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Erika Fernandez

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**Systematic search for  
Hydrocortisone Treatment of Cardiovascular Insufficiency  
in the Preterm and Late Preterm Newborn Infant**

Erika Fernandez, MD

**MSCR Data Management & Biomedical Informatics- Level II (Appendix A)**

**Abstract**

Background: Critically ill newborn infants admitted to newborn intensive care units often exhibit signs of cardiovascular insufficiency including hypotension. The suspected etiology for hypotension has been hypothesized to be caused by adrenal insufficiency. Treatment with glucocorticoids has been used for other critically ill populations, but there are limited studies in the term and late preterm newborn infant. The goal was to describe a search strategy to obtain the most relevant literature in this area of research interest.

Methods: Systematic PubMed searches in the critically ill newborn population: Adrenal insufficiency [MeSH] OR cardiovascular insufficiency [MeSH] AND glucocorticoid therapy

Results: The first search strategy resulted in missing key articles well known in the field. Because of the limited number of articles dedicated to this group of topics, the search was expanded to be more inclusive. The initial search strategies resulted in articles which did not pertain to the target population. Irrelevant articles were removed by eliminating them from the final search, using a set of predetermined criteria.

Conclusion: A significant number of articles relevant to the critically ill newborn population with putative cardiovascular or adrenal insufficiency were found in the biomedical literature using a PubMed MeSH-based search strategy.

**Background**

This literature search provides data and a bibliography for a study on short and long-term efficacy and safety of hydrocortisone given for the treatment of hypotension in critically ill, mechanically-ventilated, term and late preterm newborn infants. In the most general terms, this search strategy employs the following logic: Adrenal insufficiency OR cardiovascular insufficiency AND glucocorticoid therapy

Cardiovascular insufficiency, as defined by hypotension or other signs of shock, is a common problem in the newborn infant admitted to a Newborn Intensive Care Unit. The mechanisms that precipitate cardiovascular insufficiency in the newborn infant are

complex and incompletely understood. Adrenal insufficiency has been associated with cardiovascular insufficiency in populations of critically ill patients<sup>1</sup>.

Adrenal insufficiency in critically ill patients is also known as “relative adrenal insufficiency,” “functional adrenal insufficiency” or “critical-illness related corticosteroid insufficiency,” all of which are defined as inadequate corticosteroid activity for the degree of illness in a critically ill patient. If adrenal insufficiency underlies the cardiovascular instability in ill patients, then glucocorticoid therapy would appear to be the appropriate therapy. This paper describes the search strategy used to obtain the relevant literature in this area of research interest.

## **Methods**

The author applied a systematic search strategy using PubMed to find relevant articles to the area of research interest. The author verified the validity of the search strategy by looking for papers in the search results that were deemed as key or classic by the frequency of citation in review and randomized controlled trial papers (2-8). The final search strategy had to include these articles, be able to capture the most recently relevant published articles and exclude most articles deemed irrelevant.

The author began with a broad search using the Single Citation Matcher feature in PubMed with terms most often used by medical care providers when caring for the population of interest: hypotension and hydrocortisone. The searches were limited to newborn infants. Identifying commonly used MeSH terms found in the resulting pertinent articles, the author then used the PubMed’s MeSH database to look up the three topics (Adrenal insufficiency, cardiovascular insufficiency and Glucocorticoids) to find the most appropriate specific MeSH headings. Each of these three topics may be described or defined with other MeSH terms. For example, cardiovascular insufficiency may also be known as shock or hypotension. Glucocorticoids include two specific steroids hormones of interest (hydrocortisone and dexamethasone) and may also be known as just, “cortisol”. The MeSH heading trees for the three topics were evaluated to determine if the MeSH term used was inclusive of the most relevant terms in the tree. The author determined the appropriate MeSH terms from a selection of narrow or broad terms using the MeSH classification tree. The author performed multiple searches using the different MeSH terms for the same concept. For example, hypotension is a sign of cardiovascular insufficiency and is a “blood pressure effect.” Hypotension is often used synonymously with the term, “shock,” and both hypotension and shock are well known clinical signs of adrenal insufficiency.

Once the searches were performed, the article titles and abstracts were reviewed for relevancy. The author collected and compared the MeSH terms associated with the most relevant articles. Using the MeSH terms from this strategy, the author performed a search using the Boolean operators, “AND” and “OR”. Limits were applied for English,

Human and newborn infant (newborn to 1 month). Additional limits were not set because limiting the search to other options, such as clinical trials, resulted in the exclusion of clinical trials that were key articles. The MeSH terms of the irrelevant articles were reviewed and the search strategy was extended by adding the Boolean operator, “NOT” to the search string.

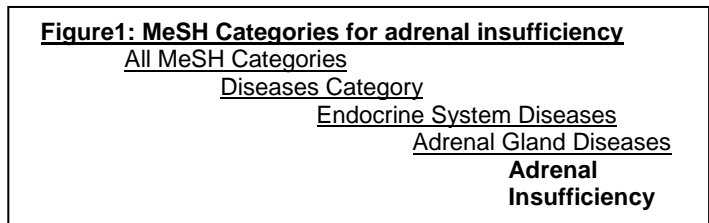
## **Results**

The author conducted a search strategy on January 21, 2011 for each of the three concepts (adrenal insufficiency, glucocorticoids and cardiovascular insufficiency) of the intended research.

### **1. Adrenal insufficiency**

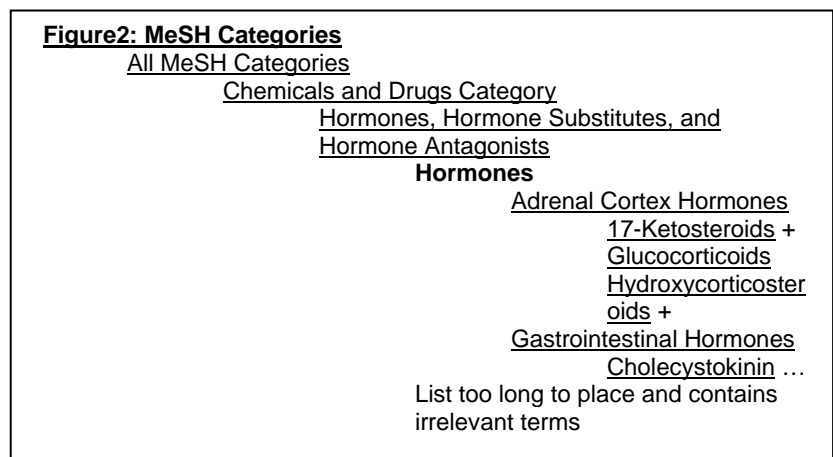
The clinical state of adrenal insufficiency may be identified by cortisol levels, or through an ACTH functional test of the adrenal glands using adrenocorticotrophic hormone (ACTH). All of the key articles included the MeSH term, “adrenal insufficiency.” Other MeSH terms found in the relevant articles (Table 1) did not add additional relevant articles to the search. A MeSH term search resulted in the MeSH category tree in figure 1. MeSH terms below adrenal insufficiency were not relevant and not more specific so we used the MeSH term “adrenal insufficiency”.

<b>Table1: MeSH terms found in key articles</b>
Adrenal insufficiency
Pituitary adrenal system
Hypothalamic-hypophysial system



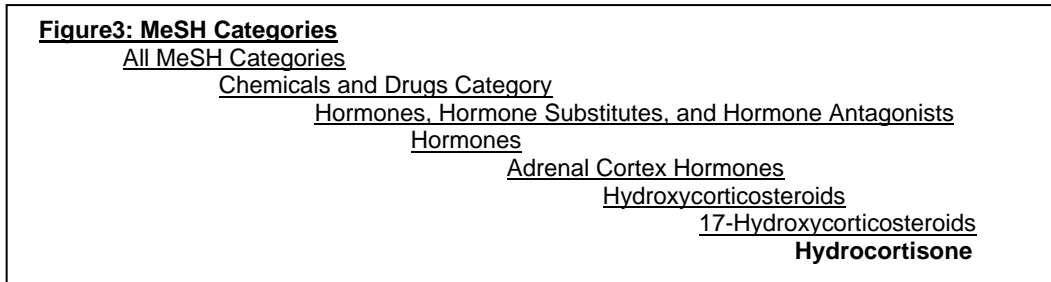
### **2. Glucocorticoids**

The focus of this research is on the use of hydrocortisone, a hormone, in the critically ill infant population. The search for the MeSH term, hormone, resulted in figure 2. Hydrocortisone is under the MeSH term, hydroxycorticosteroids but hydrocortisone is the only term of interest for the



proposed research study (figure 3). Initial research studies often used dexamethasone as the glucocorticoid to treat hypotension. Dexamethasone falls under a different MeSH

category. So the author combined the MeSH terms hydrocortisone with dexamethasone using the Boolean operator, “OR.”

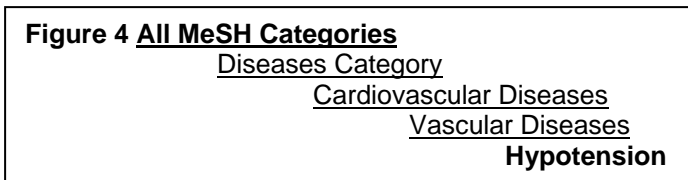


### 3. Cardiovascular insufficiency

There is no MeSH term for “cardiovascular insufficiency”. The concept of cardiovascular insufficiency is clinically described by a number of other terms including hypotension or shock. Other MeSH terms which describe this concept were identified from the key articles by displaying the MeSH terms (Table 2). Most of the key articles did use hypotension as a MeSH term. The author found the MeSH terms indented below hypotension in the MeSH tree were too narrow so “hypotension” was used for the search (figure 4). Similar MeSH terms which described the same concept were identified in those key articles that did not have hypotension as a MeSH term. MeSH terms used from the key articles were “blood pressure”, “shock” or “adrenal insufficiency”. Using more specific terms in the “shock category” tree is too restrictive so the author used the term “shock” instead.

Hypotension is thought to be a direct clinical manifestation of adrenal insufficiency so it is appropriate that “adrenal insufficiency” might easily describe cardiovascular insufficiency<sup>1</sup>. Therefore, to capture all key articles regarding the concept of cardiovascular insufficiency, the search included: hypotension (MeSH) OR blood pressure (MeSH) OR shock OR adrenal insufficiency (MeSH).

*Hypotension
*Blood pressure
*Shock
Cardiac output
Blood flow velocity
Cardiovascular system
Ventricular dysfunction
Hemodynamics



The author conducted a search **strategy for all concepts** as a group on February 17, 2011.(See Table 3.) The author reviewed the references produced for search #4 for relevancy. Irrelevant articles were checked, placed on the PubMed clipboard and their MeSH terms and limit tags reviewed. MeSH terms were identified that would eliminate many of the irrelevant articles and are listed in Table 3 in search

#5. The final search strategy included all key articles and excluded most irrelevant articles. The author excluded those references on this list of 95 citations if they pertained to rabbits, CHARGE association, mutations, Smith-Lemli-Opitz syndrome, congenital adrenal hyperplasia, adrenal hypoplasia, cerebral infarction or inhaled steroids. After removing these last 9 articles, there were 84 articles in the final search which are listed in Appendix B. The 8 key articles are in Appendix C. The key articles are variable in design but capture the key concepts.

Search #	Terms	Number of results
1	((("Hypotension"[Mesh]) OR "Blood Pressure"[Mesh]) OR "Adrenal Insufficiency"[Mesh]) OR "Shock"[Mesh]	296,273
2	("Hydrocortisone"[Mesh]) OR "Dexamethasone"[Mesh].	91,796
3	#1 AND #2	5,178
4	Apply limits to search #3 for humans, English language and newborn infants (birth –1 month)	169
5	197,390	
6	#4 NOT #5	
7	Apply limits to search #5 for Humans, English language, Newborn: birth-1 month	95
8	Review of search #7 with removed irrelevant articles	84

#### Conclusion:

This paper detailed the search strategy employed to capture all past and current key articles in the research area of adrenal insufficiency, cardiovascular insufficiency and glucocorticoid therapy in ill newborn infants. This search strategy can be utilized at regular intervals to monitor for new articles pertaining to this area of interest for research proposals, manuscripts and review papers. This search query can also be set up to run automatically with periodic results emailed to personal email accounts using a tool in a “My NCBI” account.

**Appendix A:** MSCR Data Management & Biomedical Informatics- Level II requirements

The level II course in Bio-informatics is part of the CTSC's MSCR program. The goals of this course included the following:

1. Given a specific area of research that the student is interested in, the student will be able to generate well constructed research questions that have the potential to be developed into a clinical research project.
2. Within a major bibliographic database utilize AND, OR, NOT Boolean operators; produce a search history; broaden, refine or limit a search; adapt a search strategy as needed; apply the search functions listed above to different databases and interfaces.
3. Completely and accurately cite sources used with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" format for pediatrics clinical literature.

## **Appendix B:**

References retrieved from final search (all 84).

(<sup>1-6, 9-52</sup>, 7, 8, 53-84)

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