Special Series: Science in Action: Evidence and Opportunities for Palliative Care Across Diverse Populations and Care Settings

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Opportunities to Improve Utilization of Palliative Care Among Adults With Cystic Fibrosis: A Systematic Review

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Abstract

Context. Individuals with cystic fibrosis (CF) frequently survive into adulthood, and many have multifaceted symptoms that impair quality of life.

Objective. We conducted a systematic review to investigate opportunities to improve utilization of palliative care among adults with CF.

Methods. We searched PubMed, Embase, Scopus, Web of Science, and CINAHL databases from inception until September 27, 2018, and reviewed references manually. Eligible articles were published in English, involved adults aged 18 years and older with CF, and contained original data regarding patient outcomes related to presence of advance care planning (ACP), symptom experience, and preferred and/or received end-of-life (EOL) care.

Results. We screened 652 article abstracts and 32 full-text articles; 12 studies met inclusion criteria. All studies were published between 2000 and 2018. Pertinent findings include that although 43% to 65% of adults with CF had contemplated completing ACP, the majority only completed ACP during their terminal hospital admission. Patients also reported high prevalence of untreated symptoms, with adequate symptom control reported in 45% among those with dyspnea, 22% among those with pain, and 51% among those with anxiety and/or depression. Prevalence of in-hospital death ranged from 62% to 100%, with a third dying in the intensive care unit. The majority received antibiotics and preventative treatments during their terminal hospitalization. Finally, treatment from a palliative care specialist was associated with a higher prevalence of patient completion of advanced directives, decreased likelihood of death in intensive care unit, and decreased use of mechanical ventilation at EOL.

Conclusion. Adults with CF often have untreated symptoms, and many opportunities exist for palliative care specialists to improve ACP completion and quality of EOL care. J Pain Symptom Manage 2019;58:1100–1112.

Key Words

Cystic fibrosis, patient-reported outcomes, advance care planning, advanced directives, end of life

Background

Cystic fibrosis (CF) is an autosomal recessive genetic disorder where dysfunction of the CF transmembrane regulator protein leads to multisystemic disease.[1] Most individuals with CF develop pulmonary disease characterized by progressive and severe bronchiectasis leading to early morbidity and mortality.[1] Although dramatic recent improvements in the care for persons

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with CF have increased life expectancy to between 40 and 50 years in the developed world, individuals with CF are still likely to suffer from a significant symptom burden from their progressive lung disease.[2–6]

There are limited data about the role of palliative care for individuals with CF. Most research exploring palliative care among patients with pulmonary disease has specifically focused on individuals with the respiratory disease chronic obstructive pulmonary disease (COPD), rather than those with cystic fibrosis. For this population, existing data support that integration of palliative care is associated with increased rates of advance care planning (ACP) and better control of symptoms like dyspnea.[7–9] Existing evidence also suggests that patients with advanced lung disease who die in the intensive care unit (ICU) receive fewer elements of palliative care compared with those with cancer, but involvement of palliative care specialists can help to limit burdensome or invasive treatments for patients with COPD nearing end of life (EOL).[10,11] Unlike COPD, CF is a life-long, multisystemic disease with variable morbidity and mortality, and thus, extrapolation of COPD data into CF populations may not be prudent.

To explore evidence concerning the specific palliative care needs of adults with CF and the impact of integrating palliative care specialists into the care of adults with CF, we conducted a systematic review using the broad definition of palliative care as "interdisciplinary care that focuses on improving quality of life for persons of any age who are living with any serious illness and for their families."[12] The goal of our review was to summarize the evidence concerning utilization of, and opportunities for, palliative care among adults living with and dying from CF (Table 1).

Table 1
Study Eligibility Criteria

PICOTS Question: Among adult patients with cystic fibrosis, are there opportunities for palliative care to improve patient- or caregiver-reported symptoms, advance care planning, preferred and/or receipt of end-of-life care?
Population: Adults with cystic fibrosis
Intervention: None
Comparator: None
Outcome(s): Quantitative patient and caregiver-reported symptoms, presence of advance care planning, preferred and/or receipt of end-of-life care
Timing: Any time period
Setting(s): Inpatient or outpatient

Inclusion Criteria	Exclusion Criteria
• Published before September 27, 2018 • Human participants 18 years of age and older with cystic fibrosis • Published in English • Original research with quantitative data	• Published in the gray literature • Commentaries, case reports, reviews, or published protocols • Studies that do not measure patient- or family-centered outcomes.

Methods

Search Strategy

Under the direction of a medical research librarian (C. W.), we searched PubMed, Scopus, Embase, Web of Science, and CINAHL. The search used keywords and medical subject headings representing cystic fibrosis and palliative care, such as "Cystic Fibrosis," AND "palliative," OR "end-of-life" AND "advanced care planning." Searches were limited to studies of adults aged 18 years and older, published in English from database inception to September 24, 2018, and which contained original, quantitative data regarding patient- and/or caregiver-reported outcomes related to symptom experience, presence of ACP, and preferred and/or received EOL care. References from included studies were hand searched and assessed using the same protocol. Appendix details the search strategy for the five databases. Pediatric studies were excluded as the average life expectancy for individuals with CF now extends into adulthood and we sought to capture palliative outcomes for the average dying or end-stage CF patient. We excluded gray literature, commentary or review pieces, and published protocols. The study was registered on Prospero (ID # 116537).

Study Selection

Search results were uploaded into Covidence software.[13] Duplicates were removed and screened based on the criteria in Table 1. The title, abstracts, and full texts of articles were independently reviewed by two study team members with discrepancies adjudicated through group discussion. Results are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Fig. 1).

Data Extraction

Four members of the research team (A. J., A. M., M. M., and E. R.) abstracted data from full-text articles into a preformatted template, with data fields including first author; year of publication; country; design; primary aim; population demographics, including median age, sex distribution, and median lung function (expressed as percent predicted of the forced expiratory volume in the first second [FEV1]); outcomes measured; and results. All extracted data with discrepancies were reviewed and adjudicated by group consensus; the study principal investigator (M. M.) checked all extracted data. The final results were presented in a tabular summary and summarized in a qualitative synthesis.

Data Synthesis

The data were synthesized into a descriptive summary of quantitative findings. Owing to the

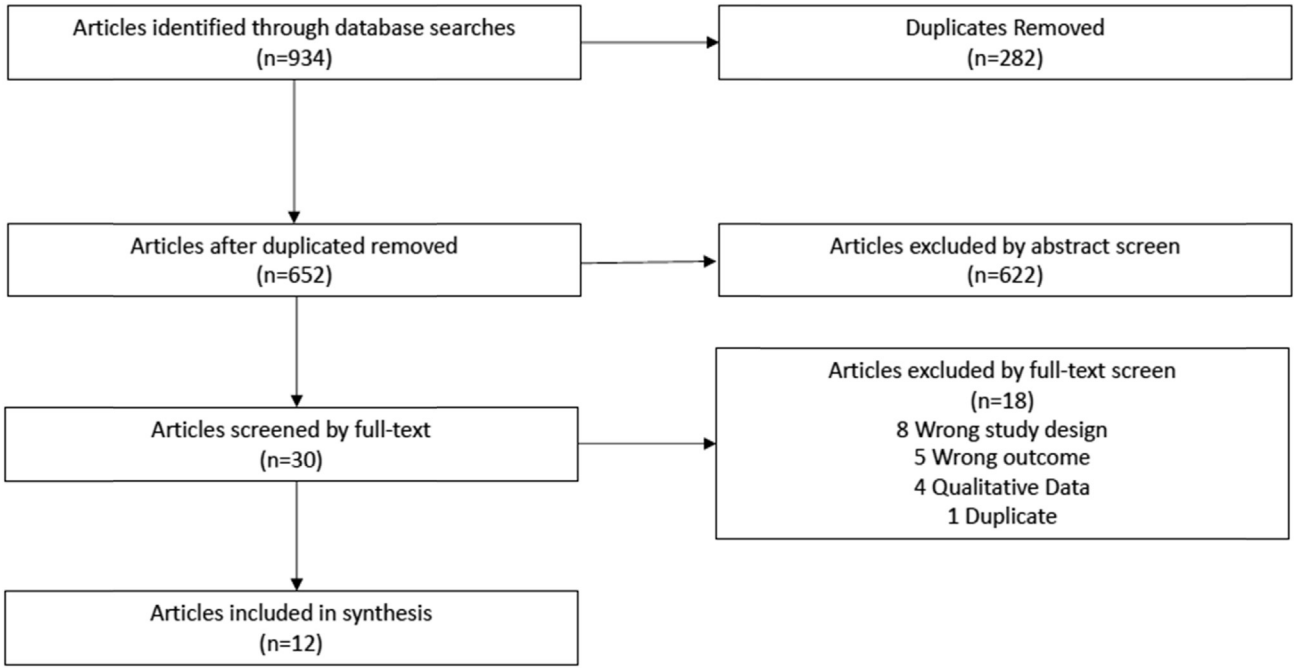

Fig. 1. PRISMA diagram.

heterogeneity of studies and outcomes, it was not possible to conduct a meta-analysis.

Quality Appraisal

The included studies were all retrospective chart reviews or cross-sectional surveys and were therefore not appropriate for existing quality assessment tools.

Results

Excluding duplicates, the database searches produced 652 articles (Fig. 1). After title and abstract screening, 32 articles remained for full text screening. Thereafter, 12 articles met final inclusion criteria summarized in Table 2. Of the 12 final articles, six were retrospective reviews, four were cross-sectional surveys of patients, one was a cross-sectional survey of CF physicians, and one was a description of a quality improvement project. Eight of the final studies were done in the U.S.,[14–21] two in the U.K.,[22,23] one in Australia,[24] and one in Canada.[25] Studies were conducted from 2000[25] to 2018.[15,20] Outcomes and themes common to the 12 studies addressed the domains of ACP, lung transplant, patient-reported symptoms, and EOL care summarized in Table 3.

Advance Care Planning

Seven of the included studies explored patient attitudes about ACP.[14,15,17–21] Three studies found that 60%–70% of adults with CF were willing to have a conversation about ACP and that the majority[17,20] (58%) had specific wishes about their future medical care.[18] Similarly, 43%–65% of study participants contemplated ACP, but actual patient ACP and/or completion of an advanced directive was very heterogeneous, ranging from 18% to 61%, and the majority of ACP was considered during the patient's terminal admission.[16–19,22] A U.S., nationwide study found that rates of ACP and advanced directive completion were significantly higher for patients enrolled in hospice.[15]

Patients had very different opinions regarding when ACP discussions should occur, with 25% of respondents of one study noting that ACP should occur when death is near and 33% believing that ACP should be completed as soon as possible.[19] One small study explored barriers to ACP discussions and found that 36% of survey respondents did not like to talk about getting very sick, 35% felt their doctor did not have time to talk with them about ACP, 32% felt unsure of which doctor would care for them at EOL, and 14% reported already having a living will and subsequently considered their ACP to be complete.[20]

Lung Transplant

Individuals listed for transplant have end-stage disease, which would otherwise result in death in the near future if not for a grafted organ. As CF leads to advanced lung disease, lung transplantation is offered to adults with CF who meet transplant selection criteria, which often vary by institution and/or geographic region. Three studies explored the impact

Table 2
Summary of Included Studies

Paper ID	Study Design	Study Aim	Demographics	Outcome (Bold)/Results
Retrospective				
Bourke S et al.[23]	Retrospective chart review of a quality improvement intervention attempting to integrate palliative care, single-center study	Describe circumstances around death, assess palliative symptoms, and assess provider perspectives around integrating a palliative specialist into the CF team from 2011 to 2014	**N:** 28 **Mean age:** 31 **Sex:** Not reported **Listed for lung transplant at time of death:** 6 (21%) **Median FEV1:** 24.6% predicted **Mean BMI:** 19.3 kg/m^2	**Total deaths**: 17 (61%) **Location of death** 15 (54%) in-hospital, 2 (7%) home **Palliative care symptom assessment** Dyspnea = 25 (89%); cough = 24 (86%); pain = 16 (57%); nausea/vomiting = 16 (57%); fatigue = 21 (75%); anxiety = 10 (36%); low mood = 8 (29%)
Chen E et al.[15]	Multicenter retrospective chart review Nationwide from 71 CF centers	Describe circumstances of death for adults with CF between 2011 and 2013	**N:** 248 **Mean age:** 29 **Sex:** 134 (54% female) **Listed for lung transplant:** 30 (12%) **Median FEV1:** 199 **FEV1 < 40%:** 83% **Mean BMI:** Not reported	**Location of death**: ICU = 97 (39%); hospital w/o palliative care = 52 (21%); home with hospice = 35 (14%); home w/o hospice = 20 (12%) **Therapies received at final admission**: mechanical ventilation = 92 (37%); IV antibiotics = 166 (67%); vasopressors = 57 (23%); routine CF medications = 186 (75%); nutritional support = 104 (42%) **Presence of ACP**: performed w patient = 144 (58%) **Palliative or hospice involvement**: 124 (50%) **Difference in care received when hospice care involved** Significantly increased ACP; significantly decreased those dying in the ICU; significantly decreased mechanical ventilation at EOL **Patients with adequate symptom control in final days of life**: controlled dyspnea = 51 (45%); controlled pain = 22 (22%); controlled anxiety = 46 (51%); controlled congestion = 31 (33%)
Dellon et al.[14]	Multicenter retrospective chart review Nationwide from 67 adult CF centers	Describe practices for ACP in U.S.-based adult CF care programs through review of 210 patients at 67 adult CF care programs who died from respiratory failure between 2011 and 2013	**Median age at death:** 29 years (range 18–73) **Sex:** 116 (55%) female **Median FEV1 year preceding death:** 33% predicted (range 13–100%) **FEV1 < 40% predicted:** 68% **Listed for lung transplant:** 27 (13%) **Received palliative care or hospice services:** 94 (46%)	**Stratification of ACP** ACP documented: 129 (61%); , 61% during hospitalization **Variables in those patients with ACP and those without** ACP documented within last month of life = 73% No ACP = 35% CF physician involved in conversation = 91% of those with ACP CF nurse involved in conversation = 46% of those with ACP Palliative care physician involved in conversation = 6% of those with ACP vs. 10% w/o. Adv directive completed = 93% of those with ACP vs. 75% w/o DNR order = 76% of those with ACP vs. 49% w/o Health care proxy = 75% of those with ACP vs. 61% w/o Listing for lung transplant did not affect ACP completion (67% vs. 61%)
Karlekar M. et al.[17]	Single-center retrospective chart review	Describe patient reported symptoms at EOL, willingness to discuss and completion of advanced care directives among CF adults referred to a palliative specialist between January 1, 2012, and June 30, 2012.	**N:** 30 **Mean age:** 28 **Sex:** 47% female; 57% partnered **Median FEV1:** N/A **Mean BMI:** N/A	**Disease severity (obstruction based on FEV1)** 10 (33%) with severe obstructive lung disease **Pain** 13 (43%) **Mental health** 15 (50%) suffered from anxiety/depression **Advanced Care Directive (ACD)** 27 (70%) Willingness to discuss ACD 5 (18%) had completed ACD 0 (0%) were documented in the medical records

(*Continued*)

Table 2
Continued

Paper ID	Study Design	Study Aim	Demographics	Outcome (Bold)/Results
Bourke et al.[22]	Single-center retrospective chart review	Describe the effect of integrating a palliative care provider in the care of patients dying from CF over a 10-year period.	**N:** 40 patient deaths **Died of progressive CF lung disease:** 35 patients (87%) **Mean age at death:** 28.6 (range 17.1–51.6) **Died after transplant:** 5 (13%)	**Location of death**: home = 4 (11%); hospital 2011 = 31 (89%); ICU w mechanical ventilation = 1 (3%); hospice = 0; palliative care = 1 (3%) **Lung transplantation status:** *those without a transplant* 16 (46%) were receiving "long-term planned palliative care"
Philip J et al.[24]	Single-center retrospective chart review	Describe the circumstances of death of patients dying of CF who did not undergo lung transplantation from 1998 to 2003.	**N:** 20 **Mean age:** 29.5 years **Sex:** 40% female **Listed for transplant:** 10 (50%) **Median FEV1:** 25% of predicted **Mean BMI:** not recorded	**ACP received**: received full active therapy till death = 6 (17%); an abrupt change from active therapy to palliative care in the last few days of life = 13 (37%) **Symptoms and treatments during end-stage disease**: breathlessness = 35 (100%); difficulty expectorating = 24 (69%); chest pain = 22 (63%); severe malaise = 19 (54%); headache = 15 (43%); anxiety/fear = 14 (40%); abdominal pain = 3 (9%); hemoptysis = 2 (6%) **Palliative treatments received**: antibiotics = 35 (100%); opiates = 29 (83%); benzodiazepines = 20 (57%); hyoscine = 4 (11%); cognitive behavioral therapy = 4 (11%); noninvasive ventilation = 10 (29%) **Place of death:** Hospital: 20 (100%) **Duration of terminal admission:** Median 19 days **Referral to palliative care during terminal admission:** three patients **DNR order:** 18 patients **Preventative care administered in last 24 hours of life:** 17 (85%) **IV antibiotics in last 24 hours of life:** 17 (85%) **Assisted ventilation in last 24 hours:** 18 (90%) **Opiate administration in last 24 hours of life:** 16 (80%)
Ford D. et al.[16]	Single-center retrospective chart review	Describe pattern of EOL care for CF adults with advanced lung disease (FEV < 30 or before lung transplantation) and effect of lung transplantation on site of death between 1995 and 2005.	**N:** 41 **Deceased:** 24 **Mean age:** not reported **Sex:** not reported **Not referred for lung transplant:** 15 (37%) **Referred for lung transplantation:** 26 (63%) **Median FEV1:** not reported **Mean BMI:** not reported	**Transplant trajectory**: No formal transplant evaluation = 15 (37%); Formal evaluation = 26 (63%); listed for transplant = 20 (77%); not listed for transplant = 6 (23%); received lung transplant = 16 (80%); did not receive lung transplant = 4 (20%) **Deaths:** 24 (59%) 15 (71%) not listed for transplant; 9 (45%) listed/received lung transplant; 2 (22%) died waiting for transplant; 7 (78%) died after transplant **Location of death:** Hospital = 16 (67%): 50% medicine ward (all not listed); 50% ICU (five listed three not listed). Home = 8 (33%). **Conventional therapies at EOL:** Chest physiotherapy = 13 (65%); antibiotics = 14 (70%); vitamins = 12 (60%); diagnostics testing = 16 (80%); oxygen therapy = 19 (95%) **Palliative therapies at EOL:** Opiates for pain = 19 (95%); opiates for dyspnea = 15 (75%); anxiolytics = 12 (60%); NIPPV = 9 (45%); "DNR" order 24 hours of death = 14 (70%).

Cross-Sectional				
Hobler MR et al.[20]	Single-center cross-sectional survey of adults with moderate-to-severe CF Mixed methods study: Semistructured interviews—Not reported in our review	Describe the results of a survey administered to adults with CF with FEV1 < 65% of predicted regarding palliative care and ACP.	**N:** 49 **Questionnaire:** 47 **Mean age:** 38 (11%) **Sex:** 50% male **Race:** Asian 0%; white 94%; mixed /other: 7%; Hispanic: 2% **Education:** High school 2(4%); HS diploma/Eq 4 (9%); Trade/college 15 (33%); College deg some grad school 16 (35%); Graduate deg 9 (20%) **Current employment:** Employed 25 (54%); self-employed- 2 (4%); homemaker 1 (2%); retired 4 (9%); unable to work 14 (30%) **Mean FEV1:** 41% (range 19-63%) **Self-assessed health status:** Excellent 0 (0%); Very good 3 (7%); Good 15 (33%); Fair 25 (54%); Poor 3 (7%)	**Willingness to be referred to palliative care**: very 58%; moderate 33%; none/little 9%. **Willingness to participate in ACP**: very 60%; moderate 31%; none/little 9%. **Willingness to discuss goals of care with family/MD**: very 61%; moderate 26%; none/little 13%. **Experience & attitude toward serious discussion with doctor**: • *Have had face-to-face discussion*: Do not know 4%; yes 4%; no 91%. • *Would like a discussion*: Do not know 49%; yes 10%; no 42%. **Experience and attitudes toward serious discussions with family** • *Have discussed preferences*: yes 61%; no 39%. • *Would like a discussion*: Do not know 39%; yes 44%; no 17%. • *Would like more discussion*: Do not know 25%; yes 68%; no 7% Barriers to serious illness conversations with clinician: Do not like to talk about getting very sick—15 (36%); *My doctor never seems to have the time to talk about issues like EOL*—14 (35%); *I would rather concentrate on staying alive than talk about death*—14 (33%); *I'm not sure which doctor would be taking care of me if I were to get very sick*—13 (32%); *I'm not ready to talk about the care I would want if I were to get very sick*—11 (26%); *I do not know what kind of care I would want if I were to get very sick*—9 (21%); *My ideas about the care I want change at different times*—9 (21%); *I have a living will, so talking with doctor is not needed*—6 (14%); *I have not felt sick enough to talk with my doctor about EOL care*—2 (4%); *I feel that talking about death can bring death closer*—1 (3%). **Facilitators to serious conversations with clinicians**: I worry about the quality of my life in the future—26 (61%); I worry that I could be a burden on friends/family if I were to become very sick—24 (57%); I have been very sick, so it is easier to talk about—22 (52%); I have had family or friends who have died, so it is easier to talk about—22 (51%)
Chen, et al.[19]	Single-center cross-sectional survey of adults with a diagnosis of CF	Describe patient perceptions about pain, dyspnea, and ACP using survey questionnaire results.	**N:** 37 responders **Surveys sent out:** 43 **Age:** 22 (IQR 22.0, 33.0) **BMI:** 21.1 (IQR 19.3, 23.4) **FEV1:** 56% (IQR 35% 81.5%) **Sex:** 45% female	**ACP:** • *Thought about impact of CF on their lifespan:* Often 16 (43%); Occasionally 12 (32%); Never 9 (24%) • *Thought about transplant:* Willing to undergo 36 (64%); Only as a last resort 12 (33%); Never 1 (3%) • *The ideal time to discuss EOL care:* At a specific point—15 (42%); Now/early—12 (33%); When death is near—9 (25%). • *Thought about a health care proxy:* not thought very much—21 (57%); very much—12 (32%); somewhat— 4 (11%); completed a health care proxy form—9 (25%). • *Comfort level talking to family about EOL care:* comfortable—30 (81%); uncomfortable—5 (14%); not sure—2 (5%). • *Comfort level talking to their CF team about EOL care:* comfortable 35 (95%); uncomfortable 2 (5%). **Chronic pain**: 9 (24%) **Dyspnea:** at rest—10 (27%); walking flat ground—20 (54%); walking upstairs—33 (89%).

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Table 2
Continued

Paper ID	Study Design	Study Aim	Demographics	Outcome (Bold)/Results
Sawicki G et al.[18]	Cross-sectional survey of adults with CF who receive care at one of 10 CF centers in the U.S.	Describe results of a patient survey of experiences with ACP reported by adults with CF.	**N:** 234 **Mean age:** 34 **Sex:** 61% female **Mean FEV1:** 64% **Mean BMI:** not reported	**Talked about ACP (ACP)**: 74% **Thought about who would serve as a health care proxy**: 65% **Had specific wishes about future medical care**: 58% **Had a health care proxy, living will, or other written instructions (act)**: 30% **Further subdivision of ACP decisions based on age, gender, FEV1** (*n*, %Talk/Thought/Wish/Act) (*$P < 0.05$, **$P < 0.01$) Age 18–24: 41, 56**/62*/43**/10** 25–34: 82, 72/54/52/25 35–44: 71, 80/77/64/44 45+: 40, 89/69/80/37 Men: 91, 67/52**/55/20* Women: 143, 78/74/61/36 FEV1% < 40: 47, 82/72/72/28 **Felt comfortable talking to a CF clinician about ACP:** 79% **Felt comfortable talking with family about AC:** 75% **N, Clinician/Family/Talked-Clinician/Talked Family/ Clinician asked/Clinician should initiate** (*$P < 0.05$, **$P < 0.01$) Total: 234, 79/75/13/68/28/50 Age 18–24: 41, 74/62*/7/45**/15*/54 25–34: 82, 73/73/8/65/27/46 35–44: 71, 84/77/19/78/41/49 45+: 40, 89/93/20/83/24/55 Men: 91, 74/68*/13/59*/25/44 Women: 143, 82/80/14/73/30/54 FEV1% < 40: 47, 83/83/28**/77/43/4
Mitchell I et al.[25]	Cross-sectional survey of physicians at 36 CF centers in Canada	Describe the circumstances surrounding the death of individuals with CF who died in Canada over a one-year period (1996).	**N:** 45 **Mean age at death:** 24 **Sex:** 42 reported, 21 (50%) female **Mean age at diagnosis:** 6.4 months **Listed for lung transplant:** 7 **BMI:** not reported **FEV1:** not reported	**Cause of death**: Respiratory 34 (75.5%); Sepsis 2 (4.4%) **Long-term oxygen use (more than one month)**: 31 (69%) **Sputum cultures**: *Pseudomonas aeruginosa* only—19 (42%); *Burkholderia cepacia* only—10 (22%). **Location of death**: Hospital ward 28 (62.2%); ICU 7 (15.6%); home 8 (17.8%); other 2 (4.4%). **Palliative care involvement:** Palliative care/comfort measures used 29 (76.3%); Palliative care never discussed 10 (25%).
Balzano J et al.[21]	Cross-sectional survey of adults with CF at a single CF center	Assess the feasibility of a Web-based survey over a nine-month enrollment period.	**N** = 74 47% Women 94% Caucasian 57% FEV1 of 40%-69% predicted	**Survey results:** 23% (17) elevated global distress 20% (15) physical symptom distress 12% (9) psychological distress 58% (43) to discuss ACP would be beneficial

ACP = advance care planning; CF = cystic fibrosis; EOL, end of life; FEV1, forced expiratory volume in the first second.

Table 3
Summary of Outcomes

Study Design	Author & Date	Description	Advance Care Planning (ACP)	Leading the ACP Conversation	Patient-Reported Outcomes	Palliative Care Involvement	Location of Death	Treatments at End-Of-Life	Lung Transplant Impact	Symptom Management
Multicentered retrospective chart review	Dellon et al. (2016)[14] $N = 210$	Examine practices for ACP in U.S.-based adult CF care programs through review of 210 patients at 67 adult CF care programs who died from respiratory failure between 2011 and 2013.	61% documented	91% physician lead	–	6% of those with ACP	–	–	67% of patients listed had an ACP	–
Multicentered Retrospective Chart Review	Chen et al. (2018)[15] $N = 248$	Examine circumstances of death for adults with CF between 2011 and 2013.	58% completed	–	See symptom management	50% hospice involved	39% ICU 21% hospital without palliative care 14% home with hospice 12% home without hospice	37% mechanical ventilation 67% IV antibiotics 23% vasopressors 75% routine CF medications 42% nutritional support	–	Adequate control: 45% dyspnea 22% pain 51% anxiety 33% congestion
Single-center retrospective chart review of quality improvement intervention	Bourke et al. (2009)[22] $N = 40$	Descriptive analysis of the effect of integrating a palliative care provider in the care of patients dying from CF.	37%—abrupt change from active therapy to comfort in last few days of life	–	100% dyspnea 69% difficulty expectorating 63% chest pain 54% severe malaise 40% anxiety 43% headache	2% received palliative care	89% hospital with 3% in ICU 11% home	83% opiates 100% antibiotics 57% benzodiazepines 29% noninvasive ventilation	46% received palliative care while listed	–
Single-centered retrospective chart review	Ford, et al. (2007)[16] $N = 41$	Examine pattern of EOL care for CF adults with advanced lung disease (FEV < 30 or before lung transplantation) and effect of lung transplantation on site of death.	70%—DNR order within 24 hours of death	–	–	–	33% hospital ward 33% ICU	65% chest physiotherapy 70% antibiotics 60% vitamins 80% diagnostic testing	77% listed 80% received donor organs	–
Single-centered retrospective chart review	Karlekar, et al. (2015)[17] $N = 30$	Describe patient-reported symptoms at EOL, willingness to discuss advanced care directives, and whether advanced care directives were completed or not.	70% willing to discuss 18% completed 0% documented in medical record	–	50% anxiety/ depression 43% pain	–	–	–	–	–
Single-centered retrospective chart review	Philip et al. (2008)[24] $N = 20$	Description of circumstances surrounding death of patients dying of CF who did not undergo lung transplant between 1998 and 2003.	–	–	–	15% palliative specialist involved	100% hospital	85% antibiotics 90% assisted ventilation	–	–

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Table 3
Continued

Study Design	Author & Date	Description	Advance Care Planning (ACP)	Leading the ACP Conversation	Patient-Reported Outcomes	Palliative Care Involvement	Location of Death	Treatments at End-Of-Life	Lung Transplant Impact	Symptom Management
Multicentered cross-sectional survey of CF physicians	Mitchell et al. (2000)[25] $N = 45$	Survey of physicians on the circumstances surrounding the death of CF patients in 1996 in one of the 36 Canadian CF centers in 1996.	–	–	–	25% palliative care never discussed 75% palliative measures used	62% hospital ward 15.6% ICU 17.8% home	–	–	–
Multicentered cross-sectional survey of CF patients	Sawicki, et al. (2008)[18] $N = 234$	Patient survey of adults with CF regarding their experiences with ACP at 10 CF centers in the U.S.	30% completed	79% CF team 75% family	–	–	–	–	–	–
Single-centered cross-sectional survey of CF patients	Chen, et al. (2017)[19] $N = 37$	Describe the results of a survey administered to adults with CF regarding perceptions about pain, dyspnea, and ACP.	25% completed proxy form	47% prefer to talk with care team 50% with family 3% with palliative care specialist	24% chronic pain 27% dyspnea at rest	–	–	–	64% willing to undergo transplant	–
Single-centered cross-sectional survey of CF patients	Hobler, et al. (2018)[20] $N = 49$	Describe the results of a survey administered to adults with CF with FEV1 < 65% of predicted regarding palliative care and ACP.	60% "very willing" to participate in conversation 61% had discussed with family 68% would like more discussion	61% "very willing" to discuss with family	–	–	–	–	–	–
Single-centered retrospective chart review of a quality improvement intervention	Bourke, et al. (2016)[23] $N = 28$	Describe circumstances around death, assess palliative symptoms, and assess provider perspectives around integrating a palliative specialist into the CF team between 2011 and 2014.	–	–	89% dyspnea 86% cough 57% pain 57% nausea/vomiting 75% fatigue 36% anxiety 29% low mood	–	54%-hospital 7% home	–	21% listed for transplant at time of death	–
Single-centered, cross-sectional survey of adults with CF	Balzano, J et al. (2016)[21] $N = 74$	Assess the feasibility of a Web-based survey among adults with CF over a nine-month enrollment period. Initial survey results reported.	58% (43) to discuss ACP would be beneficial	–	23% (17) global distress 20% (15) physical distress 12% (9) psychological distress	–	–	–	–	–

ACP = advance care planning; CF = cystic fibrosis; EOL = end of life; FEV1 = forced expiratory volume in the first second.

of lung transplant listing on EOL care and ACP among adults with CF. In a cross-sectional survey of 37 adults with CF, an overwhelming majority (97%) reported that they would want lung transplantation when they reached end-stage disease.[19] Listing for lung transplant did not appear to impact completion of ACP[14] but was associated with an increased probability of dying in an ICU.[16]

Patient-Reported Symptoms

Five single-center studies described patient-reported symptoms among adults with CF; across these studies, symptom prevalence varied as chronic pain ranged from 43% to 63%,[17,19,22,23] anxiety and depression ranged from 36% to 50%,[17,22,23] and dyspnea ranged from 89% to 100%.[22,23] In a small, single-center study from 2016, 12%–23% of survey respondents reported physical or emotional distress.[21] In a nationwide, retrospective review of adult deaths from CF in the U.S. over a two-year period, Chen et al. found that among 112 patients with dyspnea, 45% reported adequate dyspnea control; among 101 patients with pain, 22% reported adequate pain control; and among 90 patients with anxiety, 51% reported adequate anxiety control.[15]

End-of-Life Care

End-of-Life Conversations

Four studies explored initiation of ACP conversations. One multicenter study reported that a CF-trained physician led 91% of ACP conversations and that palliative care providers were rarely included.[14] Across the three remaining studies, patient preferences varied regarding who should lead an ACP conversation. In one study, 44% of respondents noted that "serious conversations" should happen exclusively among family members, whereas only 10% wanted to have a "serious conversation" with their physician.[20] In another study, 50% of respondents indicated that the patient or family should initiate EOL conversations, whereas 47% of respondents felt it was the CF care team's responsibility to initiate such conversations[19]; this same study also found that 95% of respondents were comfortable talking with their CF care team about EOL.[19] In the third study, 75%–79% of patients were comfortable talking to either family or to their CF clinician about advanced directives.[18]

End-of-Life Involvement of Palliative Care Specialists

Two studies, each from a different nation, reported on the involvement of palliative care specialists at EOL. An Australian study found that only 15% of adult CF deaths involved palliative care specialists.[24] A U.S. study tracking two years of data found that 50% of deaths of adults with CF involved palliative medicine specialists and that patients seen by palliative care specialists were significantly more likely to have completed an advanced directive, less likely to have died in an ICU, and less likely to have received mechanical ventilation at EOL.[15]

Location of Death

Six studies examined the location of death. The majority of adult decedents with CF died in the hospital, with reported prevalence of 62%–100%.[16,22,24,25] In one study where palliative care specialists were integrated into the CF care team, 54% of adults with CF died in the hospital.[23] Prevalence of patients who died in the ICU varied from 3% to 37%, whereas only 11%–33% of individuals with CF died at home.[15,16,22,25] Even in the one study where palliative care specialists were involved in EOL care, only 7% of CF adult deaths occurred in the patient's home.[23]

End-of-Life Treatments

Four studies examined the types of therapies patients received during terminal hospital admission. A high prevalence, 67%–100%, of patients received intravenous antibiotics during their terminal hospitalization.[15,16,22,24] Similarly, 75%–85% of patients received preventative therapies (i.e., protein modulator therapies, vitamin supplementation, etc.) during their terminal hospitalization.[15,16,24] The prevalence of assisted ventilation during terminal admission varied from 29% to 90% of decedents[16,22,24], whereas one large, observational study reported a 12% prevalence of mechanical ventilation used during the terminal hospitalization of adults with CF.[15] Prevalence of palliative opiate use for terminal dyspnea ranged from 80% to 95%.[16,22,24]

Discussion

In this systematic review, we have summarized findings from 12 studies that examined palliative care–related outcomes among adults with CF. Our evidence suggests significant patient interest in ACP at all stages of disease but variable and/or late actual completion of ACP. Our findings also support that adults with CF suffer from significant, often inadequately treated, symptoms, including chronic pain, dyspnea, depression, and anxiety.

CF advocacy groups agree that palliative care is important for individuals with CF. The Cystic Fibrosis Foundation's consensus guidelines state that "… palliative care may be beneficial for multidisciplinary management of symptoms that may cause suffering …"[26] and the European Cystic Fibrosis Society Guidelines note that "effective management of EOL is vital and requires … a multidisciplinary approach … including expertise in palliative care."[27] Yet, CF is a highly variable disease with morbidity and mortality varying with disease genotype and phenotype, which can

Table 4
Summary of Key Findings for CF and Palliative Care Specialists

- Adults with CF, particularly in late-stage disease, have a high and often inadequately addressed symptom burden.
- The prevalence of ACP completion among adults with CF remains low.
- Opportunities exist for CF and palliative care specialists to collaborate to improve quality of life for adults with CF and their families.
- Further high-quality research is needed.

complicate palliative care delivery and perhaps explain existing poor penetration of palliative care specialist involvement in the care of adults with CF. Importantly, the U.S. nationwide observational study of CF adult deaths by Chen et al. suggests that involvement of palliative care specialists is associated with a decreased use of invasive therapies at EOL.[15] However, although CF advocacy and expert groups recommend palliative care and existing evidence supports benefits associated with palliative care among adults with CF, our findings suggest poor access to palliative care specialists in this population. This may be due to patient and/or clinician beliefs that ACP and palliative care, if needed, should be administered by the primary pulmonology care team and/or because, in many care settings, palliative care specialists are still not routinely integrated into CF care pathways.

Among all populations referred for lung transplant, adults with CF have the best survival outcomes with median survival of 8.9 years.[28] For this reason, along with younger age and patient preference, adults with CF are often referred for lung transplantation. Existing data found that listing for lung transplant increases the risk of dying in the ICU, but the exact reason is unclear. We hypothesize that while palliative care treatments can exist concurrent to life-prolonging treatments such as lung transplant, other CF and/or transplant providers not as familiar with palliative care practices may still see the two as occurring in series, rather than parallel; consequently, these misconceptions may delay or complicate delivery of palliative care for adults with CF who are awaiting transplant.

Our evidence supports that a majority of adults with CF die in a hospital setting and up to one-third die in an ICU. These in-hospital deaths may be due to the high-symptom burden and/or late initiation of ACP in this population. Another contributory explanation is that CF disease progression is characterized by intermittent exacerbations such that whether a given hospitalization may become a terminal hospitalization can sometimes be difficult to ascertain. Better and earlier utilization of palliative care specialists, particularly to promote ACP and better discussion about patient wishes surrounding EOL care, may decrease in-hospital or in-ICU death, if desired.

The majority of adults dying from CF receive life-prolonging or preventative treatments during their terminal hospitalization. We hypothesize that this may be due to the previously described, inherent exacerbatory nature of CF, particularly when patients, families, and providers struggle to recognize and accept EOL in a young or middle-aged person with a severe chronic illness. Moreover, life-prolonging treatments provided during a terminal hospitalization may also be in an effort to progress toward lung transplant. Again, integration of a palliative care specialist may help to optimize the balance between sustaining life and alleviating suffering.

Clinical implications of this review, summarized in Table 4, are that adults with CF, particularly in late-stage disease, have a high and often inadequately addressed symptom burden and inadequate ACP. As a CF patient approaches the end stages of their disease, there are multiple opportunities where palliative care teams could partner with CF pulmonologists to provide psychosocial support for patients and their family members; specifically address EOL preferences, such as preferred site of death; and clarify patient and family goals and contingency plans particularly if advanced therapies, such as lung transplantation, are still being considered.

Our review has several limitations. The majority of included studies were retrospective, observational studies, which are innately descriptive and cannot control for bias or confounding. Several of the studies were small, single-center studies, which may not represent the broader population. The studies also took place in only four countries, so other countries' beliefs and practices are not captured. The outcomes examined in the included studies were heterogeneous and prevented meta-analysis. We believe these limitations point to the paucity of literature and multiple opportunities for future research exploring palliative care among adults with CF. For instance, given the large proportion of patients with poorly controlled palliative symptoms, investigating factors that might improve symptom control, like the expertise of a palliative care specialist, would be of value. In addition, although studies have examined completion rates and patient attitudes about ACP, the impact of ACP on palliative outcomes is not yet understood.

Conclusion

Numerous opportunities exist for palliative care and palliative care specialists to improve care among adults with CF. Existing evidence supports significant patient comfort with and desire for ACP but low prevalence

and late completion of actual ACP. Adults with CF also have a high, often untreated, symptom burden and rare out-of-hospital death. Finally and perhaps as a consequence of late ACP and frequent referral for lung transplant, adults with CF often die in the hospital, if not the ICU, and utilize aggressive treatments even during their terminal hospitalization.

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Appendix

Search Terms

PubMed

((("Cystic Fibrosis"[MESH] OR "cystic fibrosis"[TW] OR "CF"[TIAB]) AND (“Palliative care” [MH] OR "palliative care" [TIAB] OR “Hospice and Palliative Care Nursing” [MESH] OR “Hospice care”[MESH] OR "hospice care" [TIAB] OR “advance care planning”[MESH] OR “advance care planning”[TW] OR “terminal care”[MESH] OR “terminal care”[TW] OR “end of life care”[TW] OR (“Referral and Consultation”[MESH] AND (palliative [TIAB] OR hospice [TIAB])))) AND English[LA]) NOT (“Clinical Conference”[PT] OR editorial[PT] OR letter[PT])) NOT (child*[TIAB] OR pediatr*[TIAB] OR paediatr*[TIAB] OR "compassion fatigue"[TIAB])

Embase

('cystic fibrosis'/exp OR 'cystic fibrosis' OR 'fibrocystic disease'/exp OR 'fibrocystic disease' OR 'cf':ti,ab,kw) AND ('palliation'/exp OR 'palliation' OR 'palliative care'/exp OR 'palliative care' OR 'palliative consultation'/exp OR 'palliative consultation' OR 'palliative medicine'/exp OR 'palliative medicine' OR 'palliative radiotherapy'/exp OR 'palliative radiotherapy' OR 'palliative surgery'/exp OR 'palliative surgery' OR 'palliative therapy'/exp OR 'palliative therapy' OR 'palliative treatment'/exp OR 'palliative treatment' OR 'hospice and palliative care nursing'/exp OR 'hospice and palliative care nursing' OR 'palliative care nursing'/exp OR 'palliative care nursing' OR 'palliative nursing'/exp OR 'palliative nursing' OR 'hospice care'/exp OR 'hospice care' OR 'eol care'/exp OR 'eol care' OR 'end-of-life care'/exp OR 'end-of-life care' OR 'terminal care'/exp OR 'terminal care' OR 'hospice nursing'/exp OR 'hospice nursing' OR 'patient referral'/exp OR 'patient referral' OR 'referral'/exp OR 'referral' OR 'referral and consultation'/exp OR 'referral and consultation' OR 'advance care planning'/exp OR 'advance care planning') AND ('article'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) AND [english]/lim NOT (child*:ti,ab OR pediatr*:ti,ab OR paediatr*:ti,ab OR “compassion fatigue”:ti,ab)

Scopus

TITLE-ABS-KEY ((("cystic fibrosis" OR "CF" OR "fibrocystic disease") AND (("palliative" OR "palliation" OR "terminal" OR "end-of-life" OR "hospice") PRE/3 ("care" OR treat* OR medicine OR therap* OR refer* OR consult*))) AND NOT (child* OR pediatric* OR pediatric* OR “compassion fatigue”)) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re") OR LIMIT-TO (DOCTYPE, "no") OR LIMIT-TO (DOCTYPE, "sh") OR LIMIT-TO (DOCTYPE, "ip")) AND (LIMIT-TO (LANGUAGE, "English"))

Web of Science

TS=((("cystic fibrosis" OR "CF" OR "fibrocystic disease") AND (("palliative" OR "palliation" OR "terminal" OR "end-of-life" OR "hospice") NEAR/3 ("care" OR treat* OR medicine OR therap* OR refer* OR consult*))) NOT (child* OR pediatric* OR pediatric* OR “compassion fatigue”))

CINAHL

((MH "cystic fibrosis" OR TI "cystic fibrosis" OR AB "cystic fibrosis" OR TI "CF" OR AB "CF" OR TI "fibrocystic disease" OR AB "fibrocystic disease") AND ((MH “Hospice and Palliative Nursing” OR MH “palliative care” OR MH “Terminal Care+” OR MH “Hospice Care” OR MH “Advance Care Planning” OR MH “Referral and Consultation+” OR TI “Hospice and Palliative Nursing” OR TI “palliative care” OR TI “Terminal Care” OR TI “Hospice Care” OR TI “Advance Care Planning” OR TI “Referral and Consultation” OR AB “Hospice and Palliative Nursing” OR AB “palliative care” OR AB “Terminal Care” OR AB “Hospice Care” OR AB “Advance Care Planning” OR AB “Referral and Consultation+”) OR (("palliative" OR "palliation" OR "terminal" OR "end-of-life" OR "hospice") W3 ("care" OR treat* * OR medicine OR therap* OR refer* OR consult*)))) NOT (AB child* OR AB pediatric* OR AB pediatric* OR AB “Compassion fatigue” OR TI child* OR TI pediatric* OR TI pediatric* OR TI “Compassion fatigue”)