RESEARCH PROTOCOL

SHARED study

Saguenay Clinical Decision Rule for Quick Leave emergency after a diagnosis of anaphylaxis

- Protocol phase 2 -

Project to be submitted to the Ethics Committee and
CIUSSS scientist in Saguenay - Lac-St-Jean

Emergency service
CIUSSS du Saguenay - Lac-St-Jean

Department of Family Medicine and Emergency Medicine
Faculty of Medicine and Health Sciences
Université de Sherbrooke

Version of the 25 Feb. 2020

1. PROBLEM

Anaphylaxis is a condition frequently encountered in emergency departments (0.05 to 2% in the general population)[1], which is defined by a severe allergic reaction that appears quickly and has fatal potential. As a result of an anaphylaxis, a serious phenomenon called a "biphasic reaction" can occur. This reaction is the reappearance of anaphylactic symptoms several hours after treatment.

The diagnosis of anaphylaxis is based on the impairment of more than one system (muco-skin, cardiovascular, respiratory, digestive) and its definition, the most recognized, is based on the NIAID/FAAN[2] criteria developed in 2006 (Box 1). Because of its severity, the treatment of anaphylaxis requires rapid management, which relies mainly on the administration of epinephrine. Other treatments can also be used. Among other things, antihistamics can decrease skin symptoms; intravenous hydration contributes to hemodynamic stabilization; and intravenous corticosteroids may decrease the likelihood of a biphasic reaction. However, the effectiveness of the latter treatment option remains debated in the literature.

The theoretical risk of rebound reaction, or biphasic reaction, is classically described up to 72 hours after the initial anaphylactic event. The biphasic reaction is defined as a recurrence or occurrence of new signs or symptoms after the resolution of the initial reaction, without re-exposure to the allergen[3]. The potential occurrence of a biphasic reaction often warrants observation of patients for several hours in s emergency departments following de the management of the initial anaphylaxis. Although the recommendations and guidelines generally propose observation times of four to six hours, there is no clear consensus or evidence to guide this conduct. It may even be suggested to observe patients up to 24 hours[4.5.6]. To date, thereare no prognostic factors to identify a more at-risk patient who would benefit from such an observation. As thesereactions are a relatively rare phenomenon (4 to 5%, but could be as high as 20% according to some sources[5]) and the symptoms observed are usually less significant than at the initial presentation[7], itis therefore possible that a prolonged observation period is not necessary for some patients who do not have high risk factors for biphasic reaction.

Box 1: NIAID/FAAN ANAPHYLAXIS CRITERIA

Presence of one of three following criteria:

1. Sudden onset, with/without exposure to identified allergen, of skin and/or mucousness with at least 1 of 2:
1. Respiratory disease (dyspnea, wheezing, stridor, hypoxemia, ...)
2. HypoTA or Sx associated with a dysfunction of the target organs (hypotonia/collapse, syncope, incontinence, ...)
3. Probable allergen exposure and sudden onset (minutes at hours) of at least 2 of 4:
1. Skin and/or mucousness (pruritus, rash, hives, etc.)
2. Respiratory disease (dyspnea, wheezing, stridor, hypoxemia, ...)
3. HypoTA or associated Sx (hypotonia/collapse, syncope, incontinence, ...)
4. Persistent GI Sx (abdominal pain, vomiting, ...)
5. Sudden hypotension (minutes to hours) following known allergen exposure
1. Children: 30% systolic decrease
2. Adults: 30% decrease vs. basic personal systolic tension

There are no definitive predictors, but various factors of poor prognosis are recognized. These differ slightly between studies, but some seem to return quite systematically in the literature. First, the **severity of the reaction** appears to increase the risk of biphasic reaction. "Severe" means, reactions that initially required **1 dose of epinephrine,** those requiring a higher dose of epinephrine or an intravenous hydration bolus.[8] Also, patients with **hypotension, pharyngeal edema or severe respiratory distress** upon arrival at the emergency department are among the reactions considered "severe"[9]. Patients with a total duration of **symptoms greater than 30 minutes** also appear to be at greater risk[10.] On the other hand, **delayed administration of epinephrine or** a **late presentation** to the emergency department would also increase the risk of adverse developments.[11] Finally, a **history of anaphylaxis** and exposure to an **unknown allergen** would be two additional risk factors for biphasic reaction[12].

It should be noted that most studies dealing with biphasic reactions exclude patients chronically taking corticosteroids, antihistamines, or beta-blockers, as well as patients on immunosuppressants[6]. It is therefore difficult to apply any conclusions to these populations.

1. RELEVANCE

In the current context of increasing emergency department traffic aux and the introduction of newgovernment, ministerial and institutional requirementsto limit emergency room wait times and stretcher time, we believe it is essential to question our practices in order to release patients more quickly and safely by limiting the periods of unreachable observation. Our research team, composed mainly of emergency physicians, hypothesizes that if onlyone's clinical decision rules remainaivalid in the subsequent stages ofour project, it is likely that some patients who have had an anaphylactic reaction may be released much earlier than the current conduct. A simple, generalized and valid clinical decision rule would therefore be an interesting asset for the modern practice of emergency medicine.

These rules could also contribute to the satisfaction of patients who would spend less time in the ER. Also, such ruless willenprovide clear guidanceto clinicians working in lower-flow settings, where the incidence of anaphylaxis is lower and therefore clinical experience is less sharp. Finally, these ruless will beenrelevants for teaching purposes for the various learners who do internships in our emergency departments.

Our group of emergency medicine clinicians has therefore decided to start a research project to identify the rules of clinical decision following an anaphylaxis in an emergency context.. This project was developed in collaboration with the three emergency departments of Saguenay-Lac-St-Jean (Chicoutimi, Jonquière and Alma).

1. STEPS TAKEN

A review of the literature (phase 0; Rapid review) and phase 1 of the project (statistical derivation of two clinical decision rules) have already been completed. The initial "rapid review" literature review was to highlight the main elements that appeared to be predictors of a biphasic reaction. These elements led to the development of an initial clinical decision rule that included 7 variables (Table 1).

Table 1: CLINICAL DECISION RULE ORIGINALLY DEVELOPED FROM THE RAPID REVIEW OF THE LITERATURE

Promote an observation if one of the following is present:
1. Time before the first dose of 60min
2. Severe symptoms (hypoTA, respiratory sx, vomiting, intubation, syncope, incontinence)
3. Time before symptom resolution - 40 min
4. Anaphylaxis ATCD
5. Number of doses of EPI IM - 1
6. Asthma ATCD
7. No administration of glucocorticoids

Conflicting data in the literature review, a criterion included as exploratory in the "literature-based" rule

However, for the purpose of publishing our Phase 0 (literature review), the analysis of all articles included in the initial literature review (rapid review) was redone by another team member. As a result of this comprehensive review of each article, the literature review has moved from the "rapid review" to the "systematic review" type and minor changes have had to be made to the rule based on the literature review (below).

Table 2: CLINICAL DECISION RULE FROM SYSTEMATIC LITERATURE REVIEW

Promote an observation if one of the following is present:
1. Time before the first dose of 60min
2. Severe symptoms (hypoTA, respiratory sx, vomiting, intubation, syncope, **arrhythmias, diarrhea)**)
3. Time before symptom resolution - 40 min
4. Anaphylaxis ATCD
5. Number of doses of EPI IM - 1
6. **Unknown allergen**
7. No administration of glucocorticoids

Conflicting data in the systematic literature review, a criterion included as exploratory in the "literature-based" rule

Thus, in terms of the criterion of severe symptoms of the initial anaphylactic reaction, we added arrhythmias, the presence of diarrhea and we removed incontinence. The asthma history criterion was removed from the rule and we added an unknown allergen.

In Phase 1 of the study, two other clinical decision rules were derived retrospectively. By analyzing the characteristics of patients who had an anaphylactic reaction, we were able to derive a rule to identify a low-risk group of biphasic reaction (any symptom of allergy) and clinically significant biphasic reaction (i.e. meeting the criteria for an anaphylactic reaction). These rules were created with the highest possible negative predictive sensitivities and values (VPNs).

The next step is to prospectively verify whether these rules maintain their sensitivity and negative predictive value with a different sample of patients from the same population pool. The first rule assesses the probability of clinically significant biphasic reactions (sensitivity of 90%, 7 variables; Table 3) and the second, all biphasic reactions (100%, 7 variable sensitivity; Table 4).
Areas below the ROC curve were 0.896 and 0.874,respectively. Because the variables selected for each decision-making rule come from a regression model, the predicted probability of a biphasic reaction comes from the linear combination of selected variables. Depending on the coefficients calculated, each variable present in the patient will have a different weight in the decision.

TABLE 3: RETROSPECTIVELY DERIVED CLINICAL DECISION RULE FOR CLINICALLY SIGNIFICANT BIPHASIC REACTIONS

1.	ATCD allergy to a different agent than the one in question
2.	Symptoms of diarrhea
3.	ATCD allergy to the same agent as the one in question
4.	Number of doses of O.R. in the emergency room
5.	Food allergen (other than milk, egg, peanuts, seafood)
6.	Number of doses of O.R. before emergency 1
7.	ENT symptoms

TABLE 4: RETROSPECTIVELY DERIVED CLINICAL DECISION RULE FOR BIPHASIC REACTIONS (ALL SEVERITIES CONFUSED)

1.	Number of doses of O.R. in the emergency room
2.	Epi doses data different from standard doses (ped: 0.01mg/kg, adult: 0.3-0.5mg)
3.	Symptoms of diarrhea
4.	ATCD allergy to a different agent than the one in question
5.	Secondary anaphylactic reaction to iodine
6.	Secondary anaphylactic reaction to a sting or bite
7.	Secondary anaphylactic reaction to an unknown allergen

Note that the first two criteria of the rule for all the combined severity of biphasic reactions (Table 4) were, at the time of diversion, contained in a single criterion: "standard or non-standard doses of IM epinephrine." However, because this criterion contained several pieces of information, it was divided into two new criteria to simplify and clarify data collection. For the first criterion (number of doses of ER in the emergency department), not receiving repeated intramuscular doses of epinephrine decreased the likelihood of having a biphasic reaction. For the second criterion (differentear doses from standard doses), receiving standard intramuscular doses of epinephrine decreased the likelihood of having a biphasic reaction compared to receiving non-standard intramuscular doses of epinephrine.

1. GOALS AND ASSUMPTIONS

The main objective of Phase 2 of our study is to validate prospectively and on a theoretical basis the rules of clinical decisions from previous phases of our research project. This will allow us to assess the internal validity of the different rules derived in the same three circles (Chicoutimi, Jonquière, Alma). In addition, the evaluation of the results will identify the most effective rule.

The hypothesis of this study is that one of the derived rules will, when applied to a cohort of patients prospectively, adequately identify (sensitivity maintained) patients at low risk of biphasic reaction following an anaphylactic reaction.

If the results of the Phase 2 study are successful, a phase 3 will be put forward. The objective of this third phase will be to apply the most effective rule in real time to patients who have undergone an anaphylactic reaction in different hospitals of the RIUSSS of the University of Sherbrooke, i.e. to complete the validation of the rule in a different population.

In the event of an inconclusive Phase 2 result for the three rules under study, the investigators propose to group the data from Phases 1 and 2 to attempt a final diversion of a new clinical decision rule. If this ultimate diversion is quite different from the previously tested rules and is clinically plausible, a new validation attempt will be made (details below).

1. METHODOLOGICAL

Based on the three rules of clinical decision (2 derivatives and one based on the literature review), a prospective observational study will be carried out in the emergency departments of Chicoutimi, Jonquière and Alma. Data collection for this theoretical validation phase has been underway since December 2019, having received the approval of the various local research committees (ethics, scientific and convenience).

Inclusion and exclusion criteria

The inclusion criteria will be: all patients of minor or adult age who have had anaphylaxis that meet the known diagnostic criteria. In addition, if a patient presents with confirmed exposure to an allergen and symptoms that do not yet meet the anaphylaxis criteria, they may be included in the study. This will only be possible if the doctor deems that he will inevitably progress to anaphylaxis andtreat him in this way. Those who have had a reaction to taking a drug (e.g. IECA), who are known for a hereditary pathology (hereditary angioedema),immune or other pathology giving an anaphylactoid reaction will be excluded, as in Phase 1 of the study.

Sample size

The required sample size was adjusted for the primary objective based primarily on the study of sensitivity and specificity. As a low prevalence of biphasic reactions is expected, a calculation based on specificity is useless, therefore to be rejected. Thus, using the statistician involved in the study and using a sample size calculation adapted for a confidence interval on a ratio adjusted according to the Buderer[13]formula, it was determined that it was necessary to have 553 patients in total to estimate a sensitivity of at least 98% with a confidence level of 95% according to an accuracy of 5% and an expected prevalence of 6%. Note that a 10% rate was added to the initial size calculation to manage the possibility of missing data. The prevalence of 6% was determined from the prevalence of biphasic reactions observed when collecting Phase 1 data from the same study..

Data collection

In the face of a case of anaphylaxis, the doctor will have to answer a short questionnaire developed with the variables present in each of the three rules(questionnaire available in appendix). The variables were randomly arranged on the questionnaire so that no rules could be recognized or inferred. If the doctor deems that a patient who does not yet present the anaphylaxis criteria, but in the absence of ahead,willeventually progress to real anaphylaxis, he or she will have to indicate it at the appropriate location on the questionnaire. Indeed, as mentioned above, these patients will be included in the study, but we will independently analyze the results of this sample to determine if they are different from the overall results in subgroup analyses.

The questionnaire will be available at several key locations, including in the paper-based resuscitation rooms in the three emergencies where data collection will take place. The questionnaire will also be systematically placed on the file of patients with suspected anaphylaxis at triage. The doctor will be required to complete the questionnaire anonymously, but will be required to provide the patient's file number. This will be done after the initial stabilization. After completing the questionnaire, the physician will simply be able to continue to care for the patient as he would have done in accord with his standard clinical practice. No decision rules will be applied to patients. The answers provided to

the questionnaire will therefore have no impact on the clinical decisions made by the treating physician. The research team will then review each of these files to assess whether or not there was a biphasic reaction and whether it was clinically significant (according to the NIAID/FAAN[2]criteria).

At the next emergency department meetings involved, doctors will be notified of the operation of the current study. Recalls will be made as required during the course of the study to ensure the involvement of the medical profession. Administrative officers and triage nurses will also be advised to add the questionnaire to all potential anaphylaxis files.

Data analysis

Based on the data, all three rules will be theoretically applied to all included patients. This will determine which patients would have been dismissed or observed and under what rule. Subsequently, the records of these same patients will be retrospectively analyzed to determine the occurrence of biphasic reaction after the initial visit. It will be particularly interesting to assess whether the biphasic reaction occurred during the emergency observation period.

As we seek to evaluate the effectiveness of diagnostic rules, statistical analyses will focus primarily on a study of sensitivity and specificity. In order to be able to properly characterize the different derived rules, it will also be relevant to obtain the predicted positive and negative values. Confidence intervals will be built around the proportions obtained. The choice of the best derived rule will be based on the sensitivity value obtained. Indeed, we seek to maximize this parameter in order to obtain the combination of variables that will allow us to use a rule to safely discharge patients with low risk of biphasic reaction. In the event that none of the rules maintain a fairly high sensitivity and/or negative predictive value, all Phase 1 and Phase 2 data will be jointly analyzed and a re-derivation test of a statistically stronger rule will be conducted, again using logistic regression models.

Considering that the sample size has been revised, the study schedule has also been revised. It is therefore more realistic for us to expect a period of at least 2 to 3 years to complete the data collection for this phase 2. However, we propose to do an interim analysis of the results at least once a year. Data collection is currently planned for 2020 and 2021 with an initial interim analysis in May 2020. The team is ready to extend the "recruitment" period as needed to reach the 553 patients needed. Data collection is currently well underway and the goal of recruiting 200 to 250 patients per year seemsrealistic.

1. ETHICAL CONSIDERATIONS AND INSTITUTIONAL CONVENIENCE

No clinical decision rules will actually be applied to patients during this phase of the study. Doctors will therefore take care of patients according to their usual practice. In addition, the questionnaire will only be completed after the initial stabilization of the patient, and will not result in delay in its management. We therefore consider that the risk to patients associated with this study is negligible or non-existent.

To preserve the anonymity of patients, the questionnaires, once completed, will be placed in sealed envelopes. They will only be opened when the results are analysed by the doctors involved in the study. In addition, when counting the data, patients will be identified by a different random number, which will be associated with their file number. The "key file" of correlation between file numbers and identifier numbers will be securely retained by members of the search team.

The involvement of clinical staff will be minimal. The administrative officer will be responsible for putting the questionnaire sheet on the record of the user who presents himself with potential anaphylaxis when creating it. The officer will also be responsible, upon closing the emergency file, for removing the questionnaire sheet from the clinical file, ensuring that it is properly identified and keeping it in a secure stream for the study investigators..

The triage nurse, beyond her usual role of triage and identification of potential anaphylaxis cases, will also be responsible for attaching a questionnaire sheet to the file, weather permitting.

The attending physician, on the other hand, will only have to check, depending on the case, the appropriate boxes on the questionnaire sheet once his patient has stabilized.

1. SCHEDULE

Phase 2 will begin as soon as possible or in December 2019. Other steps will take place in the following months, such as:

October 2019: 1. Writing the Phase 2 protocol 2. Asks the Ethics, Scientific and Institutional Convenience Committee of the Saguenay-Lac-Saint-Jean CIUSSS for approval.
November 2019: 1. Introducing the study to emergency departments (department meetings)
December 2019 1. Start of data collection
January and February 2020: 2. Scholarship application 3. Review and Amendment of the Research Protocol (following the external evaluation requested by FRIPS)
February and March 2020: 4. Submission of the amended protocol to the Ethics, Scientific and Institutional Convenience Committee of the CiUSSS of Saguenay-Lac-Saint-Jean for approval
April 2020: 5. Statistical analysis of results (first interim analysis)
May 2020: 6. Presentation of the study at the research day of the Department of MF/MU of the University of Sherbrooke

June 2020 to April 2021: 7. Continued data collection
May 2021: 8. Second interim analysis 9. Presentation of the progress of the study at the research day of the department of MF/MU of the University of Sherbrooke
End of 2021 10. Final Analysis or Request for Extension 11. Consideration of results and possible publication 12. Creating a poster and presenting it in various contexts (to be specified) 13. Planning for Phase 3 of the project

1. POTENTIAL OUTCOMES

If one of the clinical decision rules is sufficiently effective during this phase of the study (phase 2),i.e. maintaining good sensitivity and negative predictive value, it can be applied in real time. If more than one rule is effective, the most easily applicable rule will be chosen. This will be done as part of a phase 3 study with systematic follow-up for each patient for whom the rule has been applied.

If Phase 3 proveserait conclusive,, the rule demonstrates has a strong negative predictive value during its actual clinical use and good external validity,andit will be disseminated on a larger scale. Thus, we hope to facilitate the management of anaphylaxis in the emergency room by allowing **the early and safe release** of many patients who have been treated for an anaphylactic reaction,ensuring that the risks of biphasic reactions are minimized..

The rule bearing the name of the geographic region from which it originates could help to spread the environment of the CIUSSS SLSJ. In addition, having received financial assistance and support from the MF/MU department of the University of Sherbrooke, the investigators will ensure that the name of the University and the Department they represent is clearly visible in their publication; also helping to spread the way of thisinstitution.

1. BIBLIOGRAPHIE

1. Campbell, R., Kelso, K., Walls, R., Feldweg, A., (2018). *Anaphylaxis : Acute diagnosis,* Uptodate. Repéré à https://www.uptodate.com/contents/.
2. Sampson HA, Muñoz-Furlong A, Campbell RL et coll. Second Symposium on the Definition and Management of Anaphylaxis: Summary Report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117:391-7.
3. Grunau, B., Wiens, M., Rowe, B., McKay, R., Li, J., Won Yi, T., Stenstrom, R., Schellenberg, R., Grafstein, E., Scheuermeyer, F. (2015). Emergency Department Corticosteroid Use for Allergy or Anaphylaxis Is Not Associated With Decreased Relapse, *Annals of Emergency Medicine,* 66(4), 381 - 389.
4. Cheng, A. Société canadienne de pédiatrie, Comité de soins aigus (2011), Le traitement d'urgence de l'anaphylaxie chez les nourrissons et les enfants, *Paediatric Child Health,* 16 (1), 41-6.
5. Tintinalli, J. E., Stapczynski, J. S., Ma, O. J., Yealy, D. M., Meckler, G. D., Cline, D. M., (2016), *Tintinalli's Emergendy Medicine, A Comprehensive Study Guide* (8e éd). McGraw-Hill Education.
6. Marx, John A. and al. (2014) *Rosen's Emergency Medicine : Concepts and Clinical Practice* (8e ed). Elsevier Saunders.
7. Lieberman, P., Kelso, J., Feldweg, A. (2018), *Biphasic and protracted anaphylaxis,* Uptodate. Repéré à https://www.uptodate.com/content/.
8. Mehr, S., Liew, W. K., Tang, M. L. K., (2009), Clinical predictors for biphasic reactions in children presenting with anaphylaxis, *Clinical and Experimental Allergy,* 39, 1390 - 1396.
9. Lieberman, P. and al, (2015). Anaphylaxis - a practice parameter update, *Annals of Allergy, Asthma and Immunology,* 115, 341 - 384.
10. Kim, T., Yoonm ,S. H., Lee, S., Choi, Y. H., Park, C. M., Kang, H., Cho, S., (2018), Biphasic and protracted anaphylaxis to iodinated contrast media, *European Radiology,* 28, 1242 - 1252.
11. Alqurashi, W., Stiell, I., Chan, K., Neto, G., Alsadoon, A., Wells, G., (2015), Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis, *Annals of Allergy, Asthma and Immunology,* 115, 217 - 223.
12. Alqurashi, W., Ellis, A., (2017), Do Corticosteroids Prevent Biphasic Anaphylaxis? *Journal of Allergy and Clinical Immunology*, 5(5), 1192 - 1205.
13. Syed Mustansir Hussain Zaidi et Al., Sample size estimation of diagnostic test studies in health sciences, *Proc. 14th International Conference on Statistical Science*s, Karachi, Pakistan, March 14-16, 2016, Vol. 29, pp. 239-246.

1. APPENDIX: QUESTIONNAIRE SHARED - Phase 2 study (validation)

To be filled for any patient with an anaphylactic reaction AFTER initial management but BEFORE discharge

Site of the visit: Chicoutimi Jonquière Alma □□□

Date : _____

Time of arrival in the emergency room:

The time at which this questionnaire is completed:

The patient meets the criteria for an anaphylactic reaction: yes no □□	*If answered **no** to the last question:* the patient confirms exposure to an allergen and I believe that it will inevitably evolve towards an anaphylactic reaction. yes no □□

Time of onset of symptoms:
Exact time: **- ESTIMATEd** time:

Hours of cob doses:
1[is]_____, 2,[and]_____, 3,[and] _____, 4,[and] _____, 5[and]_____, 6,[and]_____

History

ATCD allergy to an allergen other than the one involved. yes no □□
ATCD of allergy to the allergen involved. yes no □□
ANAphylaxis ATCD. yes no □□
Asthma ATCD. yes no □□

Allergen

Insect bite or bite. yes no □□
Iodine. yes no □□
Unknown allergen. yes no □□
Food allergen other than milk/peanuts/eggs/seafood. yes no □□

Symptoms

Severe symptoms (hypoTA, respiratory sx, vomiting, intubation,syncope, arrhythmias). yes no □□
ENT symptoms. yes no □□
Diarrhea. yes no □□
Time before symptom resolution - 40 minutes. yes no □□

Treatment

Time before the first dose of ear - 60 minutes. yes no □□

Number of doses of epi IM - 1. yes no ☐☐
Number of ear doses before emergency room arrival. yes no ☐☐
Number of ear doses in the emergency room. yes no ☐☐
Epi doses data different from standard doses (ped: 0.01mg/kg, adult: 0.3-0.5mg). yes no ☐☐
Administration of glucocorticoids. yes no ☐☐

Section reserved for investigators

Rb. yes no ☐☐

RBCS. oui non ☐☐

Mr. RPOU. yes no ☐☐