-treated controls without angioedema.³⁰ Other groups have not observed an association between variants in the genes encoding ACE or the bradykinin B₂ receptor and ACE inhibitor-associated angioedema.^{31,32}

Several candidate gene studies have examined the association between functional variants in genes encoding enzymes involved in the degradation of bradykinin and other vasoactive peptides and ACE inhibitor-associated angioedema. Duan and colleagues³³ identified a single nucleotide polymorphism (SNP) in the gene encoding membrane APP (*XPNPEP2*, -2399C > A, or rs3788853), which is associated with decreased plasma APP activity and angioedema in families associated with anaphylactoid reactions during hemodialysis and/or angioedema during ACE inhibitor use. The applicability of this finding to patients not on dialysis with ACE inhibitor-associated angioedema is not clear. Although patients with anaphylactoid reactions during dialysis may experience angioedema, these patients typically have hypotension, which is not a feature of ACE inhibitor-associated angioedema. In addition, membrane APP is encoded for by an X-linked gene, but ACE inhibitor-associated angioedema is more common in women than in men. A subsequent study found that the -2399A allele is associated with decreased plasma APP activity in both men and women, but the variant allele is associated with ACE inhibitor-associated angioedema only in men.³⁴

Neprilysin also degrades bradykinin and substance P. Pare and colleagues³⁵ reported an association between a polymorphism in the gene encoding neprilysin and ACE inhibitor-associated angioedema of African American ancestry in a case-control study in Tennessee as well as in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). The investigators also conducted a genome-wide association study in 175 individuals with ACE inhibitor-associated angioedema and 489 ACE inhibitor-exposed controls without angioedema from Nashville (Tennessee) and Marshfield (Wisconsin). No associations of genome-wide significance were found. Of the SNPs that were associated modestly with ACE inhibitor-associated angioedema in the Nashville/Marshfield analysis, 2 were also significantly associated with ACE inhibitor-associated angioedema (rs500766 and rs2724635) in ONTARGET cases versus controls. Rs500766 is a polymorphism in the gene encoding protein kinase C θ (PRKCC). In both the Nashville/Marshfield sample

(odds ratio [OR], 0.42; 95% confidence interval [CI], 0.28–0.63; $P = 2.97 \times 10^{-5}$ in the additive model; OR, 0.42; 95% CI, 0.26–0.67; $P = 3.04 \times 10^{-4}$ in the dominant model) and in ONTARGET (OR, 0.28; 95% CI, 0.09–0.89; $P = .03$ in the dominant genetic model), the T allele was significantly associated with a reduced risk of ACE inhibitor–associated angioedema. Rs2724635 is a polymorphism in ETS variant gene 6 (ETV6), also known as TEL (translocation ets leukemia), and the G allele was associated with an increased risk of ACE inhibitor–associated angioedema in both African Americans in the Nashville/Marshfield sample (OR, 2.78; 95% CI, 1.67–4.00; $P = 2.73 \times 10^{-5}$ in the additive model; OR, 3.23; 95% CI, 1.75–6.25; $P = 2.11 \times 10^{-4}$ in the dominant model; OR, 5.56; 95% CI, 1.85–16.6; $P = 2.01 \times 10^{-3}$ in the recessive model) and in the ONTARGET sample (OR, 3.27; 95% CI, 1.03–10.35; $P = .044$ recessive model). Both of these genes are involved in immune regulation and their association with ACE inhibitor–associated angioedema is intriguing given the clinical association of ACE inhibitor–associated angioedema with seasonal allergies and with immunosuppressant use.

Management of Angiotensin-converting Enzyme Inhibitor–associated Angioedema

The mainstays of the management of ACE inhibitor–associated angioedema remain recognition, discontinuation of the ACE inhibitor, and airway management. A question that often arises is whether patients who have had ACE inhibitor–associated angioedema can take an angiotensin receptor blocker (ARB) safely. Several studies suggest that it is safe to treat patients with a history of ACE inhibitor–associated angioedema with an ARB. In the Telmisartan Randomized Assessment in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial, 2 of 2954 patients (0.07%) randomized to telmisartan had angioedema and 3 of 2972 (0.1%) receiving placebo experienced angioedema.³⁶ In case-control or cohort studies, the risk of angioedema in ARB users is similar to that in the general population and significantly decreased compared with the rate of angioedema in ACE inhibitor users.^{37,38} On this basis, ARBs may be tried in patients who require interruption of the renin-angiotensin system. Because tissue ACE may be inhibited for up to 3 weeks after discontinuation of an ACE inhibitor and angioedema can recur during this period, it is recommended that clinicians allow 6 weeks before any trial of an ARB. Delayed recurrences beyond 6 weeks should raise the suspicion of another cause of angioedema.

The selective B₂ antagonist icatibant (D-Arg-[Hyp3, Thi5, D-Tic7, Oic8]-bradykinin) reduces the time to resolution of symptoms in patients with hereditary angioedema and has been approved by the US Food and Drug Administration (FDA) for treatment of hereditary angioedema.^{39,40} Three randomized clinical studies have assessed the effect of B₂ receptor antagonism in ACE inhibitor–associated angioedema.⁴¹ The first, a small multicenter study conducted in Germany, reported that icatibant reduced the time to complete resolution of ACE inhibitor–associated angioedema in patients of European descent.⁴¹ A second small study conducted in a single center in the United States did not find any effect of icatibant on the time to resolution of symptoms, or the severity of symptoms in patients with ACE inhibitor–associated angioedema.⁴² A third study, a multicenter study in 120 patients with ACE inhibitor–associated angioedema, also did not find an effect of the B₂ receptor antagonist icatibant on the time to discharge (Sinert and colleagues, *Academic Emerg Med* 2016 abstract).

The Bas and colleagues⁴¹ trial differed from the 2 studies showing no effect of icatibant in ACE inhibitor–associated angioedema in several important ways. In the Bas and colleagues⁴¹ study, assessment of injection site reactions might have inadvertently resulted in unblinding. The study used an active comparator rather than placebo control. All of the patients were white and 62% were male, whereas ACE

inhibitor-associated angioedema is more common among African Americans and women; these two groups were more prevalent in the negative clinical studies. Based on the lack of definitive evidence to support a benefit of B₂ receptor antagonism in ACE inhibitor-associated angioedema, icatibant is not approved for this indication.

The lack of effect of bradykinin B₂ receptor antagonism on symptoms in patients with ACE inhibitor-associated angioedema contrasts with the efficacy of B₂ receptor antagonism in hereditary angioedema.^{39,40} Likewise, ecallantide, a kallikrein inhibitor approved for the treatment of hereditary angioedema, is not effective in ACE inhibitor-associated angioedema.^{43,44} These findings suggest that substance P or other peptide substrates of ACE inhibitors can contribute to and perpetuate angioedema even when the B₂ receptor is blocked. Delay in treatment could also reduce the efficacy of B₂ receptor antagonism in patients with ACE inhibitor-associated angioedema. The mean time from the onset of symptoms to study drug administration ranged from 6.1 to 10.3 hours in clinical trials of icatibant in ACE inhibitor-associated angioedema.^{41,42}

DIPEPTIDYL PEPTIDASE 4 INHIBITORS AND ANGIOEDEMA

In recent years, new classes of drugs that decrease the degradation of vasoactive peptides implicated in the pathogenesis of angioedema have been approved. Dipeptidyl peptidase 4 (DPP4) cleaves the amino terminus dipeptide from peptides with a proline or alanine as the penultimate amino acids, including the incretins glucagonlike peptide-1 and glucose-dependent insulinotropic polypeptide. By decreasing the degradation of incretins, DPP4 inhibitors, approved for the treatment of diabetes, increase insulin secretion in a glucose-dependent manner, decrease appetite, and suppress glucose-dependent glucagon secretion.

Substance P is a substrate of both ACE and DPP4. Brown and colleagues⁴⁵ reported that concurrent DPP4 inhibitor use increases the risk of ACE inhibitor-associated angioedema. In the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 study, saxagliptin treatment was associated with an increased incidence of angioedema compared with placebo treatment (8 vs 1; $P = .04$),⁴⁶ which is an incidence of ~0.1%. The incidence of angioedema in other clinical trials of DPP4 inhibitors is often hard to discern because angioedema is conflated with hypersensitivity reactions.

COMBINED ANGIOTENSIN RECEPTOR BLOCKER/NEPRILYSIN INHIBITOR AND ANGIOEDEMA

Neprilysin degrades bradykinin and substance P, as well as natriuretic peptides. In the late twentieth century, a combined ACE/NEP inhibitor, omapatrilat, was developed for the treatment of hypertension and heart failure. Omapatrilat was never approved by the FDA but clinical trials implicated the neprilysin pathway in the pathophysiology of angioedema. In the Omapatrilat Cardiovascular Treatment Versus Enalapril (OCTAVE) double-blind, active-controlled trial in 25,302 patients with untreated or uncontrolled hypertension, the incidence of angioedema was 2.17% in the combined ACE/NEP inhibitor-treated group compared with 0.68% in the enalapril group.¹⁵ The incidence of angioedema was increased in patients of African descent in both the omapatrilat and the enalapril treatment groups.

The increased incidence of angioedema during treatment with omapatrilat compared with enalapril alone has been attributed to the concurrent blockade of 2 pathways involved in the degradation of bradykinin and substance P. Recently, the combined ARB/NEP inhibitor valsartan/sacubitril was approved for the treatment of

heart failure based on a beneficial effect on mortality compared with enalapril in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.¹⁷ In this study there were 19 cases of angioedema in the valsartan/sacubitril-treated group (0.45%) compared with 10 in enalapril-treated patients (0.24%). The use of valsartan/sacubitril may lead to a higher incidence of angioedema in clinical practice. In PARADIGM-HF, 77% of the patients enrolled in the trial had been treated previously with an ACE inhibitor and all patients were exposed to an ACE inhibitor during a run-in period.¹⁷ In addition, the number of African Americans studied was small and, as in ACE inhibitor-associated angioedema, the incidence of valsartan/sacubitril-associated angioedema is higher in patients of African ancestry compared with those of European ancestry.

TISSUE-TYPE PLASMINOGEN ACTIVATOR-INDUCED ANGIOEDEMA

Angioedema occurs in 1.3% to 7.9% of patients who are treated with recombinant tissue-type plasminogen activator (tPA) for ischemic stroke.^{47,48} In contrast, angioedema occurs rarely (0.02%) in patients given tPA in the treatment of myocardial infarction.⁴⁸ ACE inhibitor use is associated with a significantly increased risk of angioedema following recombinant tPA,^{47–49} suggesting that tPA administration leads to the production of a vasoactive ACE substrate. Molinaro and colleagues⁵⁰ reported that incubation of plasma with microgram-per-milliliter t-PA in the presence of the ACE inhibitor enalaprilat results in the generation of bradykinin. Bradykinin generation depended on the activation of plasminogen to plasmin, and subsequent activation of the contact system.

SUMMARY

Angioedema associated with medications can occur via bradykinin-mediated, histamine-mediated, or leukotriene-mediated mechanisms. A growing number of drugs may cause angioedema via bradykinin. The mainstay in treatment of nonallergic drug-induced angioedema is cessation of the offending agents.

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