National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Emergencies and injuries

Date of Review: 10 November 2015

Medication: Fresh Frozen Plasma

Indication: ACE-inhibitor induced angioedema

Background:

From the NEMLC meeting on 08 October 2015:

It was mentioned that there are 2 types of angioedema that are treated differently:
1. Bradykinin-mediated angioedema, hereditary, ACE-inhibitor induced angioedema
2. Hypersensitivity reaction.

For angioedema associated with hypersensitivity, it was mentioned that effective treatment is corticosteroids, epinephrine (adrenaline) and antihistamines. However, the commonest cause of angioedema in South Africa is ACE-induced angioedema treated with FFP.

Pragmatic implications: The challenge to differentiate between life-threatening angioedema caused by ACE-inhibitors or hypersensitivity reactions was discussed.

Way forward: It was proposed FFP be reviewed in this clinical setting.

Recommendation: Due diligence be applied to FFP with review of the evidence for acute treatment of life-threatening angioedema.

Objective
To review the evidence of FFP in the treatment of angioedema.

Search
Electronic databases (PubMed, Google Scholar, Cochrane Library) were searched using key words: "Fresh Frozen Plasma" or "FFP" AND "Angioedema" or "Ace-inhibitor induced angioedema".

Study selection
Systematic Reviews of RCTs / Randomised Clinical Trials (RCTs) / Prospective studies.
Population: patients with life-threatening angioedema (Hereditary, Acquired, Ace-i)
Intervention: FFP
Comparison: placebo / alternative treatment / standard of care
Outcomes: morbidity and mortality

Results of search
No SRs / RCTs or prospective studies were found addressing the role of FFP in angioedema. Evidence for the use of FFP in angioedema is limited to case reports.

FFP in hereditary angioedema (HEA)

Established therapies for hereditary angioedema include ecallantide (C1-inhibitor) or icatibant (Bradykinin-B2 receptor antagonist). There are no controlled studies directly comparing these agents with FFP.

1. **Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol. 2007 Apr;98(4):383-8.**

   Background and Methods: This was a retrospective review of cases of HEA treated with FFP.

   Results: For the treatment of HEA acute attack, FFP may be of potential benefit. In 12 patients with an acute attack, all 12 patients experienced an improvement in their symptoms within 45 minutes of FFP administration. In patients with HEA receiving FFP as prophylaxis (pre-procedure e.g. dental extraction), case reports suggest a potential benefit for the use of FFP. In a series of 12 patients, 11 out of 12 patients did not experience an acute attack after receiving FFP as prophylaxis.

Table 1. Patients in the Literature Receiving FFP for Acute Attacks of Hereditary Angioedema

Patient No./ age, y/sex	Reason for receiving FFP	Amount of FFP	Complications	Time to first sign of improvement, min	Changes	Reference
1/29/M	Edema of face and arm, followed by laryngeal edema requiring tracheostomy	400 mL	None	45	Complete resolution within 12 h	5
2/22/F	Back pain, abdominal pain, and vomiting	400 mL	Possible increased pain in first 20 minutes	45	Complete resolution within 90 min	5
3/29/M	Facial edema (6 visits with similar outcomes)	2 U	None	Not specified	Improved each hospital visit	8
4/19/F	Hoarseness followed by SOB requiring intubation and loss of consciousness	3 U	None	40	Improvement within 40 min	9
4/19/F	Throat swelling and severe abdominal pain	1 U	None	30	Complete resolution within 2 h	9
5/41/M	Angioedema of left forearm, abdominal colic, and vomiting	1,000 mL	None	90	Complete resolution within 12 h	10
6/71/F	Abdominal pain and vomiting	750 mL	Transient increased colicky pain in first minutes of infusion	Not specified	Pain free within 2 1/2 h	10
7/17/M	Abdominal pain and vomiting	750 mL	None	<40	Symptom free within 2 h	10
8/19/M	Facial edema	900 mL	None	Not specified	Resolution of symptoms	11
9/56/M	Lip and facial swelling	2 U	None	Not specified	Improved	12
10/24/F	Abdominal pain, vomiting, tachycardia, and hypotension	Not specified	None	Not specified	Improved	13
11/26/F	Respiratory distress, stridor, and pharyngeal edema.	1 U	None	Not specified	Some improvement	14

Abbreviations: FFP, fresh frozen plasma; SOB, shortness of breath.

Table 2. Patients in the Literature Receiving FFP for Prophylaxis for HAE

Patient No./ age, y/sex	No. of patients	FFP dosage, U	Reason for receiving FFP	Complications	Outcome	Reference
1/18/F	1	1 twice weekly	Long-term prophylaxis for HAE during pregnancy	None	Reduction in frequency and severity of attacks	4
2 and 3/34–49/ not specified	2	2 before and 2 during	Prophylaxis for tooth extraction	None	Successful prophylaxis	16
4/29/M	1	2	Prophylaxis for teeth extractions	None	Successful prophylaxis	17
5/21/F	1	2	Prophylaxis while undergoing a cesarean delivery	None	Successful prophylaxis	18
6/10/F	1	2	Prophylaxis for teeth extractions	None	Successful prophylaxis	19
7/30/F	1	3	Prophylaxis for multiple dental restorations and extractions	None	Successful prophylaxis	20
8/21/M	1	2	Prophylaxis for teeth extractions	None	Successful prophylaxis	21
9/40/F	1	2	Prophylaxis for tooth extraction	None	Failed prophylaxis during surgery on day after FFP infusion with laryngeal edema requiring intubation	22
10/45/F	1	2 before and 1 during	Prophylaxis for teeth extractions	None	Successful prophylaxis	23
11/32/F	1	2	Prophylaxis for teeth extractions	None	Successful prophylaxis	24
12/22/M	1	2	Prophylaxis for tooth extraction	Vesiculobullous lesions successfully treated with diphenhydramine	Successful prophylaxis	25

Abbreviations: FFP, fresh frozen plasma; HAE, hereditary angioedema.

FFP for angiotensin-converting enzyme inhibitor (ACE-I)-induced angioedema

ACE is involved in the degradation of bradykinin. By inhibiting ACE, and consequently increasing bradykinin levels, ACE-i are believed to cause angioedema. FFP contains kininase II, which degrades bradykinin in an identical manner to ACE, thus providing a rationale for the use of FFP in ACE-i induced angioedema.

2. **Hassen GW, Kalantari H, Parraga M, Chirurgi R, Meletiche C, Chan C, et al. Fresh frozen plasma for progressive and refractory angiotensin-converting enzyme inhibitor-induced angioedema. J Emerg Med. 2013;44(4):764-72**

   Background and Methods: This was a retrospective case series that reported on cases of patients who were treated with FFP for progressive and refractory presumed ACE-induced angioedema.

   Results: Need for intubation was avoided in one patient with tongue swelling, and reducing facial and lip swelling in one patient. There were no adverse reactions to the administered FFP reported in any patients. It was up to the treating physician how many units of FFP were administered. There was a beneficial temporal association between FFP administration and improvement of symptoms in all cases.

3. **Culley CM, DiBridge JN, Wilson GL Jr. Off-Label Use of Agents for Management of Serious or Life-threatening Angiotensin Converting Enzyme Inhibitor-Induced Angioedema. Ann Pharmacother. 2015 Sep 28. pii: 1060028015607037**

   Background and Methods: This was an extensive literature review to evaluate the role of FFP, C1 esterase concentrate (C1-INH), ecallantide, and icatibant in the management of angiotensin-converting enzyme inhibitor–induced angioedema (ACEI-IA). The results pertaining to the use of FFP are relevant to this EML Medication Review. The search was performed using PubMed (1946 through August 2015) and Embase (<1966 through August 2015). References from identified articles were reviewed. Consensus papers, practice guidelines, case reports/series, clinical trials, and meeting abstracts published in English and involving humans were included.

Results: Emerging evidence suggests that FFP may be effective for use in ACEI-IA. Positive efficacy results were reported with FFP.

Table 1. Summary of Select Published Case Reports/Series of Fresh Frozen Plasma (FFP) for ACEI-Induced Angioedema Treatment.[18-21]

First Author (Year)	Demographics	Offending Agent(s)	Angioedema Presentation	Treatment Course: Initial	Treatment Course: Outcome	Treatment Course: Second/Third-Line	Time to Stop of Progression/ Symptom Resolution and Discharge
Case reports							
Karin[18] (2002)	75-year-old Afro-Caribbean M; PMH: ischemic heart disease, hypertension	Lisinopril	Marked tongue swelling over several hours; no facial or lip swelling, normal vocal cords	S, A, E Repeat × 1	Progressive tongue swelling requiring intubation and ventilation	After 24 hours, FFP 4 units	Within 2 hours of FFP dramatic improvement, extubated and breathing spontaneously
Warrier[19] (2004)	43-year-old W; PMH: hypertension	Ramipril 10 mg twice daily for 4 days	Mar 2002: Angioedema of lips and fingers	S, A, E	Resolved; lower dose restarted, then increased to 10 mg twice daily over next week		
		Ramipril 10 mg twice daily for 3 weeks	August 2002: severe upper lip and tongue edema	S, A, E (multiple doses), H2 Other treatments: antileukotrienes, cyclosporine, IVIG	Edema persisted next few days; transferred to another facility	On transfer: FFP 2 units	Within 2-4 hours of FFP
Yates[21] (2014)	87-year-old M; PMH: hypertension, Parkinson's disease, dementia	Enalapril for years (unknown dose or exact duration)	Severe tongue edema; no itching, urticaria, or other signs of allergic reaction	FFP 2 units			Discharged 4 hours after treatment
Case series							
Hasson[20] (2013)	49-year-old AA W; PMH: diabetes, hypertension, asthma	Lisinopril (1 year), metformin (2 days)	Swelling in right lower lip that had progressed, pruritus over body, and diarrhea; no tongue, soft palate or pharynx involvement	• S, A, E, H2 • Repeat 2 hours later: S, A, E, H2	Symptom progression: respiratory distress, tongue heaviness, swelling upper and lower lips (doubled in size), and right buccal area involved	FFP 2 units (7 hours after initial treatment)	• Within 2 hours • Admitted to ICU and discharged 2 days later
	64-year-old AA M; PMH: hypertension, hepatitis C, HIV	Lisinopril 40 mg (1 year)	New onset of upper and lower lip swelling; no tongue, soft palate, or pharynx involvement	• S, A, E, H2 • Repeat 4 hours later: S, A, E, H2	Progression of lip swelling (doubling) and face swelling	FFP 3 units (7 hours after initial treatment)	• Within 4 hours • Observed in ICU with improved symptoms; signed out AMA the following day

Table 1. (continued)

First Author (Year)	Demographics	Offending Agent(s)	Angioedema Presentation	Treatment Course: Initial	Treatment Course: Outcome	Treatment Course: Second/Third-Line	Time to Stop of Progression/ Symptom Resolution and Discharge
	58-year-old Hispanic M; PMH: hypertension, episode of right facial rash and swelling 2 years after started lisinopril, but continued ACEI	Lisinopril 30 mg (~3 years)	Gradual onset of upper and lower lip swelling and itching around mouth, felt apprehensive, shortness of breath, tongue swelling; no soft palate or pharynx involvement	• S, A, E, H2 • Repeat 2 hours later: S, A, E, H2	Progression of lip and tongue swelling	FFP 2 units (2.5 hours after repeat dose)	• Within 3 hours • ICU admission; discharged 2 days later
	62-year-old Hispanic M; PMH: hypertension	Enalapril (unknown dose or duration)	Right facial and lip swelling; no tongue, soft palate, or pharynx involvement	• S, A, E, H2 • Repeat 2.5 hours later: S, A, E, H2	Lip swelling worsened	FFP 2 units (5 hours after repeat dose)	• Within 2 hours • ICU with improved symptoms; signed out AMA following day
	51-year-old AA W; PMH: hypertension, diabetes	Lisinopril (unknown dose or duration)	Lip swelling for five hours; no tongue, soft palate, or pharynx involvement	S, A, H2 (no E due to coronary artery disease)	Symptoms progressed over next 3 hours	FFP 2 units (3 hours later)	• After FFP, lip swelling stopped • ICU; discharged 2 days later
	73-year-old AAM; PMH: hypertension, chronic renal disease, diabetes	Lisinopril (unknown dose or duration)	One-day history swelling of face and tongue; no soft palate or pharynx involvement	• S, A, E, H2 • Repeat 3 hours later: S, A, E, H2	Worsening symptoms	FFP 2 units (2 hours after repeat dose)	• Within 2 hours • ICU admission with symptoms resolving the next day, transferred to floor; signed out AMA on day of transfer
	45-year-old AA M; PMH: hypertension	Enalapril 10 mg (unknown duration)	Lip swelling; no tongue, soft palate or pharynx involvement	• S, A, E, H2	Symptom progression	FFP 1 unit (3 hours after initial)	• Within 2 hours • Monitored bed; discharge next day

Abbreviations: A, histamine-1 antihistamine; AA, African American; ACEI, angiotensin-converting enzyme inhibitor; AE, antivenin; AMA, against medical advice; E, epinephrine; FFP, fresh frozen plasma; H2, histamine-2-receptor antagonist; ICU, intensive care unit; IVIG, intravenous immunoglobulin; M, man; PMH, past medical history; S, steroid; W, woman.

Summary

There is a good rationale for using FFP in the treatment of bradykinin-mediated angioedema. However, there is a lack of robust evidence in the form of prospective controlled studies supporting its use in this setting. Current available evidence is limited to case reports / case series.

References

1. Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol. 2007

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2. Hassen GW, Kalantari H, Parraga M, Chirurgi R, Meletiche C, Chan C, et al. Fresh frozen plasma for progressive and refractory angiotensin-converting enzyme inhibitor-induced angioedema. J Emerg Med. 2013;44(4):764-72
3. Culley CM, DiBridge JN, Wilson GL Jr. Off-Label Use of Agents for Management of Serious or Life-threatening Angiotensin Converting Enzyme Inhibitor-Induced Angioedema. Ann Pharmacother. 2015 Sep 28. pii: 1060028015607037