7/9/2019
Study title: Early Administration of Steroids in the Ambulance Setting: An Observational Design Trial “EASI-AS-ODT”
NCT03962894
Study Protocol and Statistical Analysis Plan

Title

Early Administration of Steroids In the Ambulance Setting: An Observational Design Trial

"EASI-AS-ODT"

Study Location

Lee County EMS: Lee EMS serves Florida's Lee County, located in southwestern Florida. Lee County's division of EMS operates under a license by the Florida Department of Health. Lee County serves a population estimated by the US Census Bureau as 739,000, 18% of whom are under 18 years of age, and 5% of whom are under 5 years of age. Lee County EMS responds to over 70,000 annual emergencies from 36 EMS stations, and the workforce is comprised of both EMT-paramedics and EMT-Basics. Per usual dispatch protocol and Lee EMS treatment protocol, the pediatric asthma patients experiencing an acute exacerbation (and all respiratory distress patients, for that matter) are treated and transported by EMT-paramedics (i.e., advanced life support (ALS)-level care), the highest level of care in the Lee County EMS system).

Nassau County Fire Rescue Department: Nassau County Fire Rescue Department serves' Florida's Nassau County, the northeastern most county in Florida. Nassau's estimated population under 18 years of age is 16,544 according to the US Census Bureau. Nassau County is comprised solely of EMT-Paramedics (approximately 120), and contains a specific standard operating protocol for pediatric asthma exacerbations.

Sarasota County EMS: Sarasota County EMS serves a Southwest Florida population of over 400,000 people, 14% of whom are under the age of 18. Sarasota EMS employs over 20 ambulance stations to serve that growing population.

Leon County EMS: Leon County EMS serves a population in Florida's panhandle of nearly 300,000, of whom 18% are under the age of 18. Leon County uses 19 ambulance crews to cover 671 square miles and serve an annual call volume of over 30,000.

Walton County Sheriff's Office Fire and Rescue Division: Walton County serves a rural population of over 70,000 persons (20% of whom are under the age of 18 years) in Florida's panhandle with over 100 providers.

Cincinnati Children's Hospital Medical Center: Investigators in Cincinnati have compiled a database of pediatric EMS encounters that include encounters before and after an EMS guideline change they performed in 2016 that added an oral steroid option (prednisolone) for children treated by EMS with an asthma exacerbation.

Baylor College of Medicine, Houston, TX: Investigators in Houston have compiled a dataset of pediatric EMS encounters that include encounters before and after an EMS guideline change performed in 2014 which added an oral steroid option (dexamethasone) for children treated by Houston EMS with an asthma exacerbation who were transported to Texas Children's Hospital.

Study Type

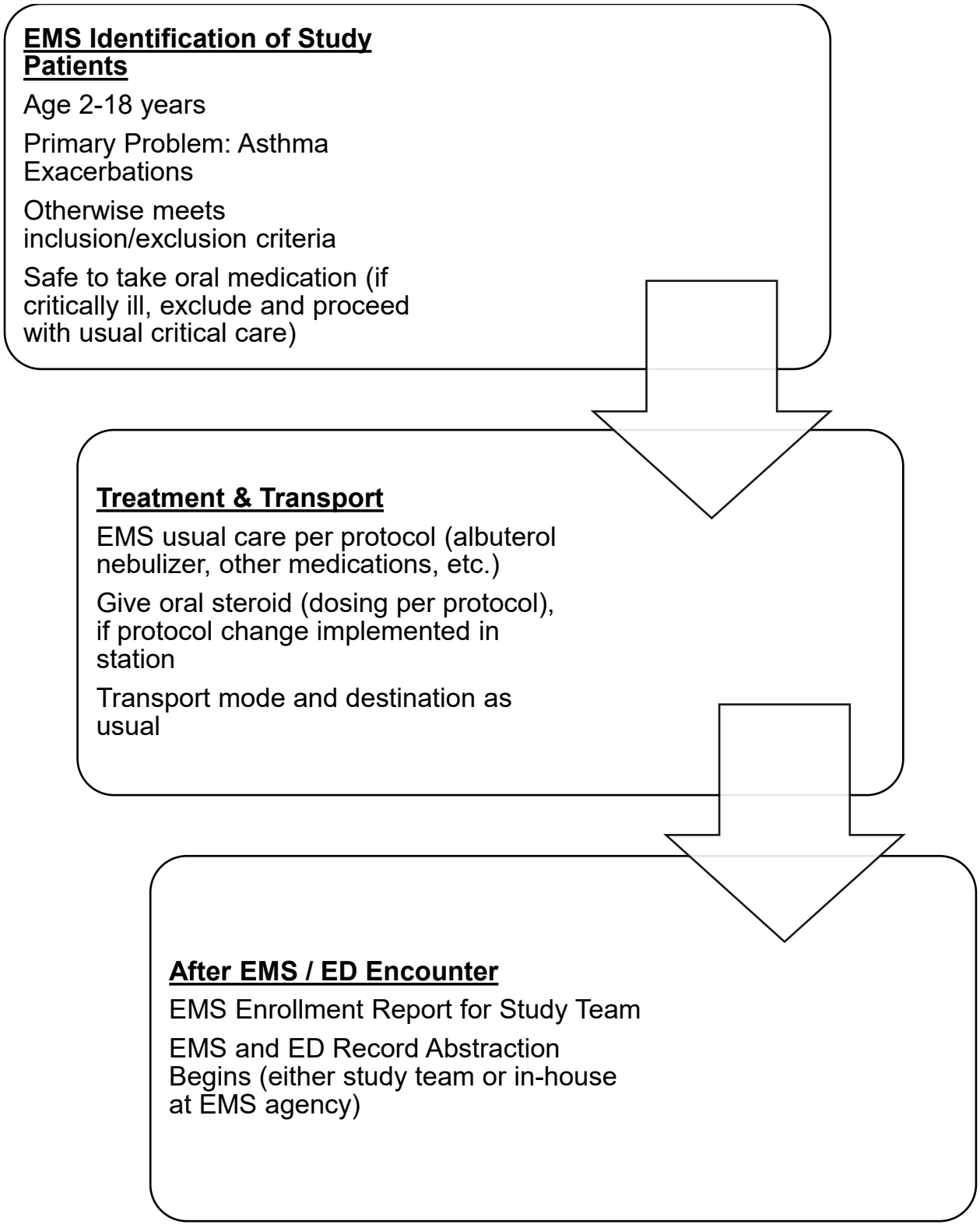
Observational study

This study is an observational study administered by EMS to pediatric asthma patients ages 2 to 18 years. In a pediatric asthma protocol update, all agencies are adding an oral steroid option for all asthma patients except for those who meet certain exclusion criteria, including those who are not stable to take an oral medication. Therefore, we will analyze outcomes from patients who do and do not receive oral steroids from EMS.

Table 1: Inclusion and Exclusion Criteria

Inclusion	**Exclusion**
Ages 2-18 years	Unconscious, hemodynamically unstable, or critically ill -> EMS will proceed with usual critical care (includes IV methylprednisolone as per protocol)
Primary problem: asthma attack	Daily or every other day CS therapy, CS given for this exacerbation at home by legal guardian or in office by medical practitioner
Safe to take an oral medication	Allergy to prednisolone or another CS
Transported by EMS to an ED	Chronic lung disease besides asthma, airway anatomic abnormalities, tracheostomy, immunocompromised, traumatic injury, pregnancy, law enforcement custody, non-English speaking

Data for 12 months before and 12 months after each EMS agency adds an oral CS option to their existing IV CS option will be abstracted from the EMS and ED EMR records. All sites will send de-identified data already linked to ED outcomes from their pre-existing EMS database via RedCap.



Study Data Variables

PHI is only collected to accomplish EMS to ED record linkage. PHI variables used for linkage are marked below. PHI will be used by local sites to accomplish this linkage. PHI will not be recorded in RedCap nor transmitted to the main site.

EMS EMR:

- Date of Service (for linkage)
- Name (for linkage)
- EMS Record Identifier (ID) (for linkage)
- Date of Birth (for linkage)
- Home Address (for linkage)
- Age
- Race
- Ethnicity
- Gender
- EMS Scene Location Address
- Any medications given prior to EMS Arrival
- All EMS vital signs and clinical assessments
- All other EMS-administered medications
- All EMS procedures
- EMS Times: Dispatch to scene arrival, scene time, transport time, ED turnaround time
- Dispatch Complaint
- Provider Primary Impression
- Provider Secondary Impression
- Injury (Yes/No)
- ED destination facility name
- Date and Time of arrival at destination facility

ED EMR: *(duplicate demographic information is collected for record linkage purposes)*

- Date of Service (for linkage)
- Name (for linkage)
- Date of Birth (for linkage)
- Home Address (for linkage)
- Age
- Gender
- Race
- Ethnicity
- Insurance (*for economic analysis*)
- Mode of Arrival
- Vital Signs
- All ED administered medications
- All ED procedures
- ED diagnoses
- ED LOS (minutes)
- ED Disposition (Admit - Yes/No/Transfer)
    - If Yes – Floor vs. ICU

- If No – any discharge prescriptions
- If Transfer – to where and why

Data and Safety Monitoring Plan (DSMP) and Data and Safety Monitoring Board (DSMB)

Per potential study sponsor (NIH/NHLBI) guidelines and at the specific request of the NHLBI's human subjects officer during administrative review, this study will employ a DSMP and charter a DSMB (see attachment DSMB charter).

OVERSIGHT RESPONSIBILITIES

Trial Oversight is provided by the Principal Investigator (PI), Dr. Jennifer Fishe, MD, and co-investigators.

The DSMB members are: Dr. Jason Lang, MD (Pediatric Pulmonologist, Duke University), Dr. Sfurti Nath, MD (UF Jacksonville Neonatologist), and Dr Jeff Harman, PhD (Health Economist / Biostatistician Florida State University), Dr. Arveen Bhasin, MD (Allergy/Pulmonology, Mayo Clinic Jacksonville) and Morgan Henson, BSH, CPH, MPH (executive secretary).

MONITORING PROCEDURES

Dr. Fishe is responsible for oversight and conduct of the study, including that the study is conducted according to the IRB-approved research plan. The IRB has approved this study with waiver of informed consent. Study data will be accessible at all times for the PI and co-investigators to review. The PI and co-investigators will review study conduct including participant accrual, loss to follow-up, and EMS treatment guideline deviations on a monthly basis, and prepare data for reports for quarterly DSMB meetings. The DSMB members will review SAEs individually in real-time once they are discovered, and AEs plus all SAEs in aggregate on a quarterly basis. The PI ensures all protocol deviations, AEs, and SAEs are reported to the IRB, treating EMS agency, and study sponsor (if applicable) according to the UF IRB requirements and those requested by the DSMB as specified in the study DSMB charter. The DSMB members will elect a chair during their first meeting.

COLLECTION, SPECIFICATION, AND REPORTING OF SAEs AND AEs

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to EMS administration of oral steroids, all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the EMS administration of oral steroids. Specific AE/SAEs that will be closely monitored for include nausea or vomiting after oral steroid administration, allergic reaction to the steroid (mild, moderate, or severe (anaphylaxis), or suspected aspiration of oral steroid. The study-specific definition of “temporally related” includes within 60 minutes of oral steroid administration.

Serious Adverse Events

An AE should be classified as an SAE if:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject’s ability to conduct normal life functions).
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Methods and Timing for Assessing AND Recording Safety variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the UF IRB, treating EMS agency, and study sponsor (if applicable) in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The reporting period for all study-defined adverse events will begin when the EMS data are abstracted (approximately weekly). AEs are reported to DSMB for their regular quarterly meetings, SAEs must be reported to the DSMB and IRB within 24 hours of becoming aware of the event.

Assessment of Adverse Events

Each reported SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to oral steroids, actions taken, and patient outcomes. To ensure consistency of SAE causality assessments, investigators will apply the following general guideline:

<u>AEs are graded according to the following severity scale:</u>

Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: the AE is clearly not related to the EMS administration of an oral steroid (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: an event that follows a reasonable temporal sequence from the EMS administration of an oral steroid, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to EMS administration of oral steroids.

Asthma Exacerbation Related Exempted Events

The following signs, symptoms, observations and events are frequently observed in association with asthma exacerbations and are exempted from regulatory reporting unless known to be caused by the study drug: dyspnea, chest pain, fever, hypoxemia, rapid pulse, rapid respiratory rate, dizziness, nausea, vomiting, anxiety, altered mental status, shortness of breath, difficulty breathing, hypokalemia (associated with administration of bronchodilators), dehydration.

AE Management

Should any patient experience an adverse event, they are in the care of emergency professionals (EMS providers who then treat and transport to ED providers) who are trained in the management of unexpected and potentially serious adverse events.

Procedures for eliciting, recording, and reporting adverse events

Specific Instructions for Recording Adverse Events

Investigators will use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

   If known at the time of reporting, a diagnosis will be reported rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it will be reported based upon the information that is currently available. If a diagnosis is subsequently established, it will be reported as follow-up information.

b. Deaths

   All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties.

   When recording a death, the event or condition that caused or contributed to the fatal outcome will be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

   A preexisting medical condition is one that is present at the start of the study. Such conditions will be reported as medical and surgical history.

   A preexisting medical condition will be reported as an AE or SAE only if the frequency, severity, or character of the condition worsens as a direct result of EMS administration of oral steroids. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent vomiting”).

d. Hospitalizations for Medical or Surgical Procedures

   Any AE that results in prolonged hospitalization will be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, will be reported as the SAE.

   Hospitalizations for the following reasons do not require reporting: Prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions, or hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Data Quality Assurance and Monitoring Plan

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. All study data will be deidentified as soon as possible (following EMS to ED

record linkage), and stored in password protected files on password protected computers in locked offices only in IRB approved phile drives. The study PI will be responsible for data quality assurance, and for timely data submission for preparation of quarterly DSMB meetings.

Safety Monitoring

This study will charter a DSMB (see DSMB charter) to monitor the study.

Human Subjects Protections

Waiver of Informed Consent

The data collected from this research study relates to data that would have already been collected on care the children would have already received based on the existing / planned future protocols for care as defined by the EMS agency contributing data for the study. *It is not practical for EMS to consent patients during emergency treatment to have their data collected, nor is it practical to ask legally authorized representatives who may or may not be present during the EMS encounter for consent in the midst of emergency treatment for data collection. Further to this, the study is not altering any aspect of EMS treatment, and therefore is retrospectively collecting data AFTER THE ENCOUNTER HAS OCCURRED.*

The use of PHI involves no more than minimal risk to the individuals because multiple steps will be taken (as noted in other sections above and below) to prevent loss of confidentiality. Also, the PHI will not be used for data reporting, since this information will be removed prior to analysis, and the subjects will be coded with a study number. Accessing the patient's records does not otherwise affect their rights or welfare, since personal information will not be released. The data collected from the pediatric population in this research study relates to care that children would have already received based on the existing protocols for care as defined by the EMS agency involved. The investigators/study team will not be directly interacting with the EMS patients. Access to the PHI (incident run number, date of birth, etc.) is necessary, in order to calculate age accurately and link separate records for the same patient encounter in the EMS and ED EMRs. The principal investigator has performed similar previous and ongoing IRB-approved pediatric EMS studies with waiver of consent. Therefore, this study could not be done without obtaining this PHI, because there would be no other way to match link the EMS to ED records or calculate age in an accurate manner.

Obtaining consent from these patients will not be feasible or practical because the care will have already been provided as defined by the EMS agencies, obtaining consent will not affect the care they already received in the prehospital settings, and attempting to obtain consent after care has already been provided would require intentionally searching the EMS database for additional personally identifying information, which would be more intrusive as this is not required for data analysis for the study.

These subjects are not likely to be encountered again by the investigators in the clinical setting, so there is no other means to provide additional information to the subjects except to contact them via mail or phone. Providing subjects with additional pertinent information after participation would not be appropriate, since it would require gathering additional personal information from the charts, such as address or telephone number, in order to communicate with them. In addition, contacting the subjects in this manner may be perceived by the subjects as an intrusion of their privacy, since gathering addresses and telephone numbers is not required to conduct this retrospective study.

Potential Risks

PHI

Research procedures also include abstracting patient data from the EMS and ED/hospital EMR. PHI must be collected in order to link EMS and ED/hospital records, after which the data will be de-identified. Linkage of EMS and ED records will commence once study personnel are notified in the daily morning report of a EMS pediatric asthma patient. Once EMS and ED records are linked, for each pediatric asthma patient (oral steroid or no oral steroid), the REDCap™ database system will be used to record data variables for analysis. REDCap™ will not contain any patient identifiers. Data will be abstracted from the patient's electronic medical record (EMR) for both the EMS and ED encounter. Data will be collected prospectively by trained study investigators (including the participating EMS agency's medical directors) and research assistants who are listed on the study IRB. Only the study investigators, research assistants, and research coordinators named on the study IRB will have access to PHI.

Statistical Analysis Plan

We will perform descriptive statistics using frequencies and percentages for categorical variables, and mean with standard deviation and median with interquartile range for continuous variables. We will perform univariate analyses with chi-square testing for categorical variables, and Wilcoxon rank sum for continuous variables comparing between the steroids and no steroids groups for equivalence testing. A p value of > 0.05 will be considered statistically significant. We will report 95% confidence intervals.

We will build hierarchical generalized linear mixed models for the primary outcome of hospitalization. For the models, we will use only complete observations and did not perform any imputations. We will report model performance using the Akaike Information Criterion (AIC).