Review Article

Hydration in Advanced Cancer: Can Bioelectrical Impedance Analysis Improve the Evidence Base? A Systematic Review of the Literature

Amara Callistus Nwosu, MBChB, MRCP, Catriona R. Mayland, MBChB, MD, FRCP, Stephen R. Mason, PhD, PGCE, BA, Andrew F. Khodabukus, MBChB, BSc, MRCP, Andrea Varro, PhD, MD, and John E. Ellershaw, MB BCh, MA, FRCP

Marie Curie Palliative Care Institute Liverpool (A.C.N., C.R.M., S.R.M., A.F.K., J.E.E.); School of Physiological Sciences (A.V.), Institute of Translational Medicine, University of Liverpool; and Aintree University Hospitals NHS Foundation Trust (C.R.M.), Liverpool, United Kingdom

Abstract

Context. Decisions surrounding the administration of clinically assisted hydration to patients dying of cancer can be challenging because of the limited understanding of hydration in advanced cancer and a lack of evidence to guide health care professionals. Bioelectrical impedance analysis (BIA) has been used to assess hydration in various patient groupings, but evidence for its use in advanced cancer is limited.

Objectives. To critically appraise existing methods of hydration status assessment in advanced cancer and review the potential for BIA to assess hydration in advanced cancer.

Methods. Searches were carried out in four electronic databases. A hand search of selected peer-reviewed journals and conference abstracts also was conducted. Studies reporting (de)hydration assessment (physical examination, biochemical measures, symptom assessment, and BIA) in patients with advanced cancer were included.

Results. The results highlight how clinical examination and biochemical tests are standard methods of assessing hydration, but limitations exist with these methods in advanced cancer. Furthermore, there is disagreement over the evidence for some commonly associated symptoms with dehydration in cancer. Although there are limitations with using BIA alone to assess hydration in advanced cancer, analysis of BIA raw measurements through the method of bioelectrical impedance vector analysis may have a role in this population.

Conclusion. The benefits and burdens of providing clinically assisted hydration to patients dying of cancer are unclear. Bioelectrical impedance vector analysis shows promise as a hydration assessment tool but requires further study in

Address correspondence to: Amara Callistus Nwosu, MBChB, MRCP, Department of Molecular & Clinical Cancer Medicine, University of Liverpool Cancer Research Centre, 200 London Road, Liverpool, L3 9TA, United Kingdom. E-mail: amaranwosu@doctors.org.uk

Accepted for publication: August 29, 2012.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2012.08.018

advanced cancer. Innovative methodologies for research are required to add to the evidence base and ultimately improve the care for the dying. J Pain Symptom Manage 2013;46:433–446.

Key Words
Palliative care, cancer, hydration, dehydration, bioelectrical impedance analysis, clinically assisted hydration

Introduction

The role of hydration in causing or alleviating suffering in patients with advanced cancer is poorly understood and remains controversial.[1] Most patients dying of cancer have reduced oral intake in their last days of life.[2] This may be related to either cancer or its treatment, and reasons include dysphagia, anorexia, nausea or vomiting, or mechanical problems such as bowel obstruction.[3,4] Accordingly, the subject of clinically assisted hydration (CAH) is emotive among patients and their carers,[3,5–7] with the omission or withdrawal of CAH potentially viewed as hastening death in some instances.[3] Decisions surrounding the administration of CAH to patients at the end of life can be challenging, with many health care professionals, patients, and carers presenting differing opinions on appropriate management.[3,8–11] The General Medical Council of the U.K. has released guidance concerning the administration of CAH at the end of life for patients who are expected to die within hours or days, and those who are not expected to die within this time frame. Clinicians are required to assess hydration status in both circumstances.[12] However, decisions about appropriate management are often difficult because of a limited understanding of hydration mechanisms in advanced cancer and a lack of evidence to guide health care professionals.[1,8]

Dehydration

Physiologically, dehydration has been defined as deficit of total body water (TBW) that is predominantly intracellular.[13] This process is associated with hypernatremia, an elevated serum osmolarity, which in turn stimulates the sensation of thirst from the thirst center.[14] Patients with advanced cancer may not fit this pattern because of differences in their fluid requirements and disease pathophysiology, when compared with noncancer populations.[15,16] In cancer, intracellular dehydration is associated with proteolysis and cachexia[17,18] and leads to an increase in antidiuretic hormone (ADH) level through stimulation of osmoreceptors or from direct release from the tumor.[19,20] Furthermore, weight loss, decreased renal perfusion, and cachexia are associated with a loss of intracellular water and solutes affecting hypothalamic osmoreceptors, which in turn stimulates ADH release.[21] ADH increases the water permeability of the distal tubule and collecting duct in the kidney, promoting water absorption and the maintenance of serum osmolarity and sodium at subnormal levels.[14] Consequently, an abnormally low osmolarity may cause symptoms such as nausea and confusion, which have been associated with dehydration.[16]

Most patients with cancer suffer from hyponatremia rather than hypernatremia.[14,15] Hyponatremia results from sodium loss in excess of free water, resulting in a low sodium and serum osmolarity.[14] Furthermore, certain medications such as selective serotonin reuptake inhibitors and nonsteroidal anti-inflammatory drugs also are associated with hyponatremia and are frequently given to patients with cancer for symptom management.[22,23]

Clinical studies suggest that patients dying of cancer may achieve adequate hydration with much lower volumes of water than those recommended for the average medical or surgical patient.[16] This may result from differences in body composition, such as decreased body weight because of cachexia and decreased clearance of free water caused by a variety of mechanisms. For example, patients with advanced cancer may have reduced insensible water losses resulting from a reduction in their

physical activity. Typically, hydration studies are based on noncancer populations and subsequent research findings may not extrapolate to patients with cancer.[24] Consequently, proffered definitions of dehydration in patients with cancer vary throughout the literature, with authors using different combinations of clinical parameters as diagnostic criteria.[13,14,25] The lack of uniformity in definitions complicates study comparisons[24] and makes decisions regarding the use of CAH difficult for clinicians. There is a need for further study in this area to address the limited research base.

Novel methods of hydration assessment, such as bioelectrical impedance analysis (BIA), have been used in some areas (e.g., in the assessment of the fluid states of edematous patients with renal failure receiving dialysis),[26] but evidence for its use in advanced cancer is limited. BIA is a safe, noninvasive, bedside method of assessing hydration.[27]

Aims

The aims of this review are:

1. To critically appraise the existing methods of assessing hydration status in patients with advanced cancer, namely physical examination and biochemical measures;
2. To identify dehydration-related symptoms in patients with advanced cancer; and
3. To review the use of BIA in the assessment of hydration and to discuss its potential use in patients with advanced cancer.

Methods

A search strategy was developed for finding relevant publications in electronic literature databases. In January 2012, four electronic databases were searched (MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Scopus) using combinations of the key words: palliative care, terminally ill, hospice, terminal care, dehydration, water-fluid balance, fluid balance, bioelectrical impedance, cancer, tumor, carcinoma, and malignancy. The search was limited to English language literature published between 1960 and 2012. The search strategy for MEDLINE is shown in Table 1 and was adapted for the other databases.

Bibliographies of relevant articles were manually searched to identify more articles for potential inclusion. Additionally, a hand search of the most recent issues (January 2010 to July 2012) of 12 relevant peer-reviewed journals was conducted: *Journal of Pain and Symptom Management*, *Journal of Palliative Care*, *Palliative Medicine*, *Journal of Palliative Medicine*, *New England Journal of Medicine*, *Lancet Oncology*, *British Medical Journal (BMJ)*, *BMJ Supportive and Palliative Care*, *The Journal of the American Medical Association*, *Annals of Internal Medicine*, *Nutrition*, and *American Journal of Clinical Nutrition*. The gray literature was searched; this literature comprised abstracts from the *American Academy of Hospice and Palliative Medicine* conferences (2010–2012), the *European Association of Palliative Care* conferences (2010–2012), the *Palliative Care Congress* (2012), the *International Congress of Palliative Care* (2010), and the *Marie Curie Research Conferences* (2011–2012). To obtain further information about the gray literature abstracts that were selected for inclusion in this study, the authors of these studies were contacted (by e-mail) and asked to provide more information about the research. Further details of studies included in this review are presented in Table 2 (available on jpsmjournal.com).

Selection Criteria

One reviewer (A. C. N.) used a stepwise procedure to identify relevant studies. Studies addressing (de)hydration assessment (physical examination, biochemical measures, symptom assessment, and BIA) in patients with advanced cancer were eligible for inclusion in the review.

Table 1
Search Strategy Applied in MEDLINE

Query Number	Query Content
#1	(((palliative care) OR hospice) OR terminally ill) OR terminal care
#2	((((cancer) OR neoplasms) OR tumor) OR carcinoma) OR malignancy
#3	dehydration
#4	(water-electrolyte balance) OR fluid balance
#5	bioelectrical impedance
#6	#1 AND #2
#7	#3 OR #4
#8	#5 AND #6
#9	#6 AND #7
#10	#8 OR #9
#11	Limit #10 to Humans and English language

For the purposes of this study, advanced cancer was defined as a diagnosis of cancer where no further curative treatment is possible, which may be associated with metastases (histological or radiological). Articles were excluded if the studies were not in English or if they primarily reported on pediatric populations.

Data Extraction

Data were extracted using a standard form to record the following themes: purpose of study, study design, participants, exclusions, sample size and statistics, dehydration definition(s), outcome measure, and study methods. The first author extracted the data from studies and discussed the results with A. F. K., S. R. M., and C. R. M. Reviewers were not blinded for authors, institutions, or journals of publication.

Quality Assessment

Because the review included studies with both quantitative and qualitative elements, a multimethods assessment tool, devised by Hawker et al.,[28] was used to evaluate the study quality. This assessment tool comprises nine areas; each area was rated on a four-point scale from one (very poor) to four (good). The areas covered were abstract and title, introduction and aims, methods and data, sampling, data analysis, ethics and bias, results, transferability or generalizability, and implications and usefulness. Consequently, each article was given a total score (maximum of 36 = good and a minimum of 9 = very poor) based on the methodological rigor. The methodological quality was assessed independently by A. C. N. and A. F. K. Both authors agreed on the quality assessment of all studies. Data were stored and analyzed using Statistical Software Package for the Social Sciences (SPSS version 20.0; IBM SPSS Inc., Chicago, IL). The methodological quality score is ordinal in nature; consequently, Spearman's rank correlation coefficient was chosen to measure pairwise correlations of scores between assessors.

Results

Results of the literature search are summarized in Fig. 1. The initial literature search using the keywords outlined in the Methods section returned 334 articles. A total of 316 of these articles were rejected after the review of the abstract as not relevant. The remaining 18 articles were examined by our inclusion and exclusion criteria. Three articles were excluded as they primarily reported noncancer populations, resulting in the inclusion of 15 studies in the review. The methodological quality of the selected studies ranged between 22 and 36. Spearman's rank correlation coefficient demonstrated a statistically significant level of agreement between assessors ($r_s = 0.846$, $P < 0.0001$). Commonly, sample size calculations were not conducted and some studies lacked descriptive information about the context, setting, and characteristics of the included (and excluded) patients. Consequently, several studies received lower scores regarding their potential transferability and generalizability. However, no study made any claim that its data could be generalized beyond the particular population of interest.

Physical Examination

The clinical assessment of hydration, through the process of physical examination, is a measure of the extracellular fluid compartment (i.e., extracellular water content, skin turgor, jugular venous pressure, and pulse).[15] However, as dehydration prominently describes an intracellular process, clinical assessment is unable to diagnose intracellular dehydration.[14] There are no routine bedside technologies that measure fluid in the intracellular space.[29] Aware of this problem, authors have attempted to address the issue by creating a distinction between dehydration defined physiologically from that derived from subjective clinical assessment.[30,31] In these instances, the term *clinical dehydration* is generally used to encompass all types of deficit fluid as they appear in the clinical setting.[24] This highlights the possible conflict between the clinical experience of dehydration compared with the biochemical and physiological definitions of dehydration commonly found in the literature.[32]

Some authors have attempted to clarify which signs are clinically relevant in the assessment of dehydration in elderly and cancer populations. Noncancer studies have found certain variables to correlate with dehydration in elderly populations; these include tongue dryness, longitudinal tongue furrows, dry mucous membranes, upper body muscle weakness,

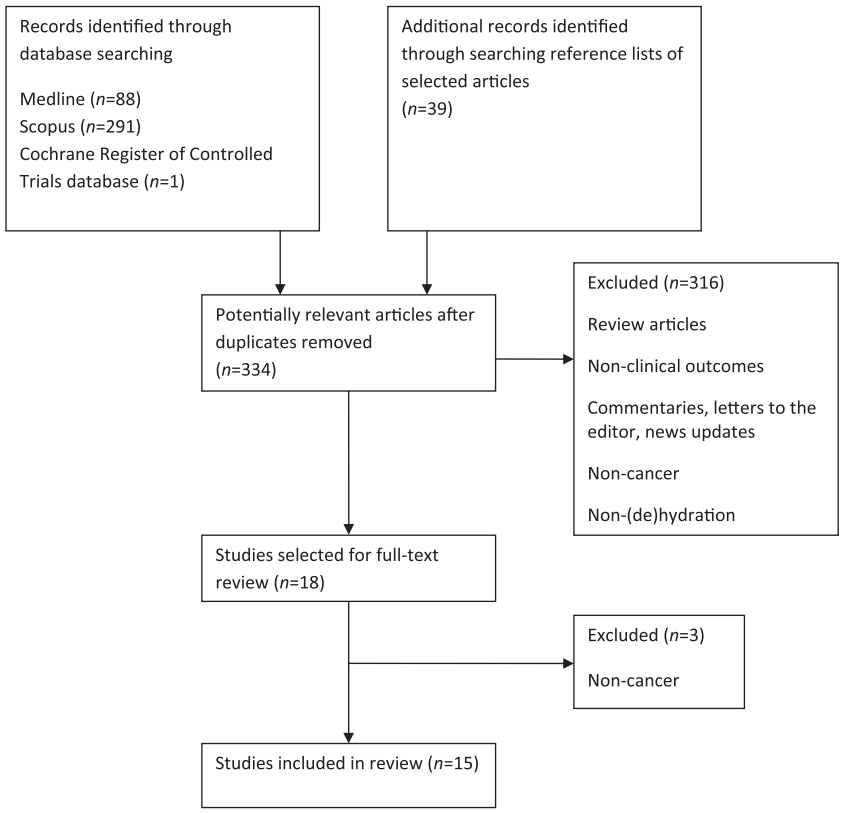

Fig. 1. Overall selection process for clinical studies included in the review.

confusion, speech difficulty, sunken eyes,[33] dry axilla,[34] a fall in systolic blood pressure, reduced laxity of sternal skin turgor, and low body mass index.[24]

Based on the outcomes of these studies, Morita et al.[35] subsequently developed a dehydration score consisting of three variables (dryness of oral mucous membranes, axillary moisture, and sunkenness of eyes). This score was used to assess dehydration, in addition to assessments of delirium and peripheral edema, in a study of CAH volume and its association with symptoms in terminally ill cancer patients with abdominal malignancies.[35] Dehydration scores were significantly lower in the patients receiving CAH in the last three weeks of life compared with the non-CAH group; however, use of CAH was associated with increases in peripheral edema. No significant difference in hyperactive delirium, communication capacity, bronchial secretions, agitation, myoclonus, or serum biochemistry was evident between the two groups. A similar study by the same authors examined the relationship between laboratory findings, artificial fluids, fluid balance, and clinical measures of dehydration in terminally ill patients with abdominal cancer.[36] The authors found no statistically significant difference in the fluid balance in patients with an increased clinical dehydration score compared with those without.[36] Myoclonus and sedation have been associated with dehydration in a study by Bruera et al.,[37] who demonstrated improvements in these variables during a randomized, controlled, double-blind trial involving dehydrated patients with cancer receiving CAH. However, these findings have not been replicated in other studies.[35]

There is conflict over the accuracy of physical findings in assessing hydration in advanced cancer. Skin turgor has been shown to poorly correlate with dehydration as patients with cancer are prone to changes in subcutaneous tissue, which may create inaccuracy in its interpretation[14,33] Postural hypotension is identified as a feature of hypovolemia (low blood volume), but lacks sensitivity as a test for dehydration.[38–40] This highlights how

different definitions of dehydration may create difficulty in interpreting study outcomes. Furthermore, postural hypotension may not be suitable in assessing some patients with advanced cancer at risk for poor mobility, falls, and taking medications known to cause hypotension, for example opioids and diuretics.[41,42] Variations in body mass caused by cachexia and edema may make body mass index measurements unsuitable.[14,15,43,44] Although part of a standard medical examination, capillary refill is only able to detect hypovolemia in children and lacks sensitivity in adults.[38,45–47]

Biochemical Measures

Biochemical tests include the analysis of blood (obtained from venipuncture) and urine samples. A change in urine and blood chemistry provides clues to the underlying cause of hydration disturbances and helps the clinician identify potential treatments. Measures such as serum urea:creatinine ratio and urine:plasma osmolality ratio have be used to assess hydration status, with ratios of ≥100 (mmol/mmol) and ≥1.2, respectively, suggesting dehydration.[13,14,24,48,49] Biochemical dehydration occurs when intracellular water is lost, leading to transmembrane water migration from the intravascular compartment under osmotic pressure and increased relative plasma sodium concentration.[14,50,51] Electrolyte abnormalities, such as hyperkalemia, may suggest underlying causative factors of dehydration and may be useful prognostic indicators.[52] Atrial natriuretic peptide (ANP) level lower than 15 pg/mL has been used to define dehydration in palliative care patients;[53] however, the validity and reliability of this measure has not yet been determined. Observational studies have found that biochemical measures of dehydration poorly correlate with symptoms, such as thirst and dry mouth.[54]

Biochemical investigations are performed for various reasons, including clinical monitoring, in advance of medical procedures, and assessment in response to change in the clinical condition of a patient. In these circumstances, abnormal renal function may prompt the clinician to consider the initiation of CAH; however, studies have shown that patients with advanced cancer may be prone to renal impairment at the end of life. The prevalence of prerenal failure in cancer inpatients was 44% ($n = 27/62$) in a study by Guo et al.;[55] no difference in length of stay was evident between patients with renal failure compared with those with normal renal function. Biochemical measures alone may not be able to detect clinically meaningful hydration changes in patients with cancer, especially if measurements are performed without a record of the patient's baseline renal function for comparison. Authors have demonstrated a worsening in renal function in patients with cancer approaching death, irrespective of whether CAH is administered or not.[35,36,56] Therefore, in advanced cancer, static abnormal renal function measurements may provide incomplete assessments of hydration status.[31] A prospective study by Waller et al.[56] examining hydration indicators in patients found 87% ($n = 59/68$) of dying patients to be biochemically dehydrated. No difference in serum biochemistry or consciousness was found between patients receiving intravenous fluids compared with those who received no fluids. The authors conclude that there is no clinical benefit to the administration of intravenous fluids in terminally ill patients with cancer.

Symptoms of Dehydration

Previous research has attempted to determine if symptom burden is related to dehydration and, consequently, whether the use of CAH improves these symptoms. The first quantitative estimate of dehydration symptoms in advanced cancer was conducted by Burge[57] in 1993. This study was a cross-sectional analysis of the symptoms of dehydration in 52 palliative care patients with cancer. A series of 100 mm visual analogue scale scores were used to evaluate the severity of seven symptoms (thirst, dry mouth, bad taste, nausea, pleasure in drinking, fatigue, and pain) experienced by patients. Fatigue was the most severe symptom (65% rated greater than 50 mm); dry mouth and thirst also were very prevalent (53.8% and 60% rated greater than 50 mm, respectively). There was no association between symptom severity and fluid intake, or between biochemical measures and thirst, a finding consistent with other studies.[33] However, Cerchietti et al.[2] demonstrated improvements in thirst and chronic nausea in symptomatic palliative care cancer patients with limited oral intake, randomized to receive either CAH or

standard medical therapy. Significant improvements in relief of thirst and chronic nausea were present in both groups at 24 hours; however, this effect was only maintained in the hydration group at 48 hours. There is little evidence to support the role of CAH in the management of delirium in advanced cancer.[58,59] A statistical analysis of hospital inpatient data of 1125 patients with advanced cancer failed to demonstrate a relationship between hydration and delirium;[60] this is a similar finding in other studies.[2,35,61] However, hyperactive delirium was found to be more prevalent in patients with advanced abdominal cancers receiving small volumes of CAH (<1 L/d) compared with patients receiving larger volumes (>1 L/d).[61]

Studies assessing oral symptoms and dehydration have found mixed results. Dry mouth and thirst were highly prevalent in a study of 82 patients with cancer receiving palliative care at risk for dehydration.[54] Of the 23 (28%) patients able to respond to the questions, 20 (87%) reported dry mouth and 19 (83%) complained of thirst. No association between thirst, dry mouth, respiratory tract secretions, and biochemical dehydration was found. Similarly, in a cohort of 88 palliative care patients, Morita et al.[53] found thirst to be highly prevalent, but poorly associated with dehydration. Interestingly, the authors found that thirst was associated with water depletion (defined by ANP). However, a lack of validity and reliability of ANP and the arbitrary cutoff level defined by the authors may indicate that this area requires further study before definitive conclusions are drawn. The effect of CAH on sensation of thirst in 30 terminal cancer patients was evaluated by Musgrave et al.[62] Nineteen patients were able to communicate thirst intensity, but no association between level of thirst, intravenous fluids, and biochemical parameters was demonstrated. Nakajima[63] explored the influence of hydration on symptoms in a series of 75 patients with advanced abdominal cancer. The study found that CAH improved oral membranous signs of dehydration but worsened peripheral edema, ascites, and chest secretions. Yamaguchi et al.[61] found no significant difference in symptom burden between patients receiving high volumes (>1 L/24 h) and low volumes (<1 L/24 h) of fluid in a multicenter, prospective, observational study of 161 patients with advanced cancer receiving CAH.

Bioelectrical Impedance Analysis

BIA is based on the flow of electrical current through the body, measured through the application of superficial skin electrodes.[64] BIA is not a direct method of monitoring body composition and TBW requires prediction equations for analysis.[27] Prediction equations have been developed using linear regression and adherence to some basic assumptions, including the shape of the body, the relationship between trunk and leg lengths, and the level of hydration (as lean body mass hydration is considered 73%) and fat fraction.[27] No universal equation exists to accommodate different populations; therefore, specific validated equations need to be selected depending on age, ethnic group, and the clinical situation being studied.[27] However, cancer (and other wasting diseases) reduces intracellular water through cachexia, such that the TBW derived from equations for normal populations will become less accurate.[15]

The limitations of BIA have been addressed by Piccoli[65] by using an alternative method of interpreting the BIA information. Use of raw BIA measures can provide direct measurements of tissue cell hydration and integrity. These approaches are independent of regression equations or weight, and can be carried out even in situations where BIA assumptions are not met (e.g., in advanced cancer). These raw measurements comprise resistance (R—the restriction to the flow of electrical current through the body, primarily related to the amount of water present in tissue) and reactance (Xc—resistive effect produced by the tissue interfaces and cell membranes) measurements (Fig. 2). Two indicators of clinical significance can be derived from the raw measurement; one is phase angle and the other is a plot of the impedance vector against a known distribution (bioelectrical impedance vector analysis—BIVA).[27,66,67]

Phase Angle. Phase angle is a derived measure obtained for the relation between the direct measures of resistance and reactance and can be calculated from raw BIA measurements (Fig. 2).[68] Part of the measured electrical current is stored by the cell membranes, which act

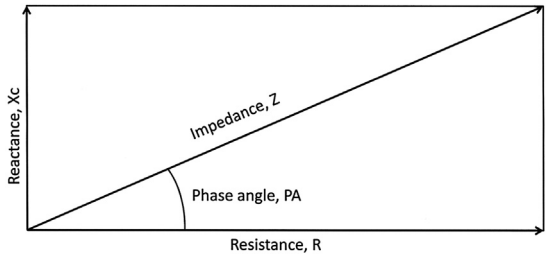

Fig. 2. Graphical representation of bioelectrical impedance analysis raw measurements: impedance, reactance, resistance, and phase angle.

as capacitors, creating a phase shift, quantified geometrically as phase angle.[27] Phase angle has been used as a prognostic marker in various patient groups, including human immunodeficiency virus,[69,70] dialysis patients,[71–73] breast cancer,[74] lung cancer,[75] colorectal cancer,[76] and pancreatic cancer.[77] Recently, studies have used the technology to evaluate hydration in advanced cancer; for example, Davis et al.[15] performed a prospective observational study using BIA in patients with advanced cancer receiving CAH. BIA was done for three consecutive days from initiation of CAH. The authors found that a greater phase angle on Day 1 of CAH predicted better survival; however, a rise in phase angle (indicating increased reactance and the distribution of fluid to the intracellular compartment) during CAH predicted shorter survival. The authors propose that an increase in phase angle during CAH reflects preexisting intracellular dehydration, which occurs in patients who are more likely to have cachexia-anorexia syndrome, and hence, a worse prognosis compared with those without a phase angle rise during CAH. This may suggest that phase angle may be able to assist in prognostication and may highlight underlying physiological differences among patients with cancer receiving CAH. Crawford et al.[78] used BIA to show that elevated metabolic rate and accumulation of body fluids were indicators of poor prognosis in a series of palliative care patients with cancer. Although interesting, these studies focus on survival and do not explore issues regarding hydration assessment or the appropriateness of using CAH in these patients.

Bioelectrical Impedance Vector Analysis. BIVA, in a fashion similar to the electrocardiogram, uses graphical vectors to provide a visual analysis of BIA data.[67] Using this method, impedance (Z) is plotted as a vector from its components R (x-axis) and Xc (y-axis), after being standardized by height (H) (Fig. 3). Confidence interval of the mean vector can be plotted to allow statistical analysis and comparison in (and between) population groups (Fig. 4). The advantage of this method is that it allows information to be obtained simultaneously about changes in tissue hydration or soft tissue mass, independent of regression equations, or body weight. Therefore, BIVA readings can be interpreted accurately even if patients are at extremes of weight or volume distribution. BIVA measurements can be compared with reference populations to enable comparisons with healthy populations and other diseases. Changes in the shape and direction of plotted vectors (vector migration) on repeated measurements in the same individual allow change in hydration status over time to be recorded.[27] BIVA has previously been used to monitor hydration change in edematous patients receiving hemodialysis and may provide a way to monitor change in hydration over time in patients with advanced cancer (e.g., during the dying phase). Although BIVA has been used to study hydration in different diseases (e.g., renal failure, cholera, and congestive cardiac failure),[26,79–86] and to undertake general body composition assessments in lung cancer[85,86]

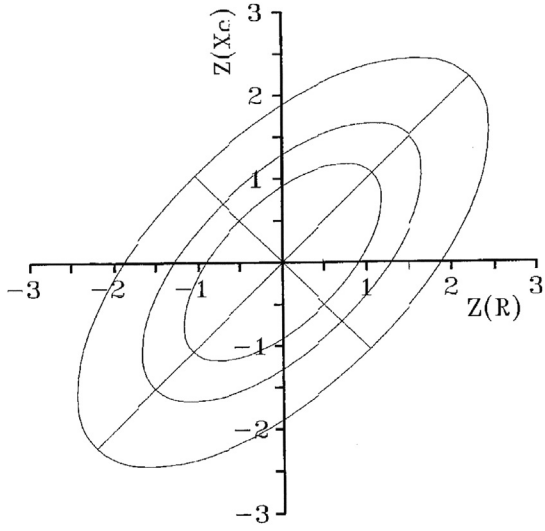

Fig. 3. Example of a bioelectrical impedance vector analysis plotted on the RXc graph with 95%, 75%, and 50% tolerance ellipses. Reproduced with permission from Piccoli et al.[67]

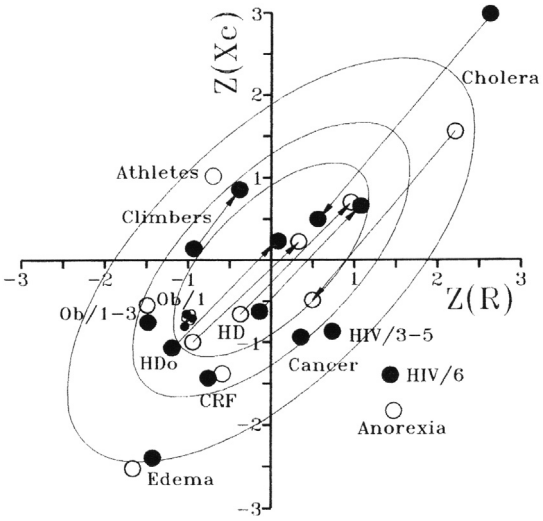

Fig. 4. Data drawn from the literature and plotted on the RXc-score graph after transformation of impedance measurements from several disease groups into bivariate Z-scores (with respect to their reference population). Solid and open circles represent male and female, respectively. A forward or backward displacement of vectors parallel to the major axis of ellipses was associated with dehydration or fluid overloading, respectively, reaching extremes out of the poles. Vectors above or below the major axis (meaning upper left or lower right half of ellipses) were associated with more or less cell mass in soft tissues, respectively, with extremes along the minor axis. CRF = chronic renal failure; HD = hemodialysis; HDo = obese hemodialysis patients; HIV = human immunodeficiency virus Stages 1–6; Ob/1–3 = obese subjects of Classes I–III; WR = Walter Reed Stages 1–6. Reproduced with permission from Piccoli et al.[67]

and cancers of the head and neck,[87] it has yet to be used to specifically assess hydration in advanced cancer.

Discussion

Clinical examination and biochemical tests are standard methods of assessing hydration, but limitations exist with these methods in advanced cancer. For example, physical examination has a low sensitivity and specificity for identifying fluid deficit.[14,88] Study outcomes are often conflicting and many variables lack evidence for their inclusion in assessing hydration status in adult patients with cancer. Historically, evidence regarding hydration assessment originates from studies in noncancer populations, and particular components of a physical examination (e.g., capillary refill and skin turgor) appear to have less significance in advanced cancer. Equally, there is disagreement about the most appropriate biochemical tests and the diagnostic criteria to diagnose biochemical dehydration. The differences between local, national, and international definitions of dehydration may cause clinicians to be unsure about the significance of biochemical results in patients with advanced cancer.

Other challenges limit the viability of clinical and biochemical assessment techniques. For example, the elderly (who comprise the majority of cancer patients) may have abnormal biochemical profiles secondary to nonhydration related factors, such as altered muscle mass and preexisting renal or metabolic conditions.[16] Repeated venipuncture may cause pain, discomfort, and be viewed as inappropriate for use in the assessment of patients with cancer in certain circumstances (e.g., in the dying phase).[89,90] Consequently, clinicians may avoid performing venipuncture in situations where the risks of causing harm may outweigh the benefits of obtaining biochemical tests. In this review, we highlighted the concept of *clinical dehydration* defined by bedside physician assessment. Clinicians may argue that there is little utility in identifying biochemical dehydration in a patient without symptoms; hence, only clinically relevant signs and symptoms of (de)hydration will be managed. However, in this population, there is a lack of agreement of which signs and symptoms are *clinically relevant*. Additionally, without an understanding of the pathophysiology of disease and its resultant symptoms, there is a risk that features of dehydration may be inaccurately interpreted and, hence, inappropriately managed. Therefore, it is important for dehydration in cancer to be appropriately defined to enable associated signs and symptoms to be identified, thus allowing appropriate management to be initiated. For example, various symptoms have been used as indicators for dehydration, but there is disagreement about the accuracy of these. Although there is some evidence to suggest that nausea is improved through the administration of CAH,[37] the association of nausea with other variables (in this study) has not been clarified. Despite a high prevalence of fatigue,[57] the use of CAH does not appear to improve this

symptom in patients with cancer.[37] Dry mouth and thirst are common in cancer; however, these variables may be unreliable indicators of (de)hydration as a result of their association with other factors.[54,57,62,91,92] One study suggests the significance of thirst when serum ANP is used to define dehydration, but the validity and reliability of this measure has not yet been determined.[53] Despite a greater prevalence of hyperactive delirium in patients receiving reduced volumes of CAH compared with larger volumes,[61] the evidence is poor for the influence of hydration on delirium in advanced cancer.[58,60] Overall there is a lack of clinical assessment tools to evaluate hydration in advanced cancer and unclear data about which symptoms are most related to dehydration. These findings, combined with the unclear benefits and burdens of CAH, make decisions about the use of CAH challenging for health care professionals.

BIA is able to assess body composition and has been used as a prognostic marker in cancer studies.[74–77] One study demonstrated that phase angle increase in patients receiving CAH was associated with increased mortality.[15] This may suggest that patients with cancer differ physiologically in their ability to handle fluids, with some more prone to adverse effects than others. The study is limited by small numbers of patients and a lack of standardization of the type of fluid prescribed and the rate of volume replacement. If a true difference exists, this may highlight the importance for clinicians to consider these factors when administering CAH. Furthermore, studies using BIA may potentially be a tool to enable clinicians to better understand hydration in advanced cancer. BIA alone is limited in its ability to assess hydration in advanced cancer;[27] however, interpretation using BIVA improves the accuracy of measuring static and dynamic hydration states.[26,67,80] The noninvasive nature of the technology may be popular for researchers keen to use novel methodologies for assessing hydration in advanced cancer. Consequently, BIVA shows promise as a method for assessing hydration and could be potentially used to further scientific study into the relationship between hydration and related symptoms. However, further study is required to establish whether measurements of fluid distribution in advanced cancer, as determined by BIA and BIVA, are clinically relevant.

This review is unique in highlighting the potential of BIVA to assess hydration in patients with advanced cancer. We have identified a lack of evidence relating to the assessment and symptomatic treatment of dehydration in cancer, a finding consistent with similar studies in this area.

We recognize that there are several limitations with this review. Although hand searching of relevant journals and gray literature took place, this was limited to the past two years, and the abstract lists were unavailable for some conferences; consequently, there is the potential that data were excluded from this review. Although a structured process for identification and inclusion of articles was adopted, the reviewers were not blinded to the authors and institutions of the reviewed articles. Consequently, there is risk of the reviewers' own bias relating to articles included or excluded from the review. Many of the included studies were small, descriptive, and unpowered studies with differing definitions of dehydration. These diagnostic definitions may have been based on biochemical criteria, clinical markers, or a combination of both; therefore, comparisons between the studies are difficult. Studies involving patients with advanced cancer present ethical and methodological challenges that are compounded by the difficult issue of (de)hydration. Consequently, researchers and ethics committees may still be learning about suitable approaches for this subject, which may currently limit the number of research studies that were available for inclusion in this review. BIA and BIVA have been used to assess body composition in several populations; however, there is a lack of studies using this technology to report on clinically relevant outcomes (e.g., symptom burden, survival, and the effect of CAH on these parameters) in advanced cancer. Additionally, we were unable to identify any literature reporting on the use of BIVA to evaluate hydration in advanced cancer. The intervention studies involving CAH used various routes of administration and different fluid preparations over differing time periods at different stages of the subjects' illness. Although the outcomes of these studies are interesting, the lack of harmony between methodology and

outcomes limits the ability of this review to synthesize data.

A lack of consensus as to how to assess hydration in advanced cancer makes decisions regarding the use of CAH difficult for the clinician. Further complexity is added because of the limited number of high quality studies assessing the benefits and burdens of CAH for this population. This review has highlighted how patients with advanced cancer may experience some benefits from receiving CAH, such as improvements in sedation, myoclonus, and nausea.[2,37] However, there is the potential to cause harm, in terms of worsening symptoms of fluid retention (e.g., peripheral edema, pleural effusion, and ascites).[8,61] On the basis of insufficient evidence, we are limited in our ability to draw definitive recommendations. Clinicians, therefore, are advised to make assessments based on the perceived benefits, risks, and burdens to the individual.[12] The clinician should be familiar with existing methods of hydration assessment and be aware of their limitations.

Further research to clarify the symptoms associated with dehydration and to highlight the benefits and burdens of CAH in patients with advanced cancer is required. Future studies need be appropriately powered, with clear definitions of (de)hydration. These studies will require innovative methodologies, for example, using advance consent of patients. Core outcome sets for hydration studies should be agreed to enable clinicians to compare, contrast, and synthesize the results of the studies more effectively. The assessment of (de)hydration should be conducted in a variety of terminal diagnoses at different stages of the illness trajectory.

Currently, no studies have used BIVA for the assessment of hydration in the advanced cancer population. Pilot studies using BIVA are required to determine its feasibility and efficacy before conclusions may be drawn. If feasible, BIVA may have a role in evaluating hydration in advanced cancer and improving knowledge of hydration in dying patients. BIVA could be used in combination with other hydration assessment methods to determine the scientific association of symptoms with dehydration, facilitating the creation of core outcome measures for hydration, which can further support intervention studies using CAH. Consequently, future studies could use BIA and BIVA to determine its usefulness in predicting and monitoring clinical response to treatments (such as CAH) and survival through static and longitudinal assessments.

Conclusions

Hydration is an important area of care for patients with advanced cancer. Limitations exist with current hydration assessment methods and there is a lack of consensus of the symptoms associated with dehydration. The benefits and burdens of providing CAH to patients dying of cancer are unclear. BIVA shows promise as a hydration assessment tool but requires further study in advanced cancer. Innovative methodologies for research are required to add to the evidence base and ultimately improve the care for the dying.

Disclosures and Acknowledgments

The authors declare no conflicts of interest. The authors thank Suzanne Beck who assisted with the literature search for this review article.

References

1. Viola RA, Wells GA, Peterson J. The effects of fluid status and fluid therapy on the dying: a systematic review. J Palliat Care 1997;13:41–52.

2. Cerchietti L, Navigante A, Sauri A, Palazzo F. Hypodermoclysis for control of dehydration in terminal-stage cancer. Int J Palliat Nurs 2000;6: 370–374.

3. Fine RL. Ethical issues in artificial nutrition and hydration. Nutr Clin Pract 2006;21:118–125.

4. Raijmakers NJ, van ZL, Costantini M, et al. Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects. Ann Oncol 2011;22: 1478–1486.

5. Parkash R, Burge F. The family's perspective on issues of hydration in terminal care. J Palliat Care 1997;13:23–27.

6. Mercadante S, Ferrera P, Girelli D, Casuccio A. Patients' and relatives' perceptions about intravenous and subcutaneous hydration. J Pain Symptom Manage 2005;30:354–358.

7. Malia C, Bennett MI. What influences patients' decisions on artificial hydration at the end of life?

A Q-methodology study. J Pain Symptom Manage 2011;42:192–201.

8. Good P, Cavenagh J, Mather M, Ravenscroft P. Medically assisted hydration for palliative care patients. Cochrane Database Syst Rev 2008;2: CD006273.

9. van der RP, Good P, Higgins I, Sneesby L. Palliative care professionals' perceptions of nutrition and hydration at the end of life. Int J Palliat Nurs 2008;14:145–151.

10. Ganzini L. Artificial nutrition and hydration at the end of life: ethics and evidence. Palliat Support Care 2006;4:135–143.

11. Dalal S, Del FE, Bruera E. Is there a role for hydration at the end of life? Curr Opin Support Palliat Care 2009;3:72–78.

12. General Medical Council. Treatment care towards end life: Good practice decision making. 2010. Available from: http://www.gmc-uk.org/guidance/ethical_guidance/end_of_life_adult_patients_not_expected_to_die_imminently.asp. Accessed August 2, 2012.

13. Mange K, Matsuura D, Cizman B, et al. Language guiding therapy: the case of dehydration versus volume depletion. Ann Intern Med 1997;127: 848–853.

14. Sarhill N, Walsh D, Nelson K, Davis M. Evaluation and treatment of cancer-related fluid deficits: volume depletion and dehydration. Support Care Cancer 2001;9:408–419.

15. Davis MP, Yavuzsen T, Khoshknabi D, et al. Bioelectrical impedance phase angle changes during hydration and prognosis in advanced cancer. Am J Hosp Palliat Care 2009;26:180–187.

16. Steiner N, Bruera E. Methods of hydration in palliative care patients. J Palliat Care 1998;14:6–13.

17. Haussinger D, Lang F, Gerok W. Regulation of cell function by the cellular hydration state. Am J Physiol 1994;267:E343–E355.

18. Haussinger D, Gerok W. Role of the cellular hydration state for cellular function: physiological and pathophysiological aspects. Adv Exp Med Biol 1994; 368:33–44.

19. Johnson BE, Chute JP, Rushin J, et al. A prospective study of patients with lung cancer and hyponatremia of malignancy. Am J Respir Crit Care Med 1997;156:1669–1678.

20. McDonald GA, Dubose TD Jr. Hyponatremia in the cancer patient. Oncology (Williston Park) 1993; 7:55–64.

21. Raftopoulos H. Diagnosis and management of hyponatremia in cancer patients. Support Care Cancer 2007;15:1341–1347.

22. Sandifer MG. Hyponatremia due to psychotropic drugs. J Clin Psychiatry 1983;44:301–303.

23. Finfgeld DL. SSRI-related hyponatremia among aging adults. J Psychosoc Nurs Ment Health Serv 2003;41:12–16.

24. Vivanti A, Harvey K, Ash S, Battistutta D. Clinical assessment of dehydration in older people admitted to hospital: what are the strongest indicators? Arch Gerontol Geriatr 2008;47:340–355.

25. Gamble JL. Chemical anatomy, physiology and pathology of extracellular fluid. Cambridge, MA: Harvard Medical School, Department of Pediatrics, 1939.

26. Piccoli A. Bioelectric impedance measurement for fluid status assessment. Contrib Nephrol 2010; 164:143–152.

27. Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. Curr Opin Clin Nutr Metab Care 2005;8:311–317.

28. Hawker S, Payne S, Kerr C, Hardey M, Powell J. Appraising the evidence: reviewing disparate data systematically. Qual Health Res 2002;12:1284–1299.

29. Kavouras SA. Assessing hydration status. Curr Opin Clin Nutr Metab Care 2002;5:519–524.

30. Thomas DR, Cote TR, Lawhorne L, et al. Understanding clinical dehydration and its treatment. J Am Med Dir Assoc 2008;9:292–301.

31. Weinberg AD, Minaker KL. Dehydration. Evaluation and management in older adults. Council on Scientific Affairs, American Medical Association. JAMA 1995;274:1552–1556.

32. Thomas DR, Tariq SH, Makhdomm S, Haddad R, Moinuddin A. Physician misdiagnosis of dehydration in older adults. J Am Med Dir Assoc 2004;5(2 Suppl):S30–S34.

33. Gross CR, Lindquist RD, Woolley AC, et al. Clinical indicators of dehydration severity in elderly patients. J Emerg Med 1992;10:267–274.

34. Eaton D, Bannister P, Mulley GP, Connolly MJ. Axillary sweating in clinical assessment of dehydration in ill elderly patients. BMJ 1994;308:1271.

35. Morita T, Hyodo I, Yoshimi T, et al. Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies. Ann Oncol 2005;16:640–647.

36. Morita T, Hyodo I, Yoshimi T, et al. Artificial hydration therapy, laboratory findings, and fluid balance in terminally ill patients with abdominal malignancies. J Pain Symptom Manage 2006;31: 130–139.

37. Bruera E, Sala R, Rico MA, et al. Effects of parenteral hydration in terminally ill cancer patients: a preliminary study. J Clin Oncol 2005;23: 2366–2371.

38. McGee S, Abernethy WB III, Simel DL. The rational clinical examination. Is this patient hypovolemic? JAMA 1999;281:1022–1029.

39. Johnson DR, Douglas D, Hauswald M, Tandberg D. Dehydration and orthostatic vital signs in women with hyperemesis gravidarum. Acad Emerg Med 1995;2:692–697.

40. Koziol-McLain J, Lowenstein SR, Fuller B. Orthostatic vital signs in emergency department patients. Ann Emerg Med 1991;20:606–610.

41. Verhaeverbeke I, Mets T. Drug-induced orthostatic hypotension in the elderly: avoiding its onset. Drug Saf 1997;17:105–118.

42. Simonds WF. The molecular basis of opioid receptor function. Endocr Rev 1988;9:200–212.

43. Sarhill N, Mahmoud F, Walsh D, et al. Evaluation of nutritional status in advanced metastatic cancer. Support Care Cancer 2003;11:652–659.

44. Morita T, Tei Y, Inoue S, Suga A, Chihara S. Fluid status of terminally ill cancer patients with intestinal obstruction: an exploratory observational study. Support Care Cancer 2002;10:474–479.

45. Schriger DL, Baraff LJ. Capillary refill—is it a useful predictor of hypovolemic states? Ann Emerg Med 1991;20:601–605.

46. Gorelick MH, Shaw KN, Murphy KO. Validity and reliability of clinical signs in the diagnosis of dehydration in children. Pediatrics 1997;99:E6.

47. Poole SR. Criteria for measurement of dehydration. Ann Emerg Med 1990;19:730–731.

48. Vullo-Navich K, Smith S, Andrews M, et al. Comfort and incidence of abnormal serum sodium, BUN, creatinine and osmolality in dehydration of terminal illness. Am J Hosp Palliat Care 1998;15: 77–84.

49. Leibovitz A, Baumoehl Y, Lubart E, et al. Dehydration among long-term care elderly patients with oropharyngeal dysphagia. Gerontology 2007;53: 179–183.

50. Berk L, Rana S. Hypovolemia and dehydration in the oncology patient. J Support Oncol 2006;4: 447–454.

51. Fried LF, Palevsky PM. Hyponatremia and hypernatremia. Med Clin North Am 1997;81:585–609.

52. Alsirafy SA, Sroor MY, Al-Shahri MZ. Predictive impact of electrolyte abnormalities on the admission outcome and survival of palliative care cancer referrals. J Palliat Med 2009;12:177–180.

53. Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Determinants of the sensation of thirst in terminally ill cancer patients. Support Care Cancer 2001;9: 177–186.

54. Ellershaw JE, Sutcliffe JM, Saunders CM. Dehydration and the dying patient. J Pain Symptom Manage 1995;10:192–197.

55. Guo Y, Hainley S, Palmer JL, Bruera E. Azotemia in cancer patients during inpatient rehabilitation. Am J Hosp Palliat Care 2007;24:264–269.

56. Waller A, Hershkowitz M, Adunsky A. The effect of intravenous fluid infusion on blood and urine parameters of hydration and on state of consciousness in terminal cancer patients. Am J Hosp Palliat Care 1994;11:22–27.

57. Burge FI. Dehydration symptoms of palliative care cancer patients. J Pain Symptom Manage 1993;8:454–464.

58. Galanakis C, Mayo NE, Gagnon B. Assessing the role of hydration in delirium at the end of life. Curr Opin Support Palliat Care 2011;5:169–173.

59. Keeley PW. Delirium at the end of life. Clin Evid (Online) 2009. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907814/pdf/2009-2405.pdf. Accessed August 2, 2012.

60. Galanakis C, Mayo N, Gagnon B. The role of hydration at the end of life. J Palliat Care 2010;26:249. (P421).

61. Yamaguchi T, Morita T, Shinjo T, et al. Effect of parenteral hydration therapy based on the Japanese national clinical guideline on quality of life, discomfort, and symptom intensity in patients with advanced cancer. J Pain Symptom Manage 2012;43: 1001–1012.

62. Musgrave CF, Bartal N, Opstad J. The sensation of thirst in dying patients receiving i.v. hydration. J Palliat Care 1995;11:17–21.

63. Nakajima N. A clinical study on the influence of hydration volume toward symptoms in terminally ill cancer patients with abdominal malignancies. Palliat Med 2012;26:462. (P23).

64. Sarhill N, Walsh D, Nelson K, Homsi J, Komurcu S. Bioelectrical impedance, cancer nutritional assessment, and ascites. Support Care Cancer 2000;8:341–343.

65. Piccoli A. Patterns of bioelectrical impedance vector analysis: learning from electrocardiography and forgetting electric circuit models. Nutrition 2002;18:520–521.

66. Piccoli A. Whole body—single frequency bioimpedance. Contrib Nephrol 2005;149:150–161.

67. Piccoli A, Pillon L, Dumler F. Impedance vector distribution by sex, race, body mass index, and age in the United States: standard reference intervals as bivariate Z scores. Nutrition 2002;18:153–167.

68. Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN Jr. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. Am J Clin Nutr 2005;82: 49–52.

69. Schwenk A, Beisenherz A, Romer K, et al. Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. Am J Clin Nutr 2000;72:496–501.

70. Ott M, Fischer H, Polat H, et al. Bioelectrical impedance analysis as a predictor of survival in

patients with human immunodeficiency virus infection. J Acquir Immune Defic Syndr Hum Retrovirol 1995;9:20–25.

71. Fein PA, Gundumalla G, Jorden A, et al. Usefulness of bioelectrical impedance analysis in monitoring nutrition status and survival of peritoneal dialysis patients. Adv Perit Dial 2002;18:195–199.

72. Mushnick R, Fein PA, Mittman N, et al. Relationship of bioelectrical impedance parameters to nutrition and survival in peritoneal dialysis patients. Kidney Int Suppl 2003;87:S53–S56.

73. Chertow GM, Lazarus JM, Lew NL, Ma L, Lowrie EG. Bioimpedance norms for the hemodialysis population. Kidney Int 1997;52:1617–1621.

74. Gupta D, Lammersfeld CA, Vashi PG, et al. Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. BMC Cancer 2008;8:249.

75. Gupta D, Lammersfeld CA, Vashi PG, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in stage IIIB and IV non-small cell lung cancer. BMC Cancer 2009;9:37.

76. Gupta D, Lammersfeld CA, Burrows JL, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. Am J Clin Nutr 2004;80:1634–1638.

77. Gupta D, Lis CG, Dahlk SL, et al. Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer. Br J Nutr 2004;92: 957–962.

78. Crawford GB, Robinson JA, Hunt RW, Piller NB, Esterman A. Estimating survival in patients with cancer receiving palliative care: is analysis of body composition using bioimpedance helpful? J Palliat Med 2009;12:1009–1014.

79. McDonald JJ, Chanduvi B, Velarde G, et al. Bioimpedance monitoring of rehydration in cholera. Lancet 1993;341:1049–1051.

80. Bozzetto S, Piccoli A, Montini G. Bioelectrical impedance vector analysis to evaluate relative hydration status. Pediatr Nephrol 2010;25:329–334.

81. Codognotto M, Piazza M, Frigatti P, Piccoli A. Influence of localized edema on whole-body and segmental bioelectrical impedance. Nutrition 2008;24:569–574.

82. Nescolarde L, Piccoli A, Roman A, et al. Bioelectrical impedance vector analysis in haemodialysis patients: relation between oedema and mortality. Physiol Meas 2004;25:1271–1280.

83. Piccoli A. Bioelectric impedance vector distribution in peritoneal dialysis patients with different hydration status. Kidney Int 2004;65:1050–1063.

84. Pillon L, Piccoli A, Lowrie EG, Lazarus JM, Chertow GM. Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis. Kidney Int 2004;66:1266–1271.

85. Toso S, Piccoli A, Gusella M, et al. Bioimpedance vector pattern in cancer patients without disease versus locally advanced or disseminated disease. Nutrition 2003;19:510–514.

86. Toso S, Piccoli A, Gusella M, et al. Altered tissue electric properties in lung cancer patients as detected by bioelectric impedance vector analysis. Nutrition 2000;16:120–124.

87. Malecka-Massalska T, Smolen A, Zubrzycki J, Lupa-Zatwarnicka K, Morshed K. Bioimpedance vector pattern in head and neck squamous cell carcinoma. J Physiol Pharmacol 2012;63:101–104.

88. Price KA. Hydration in cancer patients. Curr Opin Support Palliat Care 2010;4:276–280.

89. Waitt C, Waitt P, Pirmohamed M. Intravenous therapy. Postgrad Med J 2004;80:1–6.

90. Ross C, Cornbleet M. Attitudes of patients and staff to research in a specialist palliative care unit. Palliat Med 2003;17:491–497.

91. Glore RJ, Spiteri-Staines K, Paleri V. A patient with dry mouth. Clin Otolaryngol 2009;34:358–363.

92. McCann RM, Hall WJ, Groth-Juncker A. Comfort care for terminally ill patients. The appropriate use of nutrition and hydration. JAMA 1994;272: 1263–1266.

Table 2
Characteristics of Reviewed Studies

Study	Purpose	Design	Participants	Exclusions	Dehydration Definition	Outcome Measure	Methods	Appraisal Total Score	Conclusions
Morita et al.[35]	To explore systematically the associations between hydration volume and dehydration and fluid retention symptoms in the last 3 wk of life in terminally ill patients with abdominal malignancies.	Multicenter, prospective, observational study	*n* = *226* Fourteen oncology units, 19 palliative care units (PCUs), and four home-based palliative care programs in Japan. - Age ≥20 y - Life expectancy ≤3 mo - Incurable malignancy of lung or abdominal origin (excluding hepatic malignancies) Mean age = 68 y Male/female = 106/120	*n* = 272 - Death within 3 wk of initial assessment (*n* = 200) - Survival beyond observation period (*n* = 35) - Medical complication (*n* = 17) - Prior communication difficulty (*n* = 15) - Discharge (*n* = 5) Liver cirrhosis, renal failure, nephritis syndrome, protein-losing enteropathy, intra-abdominal shunt for ascites, hypercalcemia, endocrine disorders, and vital organ complications unrelated to underlying malignancies; surgical, radiological, or oncological treatments in the 3 wk before study inclusion; existing communication difficulty; and the use of artificial enteral nutrition.	Degree of dehydration defined on basis of three physical findings	1. Ad hoc dehydration score (0–5) 2. Peripheral edema score (0–21) 3. Pleural effusion score (0–2) 4. Ascites score (0–2) 5. Delirium (evaluated by the Memorial Delirium Assessment Scale [MDAS])	Analyses of data collected: Patients classified into two groups; the hydration group (*n* = 59) who received ≥1 L or more of artificial hydration per day both 1 and 3 wk before death, and the nonhydration group (*n* = 167) who did not.	33	Percentage of patients with deterioration in dehydration score in final 3 wk of life significantly higher in nonhydration group compared with hydration group (35% vs. 14%, *P* = 0.002). Fluid retention symptoms increased significantly in hydration group compared with nonhydration group: edema (44% vs. 29%, *P* = 0.039) ascites (29% vs. 8.4%, *P* < 0.001), pleural effusion (15% vs. 5.4%, *P* = 0.016). No significant difference in degree of bronchial secretion, hyperactive delirium, communication capacity, agitation, myoclonus, or bedsores.
Morita et al.[36]	To explore the association between 1) hydration volume and laboratory findings and 2) calculated fluid balance and the changes in clinical signs of dehydration and fluid retention during the last 3 wk of life in terminally ill patients with cancer.	Multicenter, prospective, observational study	*n* = 125 Fourteen oncology units, 19 PCUs, and four home-based palliative care programs in Japan. - Age ≥20 y - Life expectancy ≤3 mo - Incurable malignancy of lung or abdominal origin (excluding hepatic malignancies) Mean age = 67 y Male/female = 61/64	Number not given Liver cirrhosis, renal failure, nephritis syndrome, protein-losing enteropathy, intra-abdominal shunt for ascites, hypercalcemia, endocrine disorders, and vital organ complications unrelated to underlying malignancies; surgical, radiological, or oncological treatments in the 3 wk before study inclusion; existing communication	Degree of dehydration defined on basis of three physical findings	1. Ad hoc dehydration score (0–5) 2. Peripheral edema score (0–21) 3. Pleural effusion score (0–2) 4. Ascites score (0–2) Scores developed by the authors.	Secondary analyses of data collected: laboratory data, clinical assessment data, fluid balance, and oral intake. Patients classified into two groups: the hydration group (*n* = 44), who received ≥1 L or more of artificial hydration per day both 1 and 3 wk before death, and the nonhydration group (*n* = 81) who did not.	30	The mean albumin level 1 wk before death was significantly lower in the hydration group than in the nonhydration group, and the interaction between hydration group and decrease in the albumin level There was no significant difference between the groups in the mean blood urea nitrogen/creatinine (BUN/Cr), sodium, or potassium levels 1 wk before death.

(*Continued*)

Table 2
Continued

Study	Purpose	Design	Participants	Exclusions	Dehydration Definition	Outcome Measure	Methods	Appraisal Total Score	Conclusions
				difficulty; and the use of artificial enteral nutrition.					The calculated fluid balance was not significantly different between the patients with deterioration in scores of dehydration, edema, ascites, and pleural effusion during the last 3 wk and those without.
Bruera et al.[37]	To determine the effect of clinically assisted hydration (CAH) on overall symptom control in terminally ill cancer patients with dehydration.	Randomized, controlled, double-blind trial	$n = 51$ NB: Sample size calculation 54 per group - A palliative diagnosis of advanced cancer with no further treatment planned - Oral intake ≤1000 mL/d - Decreased skin turgor ≥2 s - One or more of dry mouth, thirst, decreased volume of urine output, and a darker color of urine than usual - Laboratory values consistent with dehydration obtained within 24 hours of admission to the study. - Age ≥16 y - Able to tolerate subcutaneous or intravenous (IV) fluids	$n = 13$ Patient's refusal to participate; the presence of severe dehydration, defined as a decreased systolic resting blood pressure of 30 mm Hg or lower from the patient's baseline value; low perfusion of the limbs; no urine output for 12 h or longer; a decreased level of consciousness; or evidence of severe renal failure or bilateral hydronephrosis.	Oral intake ≤1000 mL/d - Decreased skin turgor ≥2 s - One or more of dry mouth; thirst; decreased volume of urine output; a darker color of urine than usual; laboratory values consistent with dehydration, such as an elevated BUN/Cr ratio of ≥20:1	Target symptoms (hallucinations, myoclonus, fatigue, and sedation) assessed with 0–10 numeric rating scale. Mini Mental State Examination (MMSE)	Patients were randomly assigned to receive either 1000 mL (treatment group) or 100 mL (placebo) normal saline administered over 4 h for 2 d. Patients evaluated for target symptoms, global well-being, and overall benefit.	32	The administration of artificial fluids improved sedation and myoclonus in the intervention group.
Guo et al.[55]	To determine the prevalence of pre-renal azotemia in a cancer rehabilitation patient population. To evaluate the relationship of pre-renal azotemia to rehabilitation outcome, specifically length of stay and discharge destiny in these patients.	Retrospective chart review	Demographics not given. $n = 62$ Cancer patients admitted to the acute inpatient rehabilitation unit: Demographics not given	$n = 8$ Patients considered to have renal insufficiency.	BUN/Cr ratio ≥20 (pre-renal azotemia)	1. Pre-renal azotemia prevalence 2. Length of rehabilitation stay of pre-renal azotemia group compared with non–pre-renal azotemia group 3. Discharge destiny of pre-renal azotemia group compared with non–pre-renal azotemia group	Patients classified into two groups: The pre-renal azotemia group ($n = 27$) and the non–pre-renal azotemia group ($n = 35$). Secondary analyses of collected data: - Demographics - Laboratory data - Length of stay - Discharge destiny	26	Pre-renal azotemia prevalence = 44% ($n = 27/62$) No significant association between pre-renal azotemia on length of rehabilitation stay or discharge destiny.

Waller et al.[56]	Are patients with cancer dehydrated when close to death? Does the provision of IV fluids influence the state of hydration of such patients or their level of consciousness?	Cross-sectional	$n=68$Hospice inpatients: - Terminal cancer - Laboratory tests done within 48 h of death (patients selected after death) Demographics not given	Number and details not given.	Elevated sodium, specific cutoff was not defined	Differences between urea, sodium, serum osmolality, urine osmolality, urine/serum osmolality ratio, BUN/Cr ratio.Alertness scale: 1. Fully conscious 2. Responsive to visual or vocal stimuli 3. Responsive to only painful stimuli 4. Comatose The Early Warning Score is validated for the identification of medical patients at risk general deterioration.	Comparison of biochemical measurements and alertness scale measurements between groups.	26	87% ($n=59/68$) of Patients classified as dehydrated. State of consciousness correlated inversely with serum sodium and urine osmolality. Patients receiving IV fluids were not better hydrated than those without IV therapy. State of consciousness was not improved for those hydrated compare with those without IV therapy.
Burge[57]	To determine the severity and distribution of symptoms associated with dehydration in inpatient palliative care patients. To determine the association between these objective measures of dehydration.	Cross-sectional survey	$n=52$ PCU patients: - Age ≥18 y - Advanced cancer - Prognosis ≤6 wk - Ability to speak English or French - Ability to understand, consent to, and take part in study. Mean age = 64.4 y Male/female = 26/26 27% Died within 2 wk of study	$n=71$ - Confusion ($n=20$) - Weak ($n=7$) - Drowsy/coma ($n=13$) - Language ($n=7$) - Died ($n=5$) - Refused ($n=5$) - Aphasia ($n=2$) - Anxiety/agitation ($n=2$)	Dehydration not defined	Visual analogue scale (VAS) score for following symptoms: - Thirst - Pain - Dry mouth - Nausea - Bad taste - Fatigue - Pleasure to drink	Cross-sectional survey of palliative care inpatients across two hospitals. Associations between symptoms and predictor variables (fluid intake, plasma osmolality, sodium, and urea).	36	No association between severity of symptoms and fluid intake. No association between biochemical measures and thirst. Fatigue, dry mouth, and thirst are highly prevalent.
Cerchietti et al.[2]	To assess the usefulness of hypodermoclysis hydration in the relief of thirst, chronic nausea, and delirium.	Randomized controlled trial	$n=42$ NB sample size = 50 Terminal stage patients with advanced cancer with one or more of the following: - Thirst - Chronic nausea or delirium - Dehydration diagnosed on physical examination (with or without renal failure) - Inability to maintain adequate water intake ≤50 mL/d Mean age = 55.8 y (intervention), 51.7 y (control) Male/female = 17/25	Number not given	Dehydration diagnosed on physical examination (with or without renal failure)	VAS for following symptoms: - Thirst - Chronic nausea - Delirium - MMSE	Twenty patients received 1000 mL 5% dextrose in water with addition of 140 mEq/L sodium chloride per day, at an infusion rate of 42 mL/h via the subcutaneous route. Twenty-two received no fluids. VAS scores and MMSE used to compare hydrated and nonhydrated groups.	28	Both groups showed significant and equal improvements in relief of thirst and nausea at 24 h, but this improvement was only maintained in the hydration group at 48 h. Delirium did not improve significantly in either group.
Ellershaw et al.[54]	To investigate the relationship that respiratory tract secretions, thirst, and dry mouth have with level of	Prospective cohort	$n=82$ Palliative care inpatients: - Advanced cancer - Dying and taking just sips of fluid or unable	Patients were excluded if a doctor or nurse involved in the care of the patient felt that it was inappropriate for	Dehydration definition based on the presence of one or more of the following:	Self-reported symptoms (dry mouth and thirst) by patient Clinical assessment of respiratory tract secretions	Based on dehydration definition: 61 patients defined biochemically dehydrated, 21 not biochemically	34	No statistically significant relationship between respiratory tract secretions, dry mouth, thirst, and

(*Continued*)

Table 2
Continued

Study	Purpose	Design	Participants	Exclusions	Dehydration Definition	Outcome Measure	Methods	Appraisal Total Score	Conclusions
	hydration as measured by biochemical parameters, in terminally ill patients.		to take oral medications Median age = 73 y Male/female = not given All died within 5 d of entry to study.	the patient to be included in the study. No other details given.	- Serum osmolality >295 mOsmol/kg - Creatinine ≥130 μmol/L - Urea ≤12 mmol/L	Biochemical definitions	dehydrated. Comparisons made between groups.		the level of hydration.
Morita et al.[53]	To identify the association between sensation of thirst in hospice inpatients and various medical factors, especially dehydration.	Cross-sectional study	$n = 88$ Palliative care inpatients: - Age ≥18 y or older - Diagnosis of incurable advanced cancer - Physicians' estimate of 6 mo life expectancy or less. Demographics not given	$n = 96$ 1. Cognitive impairment 2. Diabetes insipidus and/or thyroid or adrenal dysfunction 3. Delirium/dementia ($n = 52$) 4. Past history of heart failure, chronic obstructive pulmonary disease, or hypertension ($n = 17$) 5. Palliative Performance Scale of ≥60 ($n = 11$) 6. Lack of laboratory examinations ($n = 6$) 7. Unable to understand VAS ($n = 5$) 8. Faulty blood sampling ($n = 5$)	Two definitions used: 1. Atrial natriuretic peptide (ANP) ≤15 pg/mL 2. Definition of Ellershaw et al[54]: - Serum osmolality >295 mOsmol/kg - Creatinine ≥130 μmol/L - Urea ≤12 mmol/L	VAS score for thirst. ANP ≤15 pg/mL. Ellershaw et al.'s definition.	Patients grouped dehydrated or nondehydratedVAS scores analyzed: - Continuously used as a dependent variable - Logistic regression analysis where patients with VAS ≥8 compared with each other. Comparison of biochemical measurements between groups.	32	No significant correlations observed between the VAS score for thirst and biochemical measures based on the Ellershaw definition. Dehydration defined by ANP level ≤15 pg/mL showed severity of thirst to be significantly associated with: - Hyperosmolality ≥300 mosmol/kg - Gastrointestinal cancer - Survival - Performance status - Oral intake - Vomiting - stomatitis Mouth breathing and opioids potential causes of severe thirst as identified from retrospective chart review.
Galanakis et al.[60]	To estimate the extent to which hydration and related risk factors influence the course of delirium over time.	Retrospective analysis of clinical trial data	$n = 1125$ Patients with advanced cancer surviving at least 3 d, receiving palliative care at centers in Quebec and Ontario as part of a clinical trial for the prevention of delirium.	$n = 1390$ Data unavailable.	Dehydration not defined	Relationship of hydration risk factors to delirium groups. Details of measures unavailable.	Data extracted from a clinical trial database. Group-based trajectory modeling and multivariate linear regression were used to identify subgroups of individuals with similar delirium trajectories during the first 30 d of admission and to determine what factors influence membership to these trajectories	22	Patients classified into six different groups based on presence/absence and course of delirium. Hydration was not predictive of delirium or group membership.

Yamaguchi et al.[61]	To clarify the longitudinal changes in patient-reported global quality of life (QoL), observational discomfort, symptoms, and fluid retention signs in patients with advanced cancer receiving guideline-based parenteral hydration therapy.	Prospective, observational study	$n = 161$ - Age >20 y - Incurable abdominal malignancy - Severely reduced oral intake (<100 kcal/d and 10 mL/d) - Available for follow-up	- Hepatic, prostate, or esophageal malignancy - Renal (creatinine >2 mg/dL) - Heart (NYHA classification >II), or liver failure (total bilirubin >2 mg/dL) unrelated to malignancy - Liver cirrhosis, nephrotic syndrome, or protein-losing enteropathy of any etiology - Intra-abdominal shunt for ascites - Hypothyroidism, adrenal insufficiency, SIADH requiring intervention - Cognitive impairment - Antitumor therapy (surgical, radiological, or chemotherapy) within 2 wk before study - Use of artificial enteral nutrition	Dehydration not defined	1. Patient-reported global QoL (using Item 30 of the European Organization for Research Treatment of Cancer Quality of Life Questionnaire-C30). 2. Observational discomfort (using the Discomfort Scale). 3. Patient reported benefit and satisfaction with CAH 4. Physical symptoms 5. Psychiatric symptoms	Patients completed questionnaires weekly (Weeks 1–4) and then every 2 wk (up until Week 12 or death). Patients received CAH accordingly to national Japanese guideline. CAH reduced to <1 L/d in patients with fluid retention signs. Patients grouped as low volume (<1 L/d) and high volume (>1 L/d)	31	No significant difference of QoL, Discomfort Score and symptoms between low- and high-volume groups. More than 80% of patients maintained all fluid retention signs. Hyperactive delirium significantly higher in small-volume hydration group in last 48 h of life (5.3% vs. 17.3%, $P = 0.009$).
Nakajima[63]	To explore the influences of hydration volume toward the symptoms during the last 3 wk of life in these patients.	Prospective, observational study	$n = 75$	Number not given	Degree of dehydration defined on basis of three physical findings	1. Dehydration score[35] 2. Peripheral edema score 3. Ascites and pleural effusion score 4. Bronchial secretion 5. Delirium (evaluated by the MDAS) Assessment schedule based on work of Morita et al.[35]	Analyses of data collected: Patients classified into two groups; the hydration group ($n = 32$) who received ≥1 L or more of artificial hydration per day both 1 and 3 wk before death, and the nonhydration group ($n = 43$) who did not.	28	The percentages of patients with deterioration in dehydration score in the last 3 wk were significantly higher in the nonhydration group than in the hydration group (35% vs. 13%; $P = 0.027$). Significantly higher fluid retention symptoms reported in the hydration group compared with the nonhydration group: edema (57% vs. 33%, $P = 0.040$), ascites (34% vs. 14%, $P = 0.037$) and bronchial secretion (44% vs. 19%, $P = 0.036$). No significant differences in the degree of pleural effusion and delirium.

(*Continued*)

Table 2
Continued

Study	Purpose	Design	Participants	Exclusions	Dehydration Definition	Outcome Measure	Methods	Appraisal Total Score	Conclusions
Musgrave et al.[62]	To evaluate the effects of IV fluids in a group of dying patients.	Cross-sectional study	$n = 19$ Inpatients on adult oncology unit: - Terminally ill - Receiving IV fluids - Prognosis of ≤10 d Demographics not given.	$n = 19$ - Survival >10 d ($n = 5$) - Died without IV ($n = 1$) - Transferred ($n = 2$) - (Semi)unconscious ($n = 11$)	Dehydration not defined	Structured questionnaire developed by the researchers. Questionnaire was reviewed for content validity by an oncologist, two specialists in oncology nursing, and two statisticians.	Patients asked to complete a questionnaire recording severity of thirst. Serum biochemistry and fluid intake and output volumes recorded. Comparisons made between variables.	24	95% ($n = 18/19$) of Patients reported thirst. No association between level of thirst with the amount of IV fluids received, BUN, and sodium levels. Little association between fluid retention signs and volume of fluid received.
Davis et al.[15]	To determine whether bioelectrical impedance analysis (BIA) correlates with hydration changes during CAH and to determine if these changes were of prognostic importance.	Prospective observational study	$n = 50$ Inpatient PCU: - Active cancer - Undergoing continuous hydration - Able to give consent Mean age = 63 y Male/female = 30/20	$n = 29$ - Delirious - Actively dying - Unable to communicate - Deferred participation - Patients with defibrillators	Dehydration not defined	Phase angle	Patients underwent BIA measurements for 3 consecutive days. Laboratory studies, patient weight and vital signs recorded. Patient survival calculated.	29	Higher phase angle before hydration predicts longer survival. Increase in phase angles during hydration predicted poorer survival and pre-existing intracellular dehydration, cachexia, or poor membrane function.
Crawford et al.[78]	To investigate whether bioimpedance spectroscopy (BIS) has the potential to improve prognostication in an outpatient clinic for patients with cancer receiving palliative care.	Observational	$n = 84$ Outpatient oncology and palliative care clinics: - Advanced cancer - Fluency in English - Age ≥18 y - Judged by their primary medical specialist to be in the palliative phase of their illness - No severe cognitive impairment Mean age = 65.9 y Male/female = not given	$n = 19$ - Declined participation ($n = 4$) - Physical decline ($n = 15$)	Dehydration not defined	BIS measures and survival time	Survival time and BIS measurements of basal metabolic rate and measurement of 11 body composition parameters (extracellular fluid (ECF), intracellular fluid (ICF), ECF/ICF ratio, fluid in trunk and arm and leg, protein mass, mineral mass, and percent of body fat) were recorded.	36	Metabolic rate and accumulation of body fluid are indicators of poor prognosis in palliative cancer patients.

NYHA = New York Heart Association Functional Classification; SIADH = symptom of inappropriate antidiuretic hormone secretion.