

I. INTRODUCTION

This report is an outgrowth of the summit meeting of the National Anemia Action Campaign (NAAC) held in Washington, DC in November 2000. NAAC convened a multidisciplinary panel of physicians and health care experts to discuss the incidence and management of anemia, as well as caregiver attitudes toward anemia. Following two days of discussion, a consensus emerged that there remains a lack of understanding of the prevalence of anemia in both the general population and in patients across various disease states. In response, Zynx Health Incorporated was commissioned to provide Amgen with a systematic review of the literature on the prevalence of anemia and its impact on a range of clinical, functional, and quality of life outcomes in six conditions of interest: rheumatoid arthritis, inflammatory bowel disease, cancer, HIV/AIDS, selected elective surgeries, and geriatric medicine.

This report provides a detailed explanation of our findings. Chapter II describes the methodology used to identify articles for inclusion in our systematic review. Chapter III details the results of our search, beginning with a general overview and proceeding to a critical review of the studies for each of the six conditions of interest. We conclude with a summary and directions for future research (Chapter IV).

II. METHODS

The goal of our search was to systematically identify and review an exhaustive list of articles on the prevalence of anemia and its impact on a range of clinical, functional, and quality of life outcomes in six conditions of interest: rheumatoid arthritis, inflammatory bowel disease, cancer, HIV/AIDS, selected elective surgeries, and geriatrics. Outcomes of interest included:¹

- *Clinical*: morbidity, mortality, hospitalization (length of stay, complications), transfusion requirements, growth and development, disease progression, responsiveness to therapy (e.g., responsiveness of tumors to radiotherapy), compliance with therapy, and adverse events due to therapy in which anemia may be a contributing or exacerbating factor.
- *Functional*: functional status, cognitive function, exercise tolerance, psychosocial/sexual function, cardiac function/morphology, and quality of life.
- *Satisfaction*: patient satisfaction with care.
- *Economic*: direct and indirect costs.

Our review focused primarily on anemia of chronic disease, but articles were not excluded if they dealt with iron deficiency anemia. Articles dealing exclusively with anemia resulting from aplastic or myelodysplastic syndromes, primary hemoglobinopathies, hematological malignancies, lymphoproliferative disorders, intra-

¹ It is important to note that, by its very nature, a systematic review suffers from publication bias. For this review, publication bias is more relevant to the outcome studies, than to the prevalence studies, as authors may not elect to publish studies with negative outcomes.

operative blood loss, other nutritional deficiencies, or drugs (including cytotoxic chemotherapy) were excluded. The components of our review are described below.

A. CITATION SEARCH

In consultation with a reference librarian, a comprehensive search strategy was developed to maximize the retrieval of articles that might include information relevant to the conditions and outcomes of interest. Separate search strategies were created for each condition.

MEDLINE and EMBASE were searched for published articles on the prevalence and impact of anemia in persons with the six conditions of interest. The MEDLINE search covered the period from January 1966 through March 2001; the EMBASE search, from January 1974 through March 2001. The search excluded foreign-language and non-human studies, as well as editorials and abstracts. An AIDSLINE search was also performed for HIV/AIDS.

B. TITLE, ABSTRACT, AND ARTICLE REVIEW

Upon completion of the online searches, we selected articles and reviewed the literature. The process of selecting articles occurred in three predefined stages: title review, abstract review, and article review. Specific rejection criteria were developed for each of these stages. A team of researchers was trained in the review process and subsequently worked in pairs for each condition of interest.

Review articles frequently appeared during the abstract and article review and were coded as “abstract rejects” or “article rejects.” However, bibliographies from these articles were searched to generate additional articles for review.

TITLE REVIEW

For each condition, two researchers independently reviewed the first 100 titles identified and noted whether each of these titles would be “accepted” or “rejected.” During this stage of the review, an article was rejected if it: 1) was a letter, editorial, or case report or 2) did not include a group, condition, or outcome of interest. Inter-rater agreement was assessed with the kappa statistic. If the kappa value was 0.6 or greater, the remaining titles were divided, and each was reviewed by only one of the two researchers. If the kappa value was less than 0.6, reviewers met to discuss discrepancies, and this was followed by another assessment of inter-rater agreement. If a sufficient level of agreement could not be achieved, both researchers reviewed all of the remaining titles, with acceptance by either resulting in the title being accepted.

ABSTRACT REVIEW

The abstract review followed a process similar to that for the title review. Fifty abstracts were reviewed for purposes of calculating a kappa score. If a kappa score of 0.7 or greater was not achieved, both researchers reviewed all abstracts. An article was excluded during the abstract review if it: 1) was a review, letter, editorial or case report; 2) dealt exclusively with an excluded type of anemia; 3) did not include either prevalence data or an outcome of interest; or 4) did not include a group or condition of interest.

Articles for which no abstract was available for review (as was often the case, particularly with EMBASE search results) were automatically forwarded to the next stage of review (article review).

ARTICLE REVIEW

One researcher reviewed articles in each condition of interest and applied the same set of rejection criteria that was used in the abstract review. A senior researcher was available for consultation.

Relevant content was abstracted using a standard form and entered into evidence tables. For each condition of interest, separate evidence tables were developed for *Prevalence* and *Outcomes*. In a few instances, articles contained information about two of the conditions of interest, and duplicate entries were accordingly made. Similarly, some articles included both prevalence and outcomes information and were cited separately in both tables.

C. CITATION TRACKING

Online searches will not retrieve relevant citations from journals that are not included in the online databases or that are not indexed in a manner that facilitates retrieval. It is, therefore, difficult to determine with certainty whether pre-specified search criteria are sufficiently accurate to capture the universe of relevant articles. For these reasons, hand searches of bibliographies from accepted articles and review articles were conducted by the same team of researchers involved in the original title, abstract, and article review

process. The hand searches resulted in retrieval of a limited number of additional articles for review; these articles are referred to as “secondary references.”

D. EXPERT REVIEW

Prior to the initiation of this project, an expert panel was established; one expert in each of the conditions of interest was included. As a final data quality check, copies of the list of accepted articles for each condition, as well as copies of the evidence tables, were sent to each expert reviewer. The experts were asked to comment on both the inclusiveness of the article list and the presentation of the evidence tables. A number of additional articles suggested by our expert reviewers were included in the final article review; these were also considered “secondary references.”

III. RESULTS

A. RESULTS OF LITERATURE SEARCH

Our online search identified a total of 10,480 titles for all conditions. After reviewing each of these titles, a total of 1,841 titles were accepted. Titles with abstracts moved to the abstract review phase. Titles without abstracts moved to the article review phase. A total of 1,155 abstracts were accepted. A total of 209 articles retrieved from online sources were accepted. Table 1 below shows the number of titles retrieved, titles accepted, abstracts accepted, and articles accepted for each condition by online source. In addition, a total of 33 articles retrieved from secondary sources (citation tracking, expert review) were accepted.

The majority of studies (of both prevalence and outcomes) were performed in cancer patients. There was a paucity of relevant studies for inflammatory bowel disease and rheumatoid arthritis. Although studies involving children were not explicitly excluded from our search criteria, the articles retrieved contained very little data about anemia in pediatric patients. As a result, most of the articles reviewed below deal almost exclusively with adults.

Table 1
Results of Citation Search

	Cancer	RA	Surgery	HIV/AIDS	IBD	Geriatrics
Titles retrieved	3933	1012	403	1090	357	3685
MEDLINE	1971	678	180	468	288	2430
EMBASE	1961	334	223	611	69	1255
AIDSLINE	1	0	0	11	0	0
Titles accepted	487	237	199	287	118	513
MEDLINE	420	149	76	159	105	477
EMBASE	67	88	123	125	13	36
AIDSLINE	0	0	0	3	0	0
Abstracts accepted	330	118	108	230	89	280
MEDLINE	274	80	42	104	85	251
EMBASE	56	38	66	124	4	29
AIDSLINE	0	0	0	2	0	0
Articles accepted	55	18	18	31	16	71
MEDLINE	46	13	13	22	16	56
EMBASE	9	5	5	8	0	15
AIDSLINE	0	0	0	1	0	0

(RA, rheumatoid arthritis; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; IBD, inflammatory bowel disease.)

B. PREVALENCE AND OUTCOMES STUDIES

The remainder of this chapter details our findings about the prevalence of, and outcomes of patients with, anemia in each condition of interest. Results of studies that encompass more than one condition of interest will be reported in each section of the report for which the results are applicable. For example, Tanaka (1999) studied rheumatoid arthritis patients scheduled for total hip or total knee arthroplasty. The findings from that study are reported in both the rheumatoid arthritis section and the surgery section of this report.

PREVALENCE

A number of facts should be kept in mind while reviewing the data on the prevalence of anemia. First, there is substantial variation in how anemia is defined. Most studies used

hemoglobin or hematocrit levels to define anemia, but there is no consensus about what values (or range of values) should be used.² Furthermore, a few studies used ICD-9-CM codes, rather than hemoglobin or hematocrit levels, to identify cases of anemia. This makes direct comparisons of the prevalence data in the various studies difficult.

Second, not all studies with reports of prevalence were actual prevalence studies. In these instances, the reporting of prevalence data was a byproduct of a more detailed methodological investigation of specific outcomes. For example, Haljamae et al (1982) report the prevalence of moderate and severe anemia among female geriatric patients with hip fractures. However, the primary purpose of the study was to evaluate risk factors associated with hip fractures.

Finally, an increase in the prevalence of anemia in certain populations is associated with disease progression. This is particularly true for HIV/AIDS and cancer patients. For example, many studies suggest that the prevalence of anemia in HIV-positive patients without AIDS is fairly low (between 0% and 20%), whereas it appears to be quite high (above 60%) in hospitalized patients with AIDS. Thus, it can be difficult to ascertain the overall prevalence of anemia in such populations.

² It is interesting to note that there is disagreement between two well-accepted grading schemes: one by the World Health Organization and the other by the National Cancer Institute and cooperative oncology groups. (AHRQ Evidence Report/Technology Assessment, Number 30, *Uses of Epoetin for Anemia in Oncology.*)

OUTCOMES

As with prevalence, there are important details to consider when evaluating the impact of anemia on our outcomes of interest. First, there is considerable variability in the types of outcomes and patients studied. Some outcomes are relatively easy to quantify (e.g., mortality, hospital length of stay); others are more subjective (e.g., patient's satisfaction with care). It can be difficult to separate out the effects of one disorder—anemia—in patients with complex conditions, such as HIV/AIDS patients with multiple opportunistic infections or cancer patients undergoing chemotherapy. Even within a single area of interest, there may be a wide range in the types of patients studied. For example, patients undergoing hip fracture repair may be quite different from those being operated on for colon cancer. For this reason, the data on outcomes should be interpreted with caution. In an effort to standardize our analysis of outcomes data, we have categorized outcomes into four major categories: clinical, functional, satisfaction, and costs and utilization.

Second, a substantial number of studies analyzed the impact not of anemia itself, but of treatment with epoetin, on clinical and functional outcomes. These studies are included because the comparison of treated versus untreated subjects allows some inference about the effects of anemia. Furthermore, trial reports often include comparisons of epoetin “responders” and “non-responders.” These observational results are included in our review, even though they are subject to inherent biases. Thus, while it may be reasonable to assume that any differences found between the epoetin responders and non-responders could be attributed to an improvement in anemia, it is possible that they resulted from other pathways.

A final issue to consider is the variability in the quality of studies reviewed. Some articles provided specific and detailed information regarding the characteristics of participants, dose and administration of study drugs, and calculation of outcomes. Other articles were less detailed and made only vague references to study populations, calculation of outcomes, and statistical methods.