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An e-Delphi Consensus Study

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Published in:
Journal of infusion nursing

DOI (link to publication from Publisher):
10.1097/NAN.0000000000000511

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

The Art and Science of Infusion Nursing

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An e-Delphi Consensus Study

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ABSTRACT

Infusion of fluids and medications is traditionally performed intravenously. However, venous depletion in patients has led to the quest for vessel health preservation. A safe, effective, acceptable, and efficient alternative is the subcutaneous route. A lack of organizational policies may contribute to the slow uptake of this practice. This modified e-Delphi (electronic) study aimed to derive international consensus on practice recommendations for subcutaneous infusions of fluids and medications. A panel of 11 international clinicians, with expertise in subcutaneous infusion research and/or clinical practice, rated and edited subcutaneous infusion practice recommendations from evidence, clinical practice guidelines, and clinical expertise within an Assessment, Best Practice, and Competency (ABC) domain guideline model. The ABC Model for Subcutaneous Infusion Therapy provides a systematic guideline of 42 practice recommendations for the safe delivery of subcutaneous infusions of fluids and medications in the adult population in all care settings. These consensus recommendations provide a guideline for health care providers, organizations, and policy makers to optimize use of the subcutaneous access route.

Key words: consensus, e-Delphi, hypodermoclysis, infusion therapy, subcutaneous, subcutaneous therapy

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We acknowledge all expert panelists, coauthors, and non-coauthors for their contribution to the building of these consensus recommendations.

Funding: *This research is supported by an unrestricted educational grant provided to Griffith University by Becton Dickinson, Canada. There is no applicable grant number. The funders have had no role in the study design; collection, analysis, and interpretation of the data; writing of the report; or decision to submit the article for publication.*

Conflicts of Interest/Author Disclosures: *D.B. reports employment with Nipro Canada and speakers honorarium from BD Canada. M.C. has received grant funding from Children's Hospital Foundation and National Health and Medical Research Council paid to her employer, Griffith University. L.B. reports employment with Needle Calm and is a non-executive director and board member at the Medical Technology Association of Australia. L.G. reports book royalties with FA Davis, Springer Publishers. C.R.-B. has received a grant for a study on an antibiotic administered by SC Route (PK), French National Drugs Agency. B.G. reports consultancy for Fresenius Kabi. For the remaining authors, none were declared.*

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DOI: 10.1097/NAN.0000000000000511

INTRODUCTION

Medications and fluids are commonly delivered in the acute and home care settings as infusions, and this is gaining prevalence in the long-term care setting.[1] Traditionally, these parenteral therapies have been administered via the intravenous (IV) route, yet an alarming 19% to 69% of peripheral intravenous catheters (PIVCs) fail before the end of treatment.[2,3] A failed PIVC may translate to patient discomfort, dissatisfaction, delays in treatment, and depletion of viable venous access.[2-4] Patient pain and suffering, as well as health care professional frustration, are furthered by repeated attempts to gain venous access, potentially leading to more invasive vascular access devices and risk of patient harm.[2,5] Patients, caregivers, and health care systems suffer the costs of these catheter failures.[2,5] In the older population, especially those living in nursing homes and long-term care facilities, the subcutaneous route is a valuable alternative in case of delirium, agitation, or poor venous access. Moreover, subcutaneous infusion is easy to perform and may be removed in order to avoid functional decline.

Venous depletion (the deterioration of a patient's vasculature), coupled with inexperience and poor decision-making of clinicians inserting these catheters, has led to a movement to optimize the experience and outcomes of peripheral infusion therapy.[6,7] There is a need for alternative drug and fluid delivery routes in patients with difficult-to-access vasculature, for oral intolerance, preservation of venous health, or clinical situations where there has been an inadequate therapeutic response to oral therapy.[8] An alternative path is the subcutaneous route, a safe, effective, acceptable, and efficient mode of delivery of infusion therapy.[1,8-11] In subcutaneous infusions, fluid is absorbed from the subcutaneous tissue to the circulation via the forces of diffusion and perfusion.[4] The recommended change in practice from direct venous access to the subcutaneous route for many infusions serves to facilitate vessel health preservation for many patients. However, incorporating subcutaneous access as a viable option to be considered alongside peripheral venous access is a paradigm shift.

The Emergency Nurses Association Clinical Practice Guideline recommends subcutaneous rehydration as an alternative to peripheral IV insertion for the mildly to moderately dehydrated pediatric and elderly patients if oral hydration has been unsuccessful.[12] The recommendation was graded as a level B, moderate recommendation, reflecting moderate clinical certainty with some minor or inconsistencies in quality evidence, applicable to emergency nursing practice. In the palliative care setting, subcutaneous infusions are common practice, especially at the end of life when clinicians use the subcutaneous route as an alternative to other routes that are not appropriate or acceptable.[13] A survey by Cabañero-Martinez et al[14] demonstrated a lack of internationally agreed-upon practice guidelines to direct the safe delivery of both fluids and medications through the subcutaneous route.

PURPOSE AND SCOPE

Objectives

The aim of this study is to address this lack of practice guidelines by developing a formal consensus- and evidence-based guideline providing a structured approach to the care of adult patients receiving subcutaneous infusions of fluids and drugs in any care setting. The guideline for subcutaneous fluids and drugs will detail essential care components of this practice to promote consistency and continuity of care and to enhance documentation and communication.[15] Practice recommendation guidelines were selected as the vehicle to provide a path and a solid reference for clinicians to follow confidently that will lead to safe subcutaneous infusion therapy practice.[14] The goal of this work is to encourage wider adoption of subcutaneous infusions globally. The aim is to accomplish this through the development of tools to support clinical decision-making by health care professionals providing subcutaneous therapy to adult patients.

The objectives of the study were the following:

1. To reach consensus on practice recommendations in guideline domains of a) assessment and device placement; b) best practices in subcutaneous infusion management; and c) competency and quality assurance in subcutaneous infusion therapy.
2. To summarize the recommendations for subcutaneous hydration in an ABC guideline framework.
3. To validate the recommendation guidelines through consensus.

The recommendation guidelines will aim to standardize care so all adult patients requiring subcutaneous infusion receive the same high-quality care that is timely, safe, and cost-effective. This research is predicated on evidence identified in a systematic review of systematic reviews of subcutaneous infusions of hydration and medication[1] performed by this research team as the first of 2 phases of this research.

Scope

The scope of these recommendation guidelines includes infusion therapies that may be administered via the subcutaneous route, including hydration and medications. This work is guided by the research question, "What are the best practice recommendations for the assessment, device placement, and management of adult patients requiring subcutaneous infusion therapy?"

The recommendation guidelines are targeted toward clinical decision-making for adults requiring short-term or long-term infusion therapy. They are intended for use by health care professionals in generalized or specialized practice, including, but not limited to, the following: nurses, physicians, pharmacists, educators, administrators, and researchers. The clinical practice recommendations are targeted toward all care settings (eg, hospitals, home care, and residential care). Due to the limited data available,

the neonatal and pediatric populations are outside the scope of this research, although it is recognized that general recommendations (excluding infusion parameters, eg, rates and volumes) may apply to the pediatric population.

METHODS

Study Design

A formal consensus process was used, incorporating a 2-step modified e-Delphi (electronic) method, based on systematic review findings and clinical expertise.[16-18] Formal systematic review-based consensus methodology was adopted to develop the international recommendation guidelines because the highly structured transparent process lends itself to explicit reporting.[17] This study is underpinned by a systematic review recently conducted by the researchers[1] that formed the evidentiary foundation to determine the safety, efficacy, acceptability, and efficiencies of subcutaneous fluids and drugs.

The e-Delphi method is designed to achieve consensus through expert opinion gathered systematically through multiple rounds, particularly useful when participants are geographically dispersed.[19] This method was selected because it is recommended for use when the research problem is not easily solved by analytical techniques but benefits from subjective judgments from a number of individuals across diverse locations and areas of expertise.[20]

Ethics Approval Statement

Ethics approval for the study was obtained from Griffith University, Australia (2019/1040). A Study Information Sheet was provided to participants who indicated consent prior to completing the survey.

Participants

Expert panel selection targeted disciplinary representation, roles in the acute care and post-acute care settings, research expertise in the content area, and geographical continent representation.[19] To ensure incorporation of key stakeholders' perspectives, experts from Australasia, North America, United Kingdom, and Europe were invited by email notification to participate, with an attachment of participant information and a consent form. Inclusion criteria required the following for participants: a) a minimum of 3 years of experience in the prescription or administration of subcutaneous hydration and medications (excluding specialized therapies, eg, insulin and immunoglobulin) for adults in any care setting; and/or b) evidence of professional productivity in terms of peer-reviewed or professional publications and research, participation in symposia, and/or teaching capacity in this field.[21] The goal was to recruit a panel of 10 to 15 members of various disciplines, such as prescribers (eg, physicians, physician assistants, or nurse practitioners), pharmacists, and nurse educators/managers/front line nurses, with research expertise in the content area and international representation.[19]

These health care professionals were identified through purposive and snowball methods.[22] Researchers practicing in this field were identified through authorship, and those recognized internationally as key opinion leaders were recruited by personal email invitation. Requests were also sent by email to relevant professional associations to forward the recruitment invitation to potential eligible members. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Study Procedures

Draft Recommendation Development

Data variables (in the form of practice recommendations) and response options were developed by the research committee (consisting of a pharmacist, infusion clinical specialist, nurse academic, and senior research assistant), based on evidence derived from their systematic review,[1] stakeholder interviews, review of international guidelines (eg, *Infusion Therapy Standards of Practice* [the *Standards*][23]) and grey literature. The framework for this research is structured as an ABC Guideline for Subcutaneous Infusion Therapy, underpinned by the Vessel Health and Preservation Model.[24] It provides a simplified approach, summarizing recommendation guidance in the domains of the following: a) assessment and device planning and placement; b) best practices in subcutaneous infusion management; and c) competency and quality.

The research committee graded the evidence for each recommendation (Tables 2-4), using the following scale adapted from the Oxford Centre for Evidence-Based Medicine (OCEBM) Level of Evidence Scale[25]: level I, systematic review of randomized controlled trials; level II, randomized trial or observational study with dramatic effect; level III, non-randomized controlled cohort/follow-up (post-marketing surveillance) study; level IV, case series, case–control studies, or historically controlled trials; level V, single descriptive and qualitative studies, mechanism-based reasoning (pathophysiologic rationale), expert opinion from clinicians or authorities; and level [C], consensus by research committee.

e-Delphi Survey Rounds

Sequential surveys were administered online via Lime Survey™. The survey, with recommendation questions, was divided into 4 sections, representing the domains of the ABC framework. It also included supporting material such as the Participant Information Sheet, instructions on how to complete the survey, and the link to the systematic review. Members of the expert panel received the survey via a web-link using their provided email address.

Members of the expert panel were asked to rate agreement with each practice recommendation, on a 9-point Likert scale, ranging from strongly agree to strongly disagree (higher score corresponding with agreement). Options were included for open text comments at the end of each domain

for participants to suggest modified statements (if possible) with rationale and possibly "Not applicable-exclude," to propose amendments to the included recommendation or suggest new definitions that were not included in the survey. No attempts were made to force consensus. The 2-round process was designed to determine "whether discrepant ratings are due to real clinical disagreement over the use of the procedure ('real' disagreement) or to fatigue or misunderstanding ('artifactual' disagreement)."[26] A third round of using an e-Conference Consensus was planned to address any remaining significant discord and obtain consensus. Upon achievement of consensus, this third round was not necessary.

Round 1 e-Delphi Survey: Review of Recommendations

The link to the survey was emailed to the participants. Respondents were asked to use the evidence from the systematic review and their clinical judgment to rate their agreement with the proposed clinical practice recommendation. Survey responses were collected and analyzed by the researchers. Recommendations ranked with a median score of 7 or higher were considered "strong" agreement and, thus, complete, while median scores ranked 4 to 6 were considered "weak" agreement, and median scores ranked 1 to 3 were considered "disagreement" and not to be included in round 2.[26,27]

Round 2 e-Delphi Survey: Review of Ratings and Recommendations

A summary report prepared by the researchers describing round 1 group responses was sent to participants via email, with the link for the round 2 of the e-Delphi process. Recommendations that achieved a median score of 7 or higher in round 1 but had some rankings from individual experts from 1 to 6 or had qualitative comments were considered. As a result, either no changes were made to the recommendation and a rationale was provided in the report of results, or minor changes to wording (9 items) were made for panelists to vote on in a second-round survey.

Panel members were asked to review the revised recommendations and give their agreement with a "yes/no" response ("yes" indicating agreement with the revised standard and inclusion in the consensus recommendations and "no" indicating exclusion from the consensus recommendations). Minor editing (eg, grammar and structure) would be allowed by the researchers, but no change to intent would be made.

Statistical Analysis

Quantitative data were analyzed using SPSS version 26.0 (IBM, Armonk, NY), which included descriptive statistics to summarize respondents' characteristics and demographic details. For each recommendation in round 1, the median, interquartile ratio, and range were calculated.[18] Descriptive statistics were calculated for round 2 of the e-Delphi process.

RESULTS

Eleven expert panel members were selected, as per the inclusion criteria, for the consensus panel in the e-Delphi process. Five members were recruited from their authorship of significant subcutaneous infusion therapy research. Fourteen responses were received from members of professional organizations, and 6 of these met inclusion criteria. The final panel included physician, nurse, and nurse practitioner experts from Australasia, North America, and Europe practicing in subcutaneous infusion therapy in the pediatric and/or adult population (Table 1). All 11 expert panel members completed both consensus rounds.

Round 1 Survey Results

All recommendations (42/42) reached consensus and, thus, were included, with 100% of median scores between 7 and 9, indicating strong agreement. There were no missing

TABLE 1

Panelists Demographic Summary

Demographic	Frequency, n (%) (n = 11)
Age (years)	
30-39	3 (27.3%)
40-49	6 (54.5%)
50-59	1 (9.1%)
60	1 (9.1%)
Gender	
Female	8 (72.7%)
Male	3 (27.3%)
Country of practice	
Italy	1 (9.1%)
United States	4 (36.4%)
Denmark	1 (9.1%)
Spain	1 (9.1%)
France	1 (9.1%)
Australia	1 (9.1%)
Singapore	1 (9.1%)
Ireland	1 (9.1%)
Patient population	
Adult	8 (72.7%)
Mixed	3 (27.3%)
Discipline	
Nurse	5 (45.6%)
Nurse practitioner	1 (9.0%)
Physician	4 (36.4%)
Clinical nurse specialist	1 (9.0%)

items reported in the survey, with 11 valid responses from the consensus panel members for each item.

The research committee reviewed all recommendations that received a score of 1 to 7 by any panelist and/or had qualitative comments of issue. Of these, 9 recommendations required minor changes by the research committee (eg, identification of applicable setting or populations), as these were significant to content and, as such, consensus agreement from panelists was required. Following revision, these recommendations accompanied by the research committee's rationales for changes were advanced to round 2 (Supplemental Table 1, available at http://links.lww.com/JIN/A106).

Round 2 Survey Results

Recommendations revised by the research committee were assessed by the expert panel members. The original recommendation and first round-related qualitative comments accompanied the revised recommendations in the survey. All 9 revised recommendations gained consensus agreement by panel members. Three recommendations had an agreement rate of 10 (91%) of 11. The research committee reviewed the 3 responses and made a minor change to the wording of 1 recommendation. The final recommendations are presented in Tables 2-4. A third consensus round planned as an e-conference consensus panel was not required due to the strong agreement among panelists in rounds 1 and 2.

Synthesis of Results

Recommendations for safe and effective delivery of subcutaneous infusion therapy are summarized in the framework for this research, the ABC Model for Subcutaneous Infusion Therapy (Figure 1). Elements of the key recommendations are presented for each domain. The model is designed to depict practice considerations to guide the safe delivery of therapy from the assessment and planning phase through management of infusions. All of these phases require multidisciplinary health care providers competent in the field of subcutaneous therapy to ensure high-quality care of adult patients requiring subcutaneous administration of fluids and medications.

DISCUSSION

This international e-Delphi study resulted in the development of 42 practice recommendations designed to support the safe and effective delivery of subcutaneous infusion of fluids and medications. Patients and clinicians are facing significant challenges with venous access based on patient characteristics or health care setting.[57,58] This study aimed to provide recommendations to support the uptake of the less invasive subcutaneous access route.[53] These consensus recommendation guidelines present a comprehensive approach to evidence-based subcutaneous infusion therapy as an alternative to IV access.

The ABC Model of Subcutaneous Infusion Therapy presents a systematic framework to describe key practice considerations. These recommendations were based on evidence synthesized by a systematic review completed by the researchers.[1] The recommendations were also compared to published practice guidelines and evaluated in context of clinical practice experience of the researchers and other experts in practice. Achieving 100% consensus in the first consensus round and from a geographically diverse and multidisciplinary panel was unexpected. This may, however, reflect the strong evidentiary underpinning of the recommendations. Despite the lack of high-level studies, the high level of consensus suggests a strong agreement with these practice considerations around the globe. Expertise of the panelists and their qualitative feedback led to only minor verbiage changes of 9 of the 42 recommendations.

The goal of this research development was to provide a subcutaneous infusion therapy resource for use in a wide variety of settings and practices. Clinicians find guidelines to be more useful as a resource to support individualized practice than a specific instrument, as there are often many variables affecting informed decision-making.[14] The recommendation guidelines present a holistic framework from assessment to quality evaluation applicable to multiple disciplines regardless of local practice variations. For this reason, specific recommendations for individual therapies or administration methods were avoided. As such, responsibilities were not delineated specific to a discipline, and language accommodating self-administration or caregiver administration were included. Scenarios specific to one therapy or one setting (eg, acute care, emergency care, chronic care) were avoided. Specific practice recommendations, such as indications and contraindications; fluid and hydration types, rates, volumes, and delivery devices; and subcutaneous access sites are described in a recent systematic review.[1]

STRENGTHS AND LIMITATIONS

The strengths of this study include the efficiency of which consensus was met. All recommendations met the requirements for acceptance during the first round. Achieving consensus in round 1 for all recommendations enabled the researchers to focus in on those that had a larger spread in agreement to enhance acceptability of the recommendations. Additional strengths include the international scope of participants, varied disciplines, specialties (eg, complex care, gerontology, home infusion, medicine, pharmacology, and vascular access), and the types of practice settings represented in the panel and the researchers. This should facilitate a broader global uptake of the recommendations for organizations, policy makers, and clinicians seeking to expand the use of subcutaneous infusion therapy in vascular access device selection.

The recommendation guidelines were structured in the ABC model to be more comprehensive than specific

TABLE 2

Recommendations for Assessment and Device Placement

Recommendation
1. Assess patient to determine if subcutaneous access is appropriate for the infusion of medications and hydration as an alternative route to intravenous access. Subcutaneous access is a vessel health preservation strategy for adults in all health care settings.[1,23,28-31] (III)
2. Assess intended duration of therapy, reason for parenteral route, properties of the solution/medication (eg, viscosity, pH, dose, volume, concentration and rate), available support and resources (if outside the hospital), patient's clinical and skin condition (including availability of appropriate tissue).[32-34] (V)
3. For the management of mild-to-moderate dehydration, assess need for subcutaneous infusion of isotonic solutions if oral route not appropriate (alternate routes include enteral, intravenous, and intraosseous). Complete an interprofessional team hydration/nutrition/electrolyte assessment to determine patient's fluid and electrolyte needs.[34,35] (V)
4. Review drug product monograph to determine labeling of medication for subcutaneous route. In the absence of marketing authorization for subcutaneous route, the organization/prescriber, including the pharmacy team, will determine if infusion of medications off-label meets organizational and/or regulatory requirements and is supported in the literature.[8,34,36,37] (III)
5. Collaborate with the health care team and patient to perform a risk/benefit analysis with the patient/caregiver to determine appropriateness of subcutaneous infusions, establishing the goals of treatment. Ensure treatment is consistent with patient's plan of care; obtain consent as per organizational policy.[1,33] (III)
6. Ensure subcutaneous medications and hydration prescribed are at rates, frequency, and volumes/dosage appropriate for the patient's age, weight, clinical condition, individual subcutaneous absorption, laboratory values, and as recommended by the drug manufacturers or supporting literature and generally not exceeding those used for IV infusions.[23,32,34] (V)
7. Ensure prescriptions include medication/solution, dose/volume, route, rate, frequency (eg, once daily), duration of infusion (eg, over 8 hours), and end date.[34,35] (V)
8. Avoid infusion rates >5 mL/h for medications (unless recommended by manufacturer, eg, subcutaneous immunoglobulin). Slow infusion rates and use of diluted solutions have been recommended in the literature for subcutaneous antibiotics.[1,23,32,37] (III)
9. Select a site for subcutaneous access with intact skin and adequate subcutaneous tissue (eg, minimum 1.0-2.5 cm thickness), assessing and addressing patient comfort, needle fear, mobility, safety, and preference (to identify optimal position or location for the patient).[1,32-35,38] (III)
10. Consider use of 2 or more sites as required for high-volume solutions (eg, up to 1 L/d per site).[1,28-31,33] (III)
11. If multiple subcutaneous infusions are prescribed, determine if they are compatible and can be administered in the same infusion. If using more than 1 subcutaneous set simultaneously (or bifurcated needle sets), use a separate site for each set.[39] (V)
12. To aid in dressing adhesion, remove excess hair from insertion site with clippers or scissors (do not shave or use a depilatory).[40] (V)
13. Perform hand hygiene and don gloves. Perform skin antisepsis, preferably using chlorhexidine-based solution, using a single-use applicator, and allow to dry naturally (without wiping, fanning, or blowing on skin).[23,32,34,40] (V)
14. Use a nonmetal cannula appropriate for the patient and infusate, preferably with a short length (to avoid intramuscular injection) and small gauge (eg, 24-27 gauge); larger gauges (eg, 22 gauge) may be required for higher flow rates.[1,23,32,34,39-43] (III)
15. Prime the subcutaneous access device with either 0.9% sodium chloride or the prescribed medication/solution (to expel any air). For specific medications, such as immunoglobulins, which may be irritating to the intradermal space, consider partially priming the cannula, stopping prior to the tip of the cannula ("dry-priming approach").[32,33,39,44] (V)
16. Using aseptic nontouch technique, insert cannula to establish subcutaneous access. Insert short cannula (<6 mm) at a 90° angle, using a skin fold lift in the slim patient to lift the skin away from the muscle fascia. To insert a longer cannula or cannula of any length in lean adults, arm or thigh sites (which have less subcutaneous tissue), use a 45° angle and/or use a skin fold lift to minimize the risk of intramuscular injection.[1,33,34,39,40,42-45] (III)
17. Remove the metal stylet (if applicable) and dispose in sharps container.[39] (V)
18. If blood return is present during device placement, remove and insert new device at new site.[32] (V)
19. Aseptically apply a transparent semipermeable membrane dressing (if not integrated with the cannula) over the site (to protect sites and devices, allow moisture vapor permeability, and allow for site assessment). Use skin injury mitigation strategies (eg, alternate dressings, skin barrier prep) when necessary.[32,34,44] (III)
20. Document the patient assessment, patient consent, device placement (including cannula type, size, and site), patient response, complications, or missed attempts.[34] (V)

Abbreviations: (I), level I evidence: systematic review of randomized controlled trials; (II), level II evidence: randomized trial or observational study with dramatic effect; (III), level III evidence: non-randomized controlled cohort/follow-up (post-marketing surveillance) study; (IV), level IV evidence: case series, case-control studies or historically controlled trials; (V), level V evidence: single descriptive and qualitative studies, mechanism-based reasoning (pathophysiologic rationale), expert opinion from clinicians or authorities; (C), level [C] evidence: consensus by research committee.

TABLE 3

Recommendations for Best Practice in Subcutaneous Infusions Management

Recommendation
21. Initiate and regulate the flow rate of the infusion at prescribed rate. Use the infusion control device appropriate for the type of therapy. (The following devices have been reported for use with: (i) hydration- electronic infusion device and gravity infusion[31,37,45-47] and (ii) medications- mechanical infusion device [eg, syringe driver, elastomeric], electronic infusion device).[1,8,30,34,37,46,48] (III)
22. Change administration sets used for continuous infusions at least every 7 days, every 24 hours for intermittent infusions, and immediately if system integrity is compromised or as per organizational policy.[23,32,34] (V)
23. Prime all air out of administration set prior to initiation of therapy. Label administration sets with date initiated and initials. Place label identifying subcutaneous access device near device connection on administration set.[32,40] (V)
24. Monitor patient, assessing site and infusion, regularly after starting infusion, as per organizational policies (eg, 30- 60 minutes after starting infusion and every shift/visit). In the outpatient or home care setting, teach patient/caregiver to assess site and infusion, reporting any concerns immediately.[32,34] (V)
25. Assess patient's tolerance and response to treatment. For subcutaneous hydration, initially include at least daily reassessments of response to therapy, clinical fluid status, laboratory values (urea, creatinine, and electrolytes), fluid balance charts, vital signs, and weight measurement twice weekly and adjust care plan accordingly. Patients on longer-term subcutaneous hydration whose condition is stable may be monitored less frequently, although decisions to reduce monitoring frequency should be detailed in their care plan.[35] (V)
26. Employ strategies to prevent, identify, and manage infusion complications, which depend mainly on the infusate and infusion rate.[1,8] (III)
27. For initiation and maintenance of subcutaneous hydration and some medications, consider the use of hyaluronidase for continuous subcutaneous infusions to facilitate the dispersion and absorption of the infusate, particularly if the infusion is not well tolerated due to swelling or pain or is running slowly.[1,8,34,49-53] Consider hyaluronidase with the administration of the following medications that have been shown to enhance absorption of medications (eg, ceftriaxone, hydromorphone, immunoglobulin, midazolam, morphine, ondansetron, potassium, and trastuzumab).[8,28,54] (III)
28. Hyaluronidase dosage and protocols vary. Consider injecting hyaluronidase prior to infusion (eg, 150-300 units) or, if compatible, to the hydration fluid. Patients taking salicylates (eg, aspirin), steroids, or antihistamines may require a larger dose of hyaluronidase for equivalent dispersing effect.[1,8,34,50-53,55] (III)
29. Consult drug information references to determine stability/compatibility of hyaluronidase with infusates.[23] (V)
30. Assess for adverse reactions to hyaluronidase (eg, mild local access site, allergic, or anaphylactic-like reactions).[23] (V)
31. Prior to accessing a needle-free connector on end of access device, perform active disinfection with a vigorous mechanical scrub using an antiseptic wipe, or use a disinfectant cap, and allow solution to dry.[35] (V)
32. For administration of multiple solution/medications, consider using a separate subcutaneous access device for each medication. If using one device, and solutions/medications are compatible, do not flush between medications; if not compatible, flush device with sterile preservative-free 0.9% sodium chloride (volume of device and any add-on devices). The use of multiple sites versus multiuse sites for medication administration is an unresolved issue due to lack of evidence.[32,33,39] (V)
33. Replace access device, using new subcutaneous access device and site as clinically indicated based on patient comfort and access site assessment findings (eg, erythema, swelling, leaking, local bleeding, bruising, burning, abscess, or pain). Consider reported duration of therapy for frequency of site rotation (eg, reports of 24-48 hours or after 1.5-2.0 L of hydration solution; every 2-7 days for continuous medication infusions or with each intermittent infusion such as immunoglobulin G).[1,8,32,34,56] (V)
34. Change the dressing with each subcutaneous site rotation and immediately if the integrity of the dressing is compromised.[32,34] (V)
35. Teach patient and/or caregiver to monitor the site, response to therapy, infusion device, and post-removal care. If self-administration is being performed, validate learning of patient and/or caregiver in subcutaneous infusion management.[31] (III)
36. Discontinue infusion therapy when indicated: stop the infusion, remove the dressing and subcutaneous set, and apply dry dressing over site. [C]
37. Document fluid/medication, volume, rate and time administered, care provided, assessments, complications, response to treatment, and other related interventions or communications. [C]
Abbreviations: (I), level I evidence: systematic review of randomized controlled trials; (II), level II evidence: randomized trial or observational study with dramatic effect; (III), level III evidence: non-randomized controlled cohort/follow-up (post marketing surveillance) study; (IV), level IV evidence: case series, case-control studies or historically controlled trials; (V), level V evidence: single descriptive and qualitative studies, mechanism-based reasoning (pathophysiologic rationale), expert opinion from clinicians or authorities; (C), level [C] evidence: consensus by research committee.

to guide the thought process and decision-making of the clinician. The recommendations in the ABC model direct the clinician from consideration of subcutaneous route for therapy through evaluation of the desired treatment, the assessment of the patient candidacy for this therapy, the considerations in administration and monitoring, and the evaluation of the therapy success. Recommendations address both subjective and objective

TABLE 4

Recommendations for Competency and Quality in Subcutaneous Infusion Therapy

Recommendation
38. Organizations should establish systems to ensure that all health care professionals involved in prescribing and/or administering subcutaneous infusions are trained on the principles covered in these recommendations and are then formally assessed and reassessed at regular intervals to demonstrate competence (knowledge, skills, and judgment).[31,34,35,38] (IV)
39. Organizations should consider designating clinician lead/resource for infusion therapy, responsible for training, clinical governance, audit and review of subcutaneous fluid prescribing, and patient outcomes.[8] (V)
40. Organizations should monitor quality outcomes related to subcutaneous infusion therapy. [C]
41. Consider quality standards such as: i) infusion fluids clinical lead/resource; ii) health care professionals' competencies; and iii) identifying and reporting consequences of fluid mismanagement (eg, pulmonary edema or hypovolemia).[8] (V)
42. Encourage and participate in research to promote evidence-based decision-making and clinical practice in the administration of subcutaneous infusions of hydration and medications.[38] (V)

Abbreviations: (I), level I evidence: systematic review of randomized controlled trials; (II), level II evidence: randomized trial or observational study with dramatic effect; (III), level III evidence: non-randomized controlled cohort/follow-up (post marketing surveillance) study; (IV), level IV evidence: case series, case-control studies or historically controlled trials; (V), level V evidence: single descriptive and qualitative studies, mechanism-based reasoning (pathophysiologic rationale), expert opinion from clinicians or authorities; (C), level [C] evidence: consensus by research committee.

parameters to be assessed. The final domain of the model includes recommendations around the practice of subcutaneous infusion, including the education and competency of staff, the quality controls, and application of research in practice.

Limitations of this study identified at the start included the potential for a small number of participants who fit the inclusion criteria, limits in evidence available to support some recommendations, the language of the study, and that the recommendations are only suitable

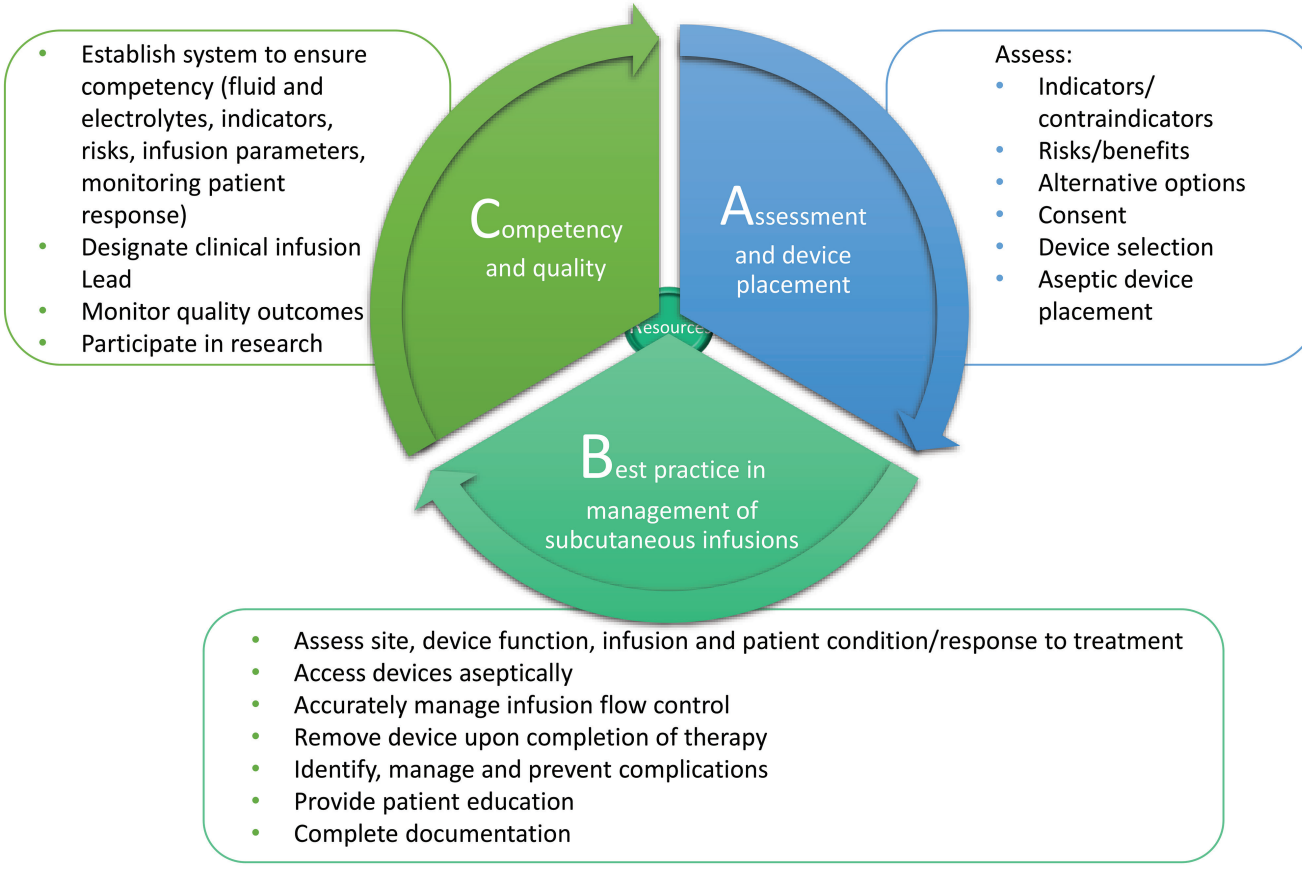

Figure 1 ABC Model of Subcutaneous Infusion Therapy.

for adults in health care settings. The impact of these limitations was mitigated as much as possible in the study design and evaluation. No differences were observed in the acceptance of the recommendations or the comments by panelists based on international borders, health care systems, or practice settings.

Language and cultural variances did not appear to be as much of a limitation as feared when the recommendations and surveys were performed in English. Comments during round 1 of consensus did not indicate that there was confusion in any of the chosen verbiage; however, the application and integration into practice may be impacted.

There is no agreement on the number of participants in the e-Delphi consensus process[59]; however, it has been reported that 10 to 15 participants is the norm.[60] Although the number was sufficient for consensus and did provide a wide geographical setting and demographic variance, the researchers had hoped to have more pharmacy representation (although one of the lead researchers is a clinical pharmacist) and participants representing South and Latin America. Representation from Canada, as well as further representation from the United States and Australia, was included within the lead investigator team. Due to the timing and the unexpected pandemic (COVID-19) affecting so many practices, potential panelists were burdened and slow to respond to original requests to participate. Some organizations did not respond to requests for panelist recommendations. Due to how quickly consensus was met, this may not have impacted the results.

The recommendation guidelines include reference to a larger scope of medications administered subcutaneously as an alternate to IV administration. Common subcutaneous infusions of analgesics, as well as the administration of antibiotics,[36,60] antiepileptics, anxiety treatments, and newer biological therapies, are included based on the evidence from systematic review.[1] For these therapies, administration by the subcutaneous route can safely bring improved outcomes, especially for patients with safety concerns and limited venous access options. More research is needed to strengthen and expand recommendations regarding these therapies, including the bioavailability of medications appropriate for the subcutaneous route.

Future areas of research were identified during this study that could impact quality of life and economic outcomes, as well as health care resource utilization. More evidence is needed for the specific administration parameters for fluids and medications so specific care algorithms can be developed. During the systematic review used as a foundation for this research, it was found that there were limitations to the amount of evidence published on subcutaneous infusion as an alternative administration. More research is needed to increase the use of subcutaneous infusion practice, evaluate the reduction of negative outcomes by using this as an alternative to IV administration, and identify the populations who will most benefit from this administration method. More data are needed to support the use of subcutaneous administration as a tool in venous access preservation for chronic illnesses, a means to allow for a safer alternate site of care or self-administration, reductions in negative outcomes from venous catheters, and reduction in infection rates related to catheter placement and use.

An additional area for research is the development of specific integrated care pathways for subcutaneous infusions. Although one of the original visions of the researchers was to pursue this, the evidence was unable to support it, especially in the face of multiple patient and infusate variables, limited research published using large patient populations, and variances in practice settings and health care systems; thus, developing specific pathways and decision trees was not possible. Using the ABC Model of Subcutaneous Infusion Therapy and the consensus recommendations, individual organizations or practice groups may be successful in developing and piloting these pathways. Although health information technology-supported clinical pathways have been shown to improve patient outcomes, quality of care and health care resource utilization, the study scope precluded this scope of work[61]; however, it may be considered by organizations implementing this guideline.

CONCLUSION

This e-Delphi study has produced international expert consensus-based recommendations for the safe and effective delivery of subcutaneous infusion of fluids and medications. The ABC Model of Subcutaneous Infusion Therapy presents a systematic approach to the care of adult patients receiving subcutaneous infusions of fluids and drugs in any care setting. This model addresses assessment and device placement, best practices for infusion management, and competency evaluation in a quality program. This framework offers a guide for health care providers, organizations, and policy makers in the safe delivery of infusion therapy via the subcutaneous route. Further research is required to develop algorithms incorporating subcutaneous access as a vascular access alternative.

REFERENCES

1. Broadhurst D, Cooke M, Sriram D, Gray B. Subcutaneous hydration and medications infusions (effectiveness, safety, acceptability): a systematic review of systematic reviews. *PloS One*. 2020;15(8):e0237572. doi:10.1371/journal.pone.0237572
2. Helm RE, Klausner JD, Klemperer JD, Flint LM, Huang E. Accepted but unacceptable: peripheral IV catheter failure. *J Infus Nurs*. 2015;38(3):189-203. doi:10.1097/NAN.0000000000000100
3. Murayama R, Uchida M, Oe M, et al. Removal of peripheral intravenous catheters due to catheter failures among adult patients. *J Infus Nurs*. 2017;40(4):224-231. doi:10.1097/NAN.0000000000000168

4. Caccialanza R, Constans T, Cotogni P, Zaloga GP, Pontes-Arruda A. Subcutaneous infusion of fluids for hydration or nutrition: a review. *JPEN J Parenter Enteral Nutr*. 2018;2(2):296-307. doi:10.1177/0148607116676593
5. Civetta G, Cortesi S, Mancardi M, et al. EA-DIVA score (Enhanced Adult DIVA score): a new scale to predict difficult preoperative venous cannulation in adult surgical patients. *J Vasc Access*. 2019;20(3):281-289. doi:10.1177/1129729818804994
6. Armenteros-Yeguas V, Garate-Echenique L, Tomas-Lopez MA, et al. Prevalence of difficult venous access and associated risk factors in highly complex hospitalised patients. *J Clin Nurs*. 2017;26(23-24):4267-4275. doi:10.1111/jocn.13750
7. Hallam C, Weston V, Denton A, et al. Development of the UK Vessel Health and Preservation (VHP) framework: a multi-organisational collaborative. *J Infect Prev*. 2016;17(2):65-72. doi:10.1177/1757177415624752
8. Duems-Noriega O, Ariño-Blasco S. Subcutaneous fluid and drug delivery: safe, efficient and inexpensive. *Rev Clin Gerontol*. 2015;25(2):117-146.
9. Rouhani S, Meloney L, Ahn R, Nelson BD, Burke TF. Alternative rehydration methods: a systematic review and lessons for resource-limited care. *Pediatrics*. 2011;127(3):e748-e757. doi:10.1542/peds.2010-0952
10. Annes LMB, da Cunha Andrade RGA, de Albuquerque Pontes IE, Sena GR, Telles J, de Orange FA. Subcutaneous versus intravenous rehydration in hospitalized older adults: a meta-analysis. *J Infus Nurs*. 2020;43(5):283-291. doi:10.1097/NAN.0000000000000388
11. Danielsen MB, Andersen S, Worthington E, Jorgensen MG. Harms and benefits of subcutaneous hydration in older patients: systematic review and meta-analysis. *J Am Geriatr Soc*. 2020;68(12):2937-2946. doi:10.1111/jgs.16707
12. Emergency Nurses Association. Clinical practice guideline: difficult intravenous access. www.ena.org/docs/default-source/resource-library/practice-resources/cpg/difficultivaccesscpg.pdf?sfvrsn=9944da58_122015
13. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions In Palliative Care:* Oxford University Press; 2016.
14. Cabañero-Martinez MJ, Ramos-Pichardo JD, Velasco-Álvarez ML, Garcia-Sanjuan S, Lillo-Crespo M, Cabrero-Garcia J. Availability and perceived usefulness of guidelines and protocols for subcutaneous hydration in palliative care settings. *J Clin Nurs*. 2019;28(21-22):4012-4020. doi:10.1111/jocn.15036
15. Cortis LJ, Ward PR, McKinnon RA, Koczwara B. Integrated care in cancer: what is it, how is it used and where are the gaps? A textual narrative literature synthesis. *Eur J Cancer Care*. 2017;26:e12689. doi:10.1111/ecc.12689
16. Khemani R, Smith L, Zimmerman J, et al. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5 Suppl 1):S23-S40. doi:10.1097/PCC.0000000000000432
17. Loblaw DA, Prestrud AA, Somerfield MR, et al. American Society of Clinical Oncology Clinical Practice Guidelines: formal systematic review-based consensus methodology. *J Clin Oncol*. 2012;30(25):3136-3140. doi:10.1200/JCO.2012.42.0489
18. Schults J, Kleidon T, Chopra V, et al. International recommendations for a vascular access minimum dataset: a Delphi consensus-building study. *BMJ Qual Saf*. 2020;30(9):722-730. doi:10.1136/bmjqs-2020-011274
19. Keller HH, McCullough J, Davidson B, et al. The integrated nutrition pathway for acute care (INPAC): building consensus with a modified Delphi. *Nutr J*. 2015;14:63. doi:10.1186/s12937-015-0051-y
20. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. *PLoS One*. 2011;6(6):e20476. doi:10.1371/journal.pone.0020476
21. Bourrée F, Michel P, Salmi LR. Consensus methods: review of original methods and their main alternatives used in public health [in French]. *Rev Epidemiol Sante Publique*. 2008;56(6):e415-e423. doi:10.1016/j.respe.2008.09.006
22. Taylor RM, Feltbower RG, Aslam N, Raine R, Whelan JS, Gibson F. Modified international e-Delphi survey to define healthcare professional competencies for working with teenagers and young adults with cancer. *BMJ Open*. 2016;6(5):e011361. doi:10.1136/bmjopen-2016-011361
23. Gorski L, Hadaway L, Hagle M, et al. Infusion therapy standards of practice. *J Infus Nurs*. 2021;44(15):1-224.
24. Moureau NL, Carr PJ. Vessel health and preservation: a model and clinical pathway for using vascular access devices. *Br J Nurs*. 2018;27(8):S28-S35. doi:10.12968/bjon.2018.27.8.S28
25. OCEBM Levels of Evidence Working Group. *The Oxford 2011 Levels of Evidence*. Oxford Centre for Evidence-Based Medicine; 2011. https://www.cebm.net/
26. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR. *The RAND/UCLA Appropriateness Method User's Manual*. Rand Corp; 2001.
27. Adleman J, Gillan C, Caissie A, et al. Development of a quality and safety competency curriculum for radiation oncology residency: an international Delphi study. *Int J Radiat Oncol Biol Phys*. 2017;98(2):428-437. doi:10.1016/j.ijrobp.2016.11.031
28. Arthur AO. Innovations in subcutaneous infusions. *J Infus Nurs*. 2015;38(3):179-187. doi:10.1097/NAN.0000000000000099
29. Health Quality Ontario. Home-based subcutaneous infusion of immunoglobulin for primary and secondary immunodeficiencies: a health technology assessment. *Ont Health Technol Assess Ser*. 2017;17(16):1-86.
30. Stoner KL, Harder H, Fallowfield LJ, Jenkins VA. Intravenous versus subcutaneous drug administration: which do patients prefer? A systematic review [published online ahead of print Jul 12, 2014]. *Patient*. doi:10.1007/s40271-014-0075-y
31. Vidal MMD, Hui DMD, Williams J, Bruera EMD. A prospective study of hypodermoclysis performed by caregivers in the home setting. *J Pain Symptom Manage*. 2016;52(4):570-574.9. doi:10.1016/j.jpainsymman.2016.04.009
32. Canadian Vascular Access Association. *Canadian Vascular Access And Infusion Therapy Guidelines*. Pappin Communications; 2019.
33. Gabriel J. Subcutaneous fluid administration and the hydration of older people. *Br J Nurs*. 2014;23(14):S10-S14. doi:10.12968/bjon.2014.23.sup14.s10
34. Royal College of Nursing. *Standards for Infusion Therapy: 4th Edition*. Royal College of Nursing; 2016.
35. National Institute for Health and Care Excellence. Intravenous fluid therapy in adults in hospital. *Nice Clin Guidel*. 2017:1-26.
36. Colin E, Baldolli A, Verdon R, Saint-Lorant G. Subcutaneously administered antibiotics. *Med Mal Infect*. 2020;50(3):231-242. doi:10.1016/j.medmal.2019.06.007
37. Fonzo-Christe C, Vukasovic C, Wasilewski-Rasca A-F, Bonnabry P. Subcutaneous administration of drugs in the elderly: survey of practice and systematic literature review. *Palliat Med*. 2005;19(3):208-219. doi:10.1191/0269216304pm1006oa
38. Gomes NS, Silva A, Zago LB, Silva E, Barichello E. Nursing knowledge and practices regarding subcutaneous fluid administration. *Rev Bras Enferm*. 2017;70(5):1096-1105. doi:10.1590/0034-7167-2016-0424
39. Gabriel J. A guide to subcutaneous infusion. *Br J Nurs*. 2019;28(Sup14c):1-7. doi:10.12968/bjon.2019.28.Sup14c.1
40. Gabriel J. The use of subcutaneous infusion in medication administration. *Br J Nurs*. 2013;22(14):S6, S8, S10 passim. doi:10.12968/bjon.2013.22.Sup14.S6

41. Macmillan K, Macmillan A, Bruera E, Kuehn N, Selmser P. A prospective comparison study between a butterfly needle and a Teflon cannula for subcutaneous narcotic administration. *J Pain Symptom Manage*. 1994;9(2):82-84. doi:10.1016/0885-3924(94)90160-0
42. Neo SH-S, Khemlani MH, Sim LK, Seah AST. Winged metal needles versus plastic winged and nonwinged cannulae for subcutaneous infusions in palliative care: a quality improvement project to enhance patient care and medical staff safety in a Singaporean hospital. *J Palliat Med*. 2016;19(3):318-322. doi:10.1089/jpm.2015.0085
43. Torre MC. Subcutaneous infusion: non-metal cannulae vs metal butterfly needles. *Br J Community Nurs*. 2002;7(7):365-369. doi:10.12968/bjcn.2002.7.7.10636
44. Immunoglobulin National Society. *Immunoglobulin Therapy Standards of Practice 2nd Edition*. Immunoglobulin National Society; 2018.
45. Australian Diabetes Educators Association. Clinical guiding principles for subcutaneous injection technique: technical guidelines. https://www.adea.com.au/wp-content/uploads/2015/11/Injection-Technique-Final-digital-version2.pdf2017
46. Forbat L, Kunicki N, Chapman M, Lovell C. How and why are subcutaneous fluids administered in an advanced illness population: a systematic review. *J Clin Nurs*. 2017;26(9/10):1204-1216. doi:10.1111/jocn.13683
47. Frisoli AJ, de Paula AP, Feldman D, Nasri D. Subcutaneous hydration by hypodermoclysis: a practical and low cost treatment for elderly patients. *Drugs Aging*. 2000;16(4):313-319. doi:10.2165/00002512-200016040-00007
48. Gaudet LM, Singh K, Weeks L, Skidmore B, Tsertsvadze A, Ansari MT. Effectiveness of terbutaline pump for the prevention of preterm birth: a systematic review and meta-analysis. *PloS One*. 2012;7(2):e31679. doi:10.1371/journal.pone.0031679
49. Bruera E, Belzile M, Watanabe S, Fainsinger RL. Volume of hydration in terminal cancer patients. *Support Care Cancer*. 1996;4(2):147-150. doi:10.1007/BF01845764
50. Bruera E, Neumann C, Pituskin E, Calder K, Ball G, Hanson J. A randomized controlled trial of local injections of hyaluronidase versus placebo in cancer patients receiving subcutaneous hydration. *Ann Oncol*. 1999;10(10):1255-1258. doi:10.1023/a:1008331727535
51. Challiner YC, Jarrett D, Hayward MJ, al-Jubouri MA, Julious SA. A comparison of intravenous and subcutaneous hydration in elderly acute stroke patients. *Postgrad Med J*. 1994;70(821):195-197. doi:10.1136/pgmj.70.821.195
52. Rochon PA, Gill SS, Litner J, Fischbach M, Goodison AJ, Gordon M. A systematic review of the evidence for hypodermoclysis to treat dehydration in older people. *J Gerontol A Biol Sci Med Sci*. 1997;52(3):M169-M176. doi:10.1093/gerona/52a.3.m169
53. Wilhelm K. A systematic review of hyaluronidase-assisted subcutaneous fluid administration in pediatrics and geriatrics and its potential application in low resource settings. The University of Arizona; 2017. https://repository.arizona.edu/bitstream/handle/10150/623621/WilhelmK%20Thesis.pdf?sequence=2
54. Lingman-Framme J, Fasth A. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. *Drugs*. 2013;73(12):1307-1319. doi:10.1007/s40265-013-0094-3
55. Slesak G, Schnürle JW, Kinzel E, Jakob J, Dietz PK. Comparison of subcutaneous and intravenous rehydration in geriatric patients: a randomized trial. *J Am Geriatr Soc*. 2003;51(2):155-160. doi:10.1046/j.1532-5415.2003.51052.x
56. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Oncol*. 2013;31(1):111-118. doi:10.1200/JCO.2012.44.6518
57. Schults J, Calleja P, Slaughter E, et al. Peripheral intravenous catheter insertion and use of ultrasound in patients with difficult intravenous access: Australian patient and practitioner perspectives to inform future. *PLoS One*. 2022;17(6):e0269788. doi:10.1371/journal.pone.0269788
58. Marsh N, Webster J, Larsen E, Cooke M, Mihala G, Rickard C. Observational study of peripheral intravenous catheter outcomes in adult hospitalised patients: a multivariable analysis of peripheral intravenous catheter failure. *J Hosp Med*. 2018;13(2):83-89. doi:10.12788/jhm.2867
59. Adebiyi BO, Mukumbang FC, Okop KJ, Beytell A-M. A modified Delphi study towards developing a guideline to inform policy on fetal alcohol spectrum disorders in South Africa: a study protocol. *BMJ Open*. 2018;8(4):e019907. doi:10.1136/bmjopen-2017-019907
60. Hernández-Ruiz V, Forestier E, Gavazzi G, et al. Subcutaneous antibiotic therapy: the why, how, which drugs and when. *J Am Med Dir Assoc*. 2020;22(1):50-55.e6. doi:10.1016/j.jamda.2020.04.035
61. Neame MT, Chacko J, Surace AE, Sinha IP, Hawcutt DB. A systematic review of the effects of implementing clinical pathways supported by health information technologies. *J Am Med Inform Assoc*. 2019;26(4):356-363. doi:10.1093/jamia/ocy176