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SUMMARY WITH CRITICAL APPRAISAL

Intravenous Multivitamin Therapy Use in Hospital or Outpatient Settings: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

IV	intravenous
SR	systematic review

Context and Policy Issues

Nutritional deficits can lead to side effects such as diarrhea, weight loss, inflammation of the tongue, and anemia, among other symptoms.[1,2] Malabsorption issues (issues absorbing macronutrients and micronutrients from food) can cause nutrient deficits and may be caused by damage to the intestines, (such as damage through gastrointestinal disorders) or through surgery (such as a removal of a portion of the intestine). Examples of other causes of nutrient deficits include major burns (causing hypermetabolism),[3] or acute kidney injury requiring renal replacement therapy.[4] Individuals with nutrient deficits may require additional nutrient supplementation, often in the form of oral supplementation, intravenous (IV) supplementation, or nasogastric supplementation. Nutrient supplementation has also been used in patients with chronic alcohol use disorders or in individuals who are intoxicated.[5] Some IV administered solutions of multivitamins are colloquially termed "banana bags" and may contain a litre of IV fluid infused over 24 hours with a combination of thiamine, folic acid, magnesium, and a multivitamin.[5] Other solutions are colloquially termed "Myer's cocktails" and may contain vitamin C, B complex, magnesium chloride, calcium gluconate, hydroxocobalamin, pyridoxine hydrochloride, and dexpanthenol.[6]

Micronutrient infusion through IV has increased in popularity, especially among independent complementary and alternative medicine clinics,[6] or in emergency departments, but its efficacy in certain populations, such as in individuals with alcohol use disorders is debated.[7] The purpose of this review is to examine the clinical effectiveness of IV multivitamin therapy in patients that may require nutrient supplementation, who are not on total parenteral nutrition. This is in comparison to either no supplementation, or standard oral supplementation in patients who can orally ingest food. Additionally, the purpose of the review is to examine evidence-based guidelines regarding the use of IV multivitamin therapy.

For the purposes of this report, "IV multivitamin therapy" includes vitamins and other micronutrients, such as minerals, as the classic "Myer's cocktail" and "banana bags" both contain a mixture of vitamins and minerals.

This report is an upgrade of a previous 2020 CADTH Reference List titled "Intravenous Multivitamin Therapy Use in Hospital or Outpatient Settings: Clinical Effectiveness and Guidelines";[8] therefore, studies identified in that report were evaluated for potential inclusion in this review.

Research Questions

1. What is the clinical effectiveness of intravenous multivitamin therapy in a hospital or outpatient setting?
2. What are the evidence-based guidelines for using intravenous multivitamin therapy in a hospital or outpatient setting?

Key Findings

One systematic review was identified with a scope broad enough to include potentially relevant primary studies, however this systematic review did not include any primary studies with relevance to the research questions for this report. Additionally, no evidence-based guidelines were identified. Therefore, no conclusion can be provided regarding intravenous multivitamin or micronutrient supplementation for patients with malabsorption issues, patients post-surgery, and patients with burns, trauma, intoxication, or other serious infectious diseases either in a hospital or in an outpatient setting.

Methods

Literature Search Methods

This report is an update of a literature search strategy developed for a previous CADTH report.[8] For the current report, a limited literature search was conducted on key resources including MEDLINE, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused internet search. No filters were applied to limit the retrieval by study type. The initial search was limited to English-language documents published between January 1, 2015 and January 8, 2020. For the current report, database searches were rerun on September 14, 2020 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since January 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-2: Patients with malabsorption issues (e.g., irritable bowel syndrome, anorexia, bulimia) post-surgery/ post-bariatric surgery, burns, trauma, intoxication, or serious infectious diseases (e.g., *Clostridioides difficile*)
Intervention	Q1-2: IV multivitamin therapy (also known as Classic Myers' Drip, "banana bag", IV 12 or IV 1000 formulation)
Comparator	Q1: Oral multivitamin therapy, no vitamin therapy, IV saline, IV Ringer's lactate Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., hospital readmission, length of stay, adverse events) Q2: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews randomized controlled trials, non-randomized studies, evidence-based guidelines

IV = intravenous.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic

reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Guidelines with unclear methodology were also excluded. Studies using combination IV and oral or nasogastric tube supplementation, or IV supplementation preceding a different route of administration with no separate results presented for IV supplementation alone were excluded.

Critical Appraisal of Individual Studies

The included publication was critically appraised by one reviewer using A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[9] as a guide. Summary scores were not calculated for the included study; rather, the strengths and limitations of the included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 396 citations were identified in the literature search, 382 from the original Reference List search,[8] and 14 from the updated search. Following screening of titles and abstracts, 390 citations were excluded and six potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, five publications were excluded for various reasons, and one publication met the inclusion criteria and was included in this report. This comprised one systematic review (SR).[10] Appendix 1 presents the PRISMA[11] flowchart of the study selection.

The original CADTH Reference List[8] included Rehou et al[12] as a potentially relevant article based on screening the abstract alone, however upon review of the full text, it was excluded due to the intervention including an IV supplement preceding a enterally administered supplement, without separate results presented for IV supplementation alone. This enteral supplementation was not clear in the abstract. The inclusion of oral supplementation in the intervention group, initiated after the IV supplementation and not matching the oral supplementation provided to the control group, makes it not possible to determine how much effect was driven by the IV supplementation alone. Therefore, a conclusion regarding IV supplementation was not possible.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

One SR[10] was identified with relevance to the research questions, but did not include any relevant primary studies. It was published in 2016 in the Cochrane Database of Systematic Reviews. The SR is the seventh update of a review first published in 2000 and was published by authors from the UK, including randomized and quasi-randomized trials.[10]

The scope of the SR was all nutritional interventions for older patients within the first month of experiencing a hip fracture. This was broader than the scope of this Rapid Response report, but the search and inclusion criteria included IV multivitamin interventions, so it was eligible for this review.[10] In the included SR, the eligible articles focused on older people recovering from any type of hip fracture, not including trials focusing on young populations, people with multiple traumas, or people with pathological fractures.[10] The interventions of interest in the included SR were multi-nutrient supplements given orally, enterally or

through IV, or dietetic assistance. The eligible comparators were supplements containing less or none of these components, lower doses, placebo or no treatment.[10] Outcomes that were eligible for inclusion in the relevant SR[10] were mortality, morbidity, complications, length of stay in care, quality of life and functioning, healing of the fracture, care required and carer burden, and economic outcomes. However, none of the included studies in this SR were specific to the intervention of interest for this report, (i.e., none evaluated IV multivitamin supplementation alone).

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

The included SR[10] was a high-quality review following Cochrane SR methods, with a prior published protocol. It had adequate reporting of included studies and methods, a comprehensive and thorough search strategy, and two independent assessors evaluated the data and performed study selection. One methodological limitation of the report was the reasoning for the decision to include only randomized and quasi-randomized trials was not provided.[10]

Summary of Findings

Clinical Effectiveness of IV Multivitamin Therapy

One study within the included SR examined IV multivitamin therapies; however, this was in combination with oral multivitamin feeding (three days IV feeding followed by seven days oral feeding). There were no separate results for IV feeding in comparison to standard care; therefore, there were no relevant results to summarize from the included SR.[10]

Guidelines

No evidence-based guidelines were identified regarding IV multivitamin therapy.

Limitations

This review was limited by the scarcity of articles examining IV multivitamin supplementation alone, as it does not appear to be a frequently examined route of administration in the literature in comparison to other routes of administration, such as orally or enterally administrated multivitamins. This may be because nutrient supplementation in patients who can swallow is more likely to be done orally, as IV and nasogastric supplementation is often indicated for severely malnourished patients in which oral supplementation is inadequate.[10] There were some studies identified that examined combination IV and oral therapies. Finally, no evidence-based guidelines were identified.

Conclusions and Implications for Decision or Policy Making

One SR[10] was identified with a scope broad enough to include potentially relevant studies, however this SR did not include any primary studies that met eligibility criteria for this review. Therefore, no conclusion can be provided regarding IV multivitamin or micronutrient supplementation for patients with malabsorption issues, patients who underwent surgery, and patients with burns, trauma, intoxication, or serious infectious diseases in a hospital or outpatient setting.

No evidence-based guidelines were identified with relevance to the research questions. However, one expert consensus paper and one recommendation paper with unclear methodology[2,5] were identified regarding adult patients and regarding alcohol-associated vitamin and electrolyte deficiencies, respectively. One article recommends IV micronutrient supplementation in some specific cases (i.e., specific losses, increased oxidative stress, and insufficient enteral intakes in inflammatory patients)[2] and one article suggests not providing the classic "banana bag" for patients admitted to the intensive care unit with symptoms either mimicking or masking Wernicke's encephalopathy, instead suggesting an alternative IV formulation.[5] However, the methodology for the development of these statements was unclear, and these recommendations were not graded, and therefore the methods were not considered to be rigorous enough to constitute an evidence-based guideline. These statements should be interpreted with caution.

Both this report and the original Reference List published in 2020[8] specifically examined IV multivitamin supplementation. However, this report differs from the original Reference List published in 2020, as the Reference List included a non-randomized study in the main body that appeared relevant based on the abstract.[8] Upon examination of the full text, it was determined that this report was not eligible for inclusion in the current review as the results were reported after patients had received both IV supplementation and oral supplementation.[12] This was not clear in the abstract.

Overall, the effectiveness of IV multivitamin or micronutrient supplementation in post-surgical patients or in patients with malabsorption issues, burns, trauma, intoxication, or serious infectious diseases is unclear. Future primary research may include IV supplementation alone for patients who are not on total parenteral nutrition, or reviews that include combination IV and oral therapies, as this may reflect another method of nutrient supplementation that may be more common in clinical practice. Therefore, decision-making and policy changes around the use of IV multivitamin supplementation may need to consider combination therapies as a potential practice of relevance.

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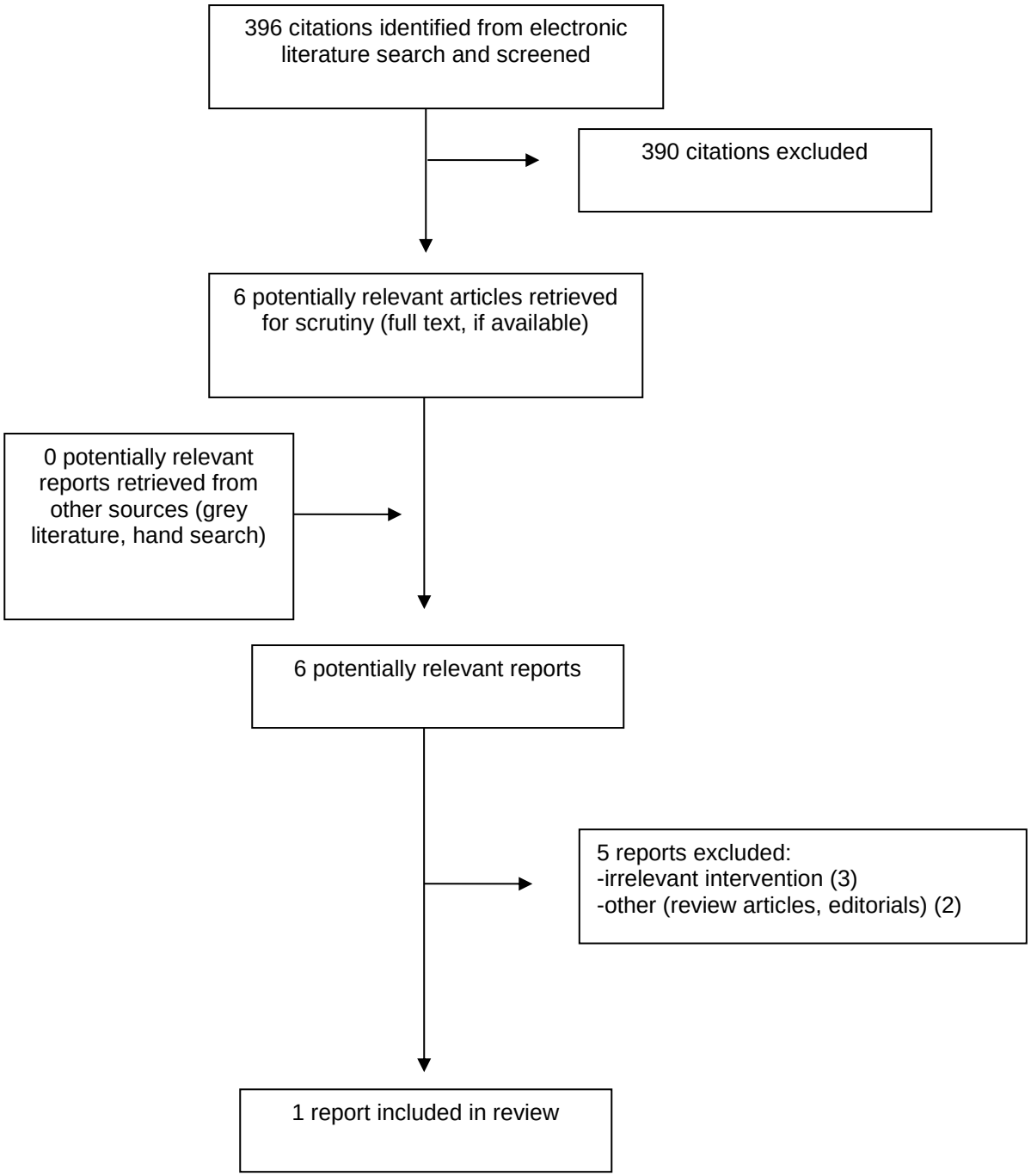
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Avenell (2016)[10] **UK** **NIHR via Cochrane Infrastructure funding to the Cochrane Bone, Joint and Muscle Trauma Group**	*Study Designs:* RCTs and quasi-RCTs *Databases:* • Cochrane Bone, Joint and Muscle Trauma Group Specialised Register • CENTRAL • MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • Embase • CAB abstracts • CINAHL • Trial registers • Reference lists *Data range of search:* Up to November 2015 *Number of Included Studies:* 41 trials (37 RCTs, 4 quasi-RCTs) *Number of Relevant Studies:* 0[a]	Patients with hip fracture	Nutritional interventions within one month of hip fracture	• All-cause mortality • Morbidity • Postoperative complications (e.g., wound infections, pressure sores, deep venous thromboses, respiratory and urinary infections, CV events) • 'Unfavourable outcomes'[b] • LOS and rehabilitation unit stay • Postoperative functional status (i.e., cognitive functioning, Mobility and ability to perform activities of daily living) • The level of care and extent of support required after discharge • Patient perceived quality of life after discharge • Fracture healing • Putative side effects of treatment (e.g. diarrhea, aspiration pneumonia, specific intravenous line complications) • Patient tolerance of or compliance with nutrition interventions • Carer burden and stress • Economic outcomes.

CAB = Commonwealth Agricultural Bureaux; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing & Allied Health Literature; CV = cardiovascular; LOS = length of stay; NIHR = National Institute of Health Research; RCT = randomized controlled trial.

[a] One study included IV multivitamin therapy (1000mL Vitrimix with trace elements, water, and fat-soluble vitamins added) in combination with oral MV therapy (7 days of 400mL Fortimel)

[b] Defined as "the number of trial participants who died plus the number of survivors with complications... [or] mortality or survivors with a major complication or two or more minor complications" Page 8

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[9]

Strengths	Limitations
Avenell (2016)[10]	
• The research questions and inclusion criteria for the review were clear • Clear protocol published prior to review • Literature search strategy comprehensive and thorough • Study selection and data extraction done in duplicate • Appropriate critical appraisal method used • Included studies clearly and adequately reported on • Publication bias funnel plots provided and described for outcomes and interventions with sufficient data • Conflicts of interest and sources of funding reported	• No explanation for not including non-randomized studies (i.e., cohort and case control)

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.