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Non-beneficial treatments in hospital at the end of life: a systematic review on extent of the problem

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Abstract

Purpose: To investigate the extent of objective 'non-beneficial treatments (NBTs)' (too much) anytime in the last 6 months of life in routine hospital care.
Data sources: English language publications in Medline, EMBASE, PubMed, Cochrane library, and the grey literature (January 1995–April 2015).
Study selection: All study types assessing objective dimensions of non-beneficial medical or surgical diagnostic, therapeutic or non-palliative procedures administered to older adults at the end of life (EOL).
Data extraction: A 13-item quality score estimated independently by two authors.
Results of data synthesis: Evidence from 38 studies indicates that on average 33–38% of patients near the EOL received NBTs. Mean prevalence of resuscitation attempts for advanced stage patients was 28% (range 11–90%). Mean death in intensive care unit (ICU) was 42% (range 11–90%); and mean death rate in a hospital ward was 44.5% (range 29–60%). Mean prevalence of active measures including dialysis, radiotherapy, transfusions and life support treatment to terminal patient was 7–77% (mean 30%). Non-beneficial administration of antibiotics, cardiovascular, digestive and endocrine treatments to dying patients occurred in 11–75% (mean 38%). Non-beneficial tests were performed on 33–50% of patients with do-not-resuscitate orders. From meta-analyses, the pooled prevalence of non-beneficial ICU admission was 10% (95% CI 0–33%); for chemotherapy in the last six weeks of life was 33% (95% CI 24–41%).
Conclusion: This review has confirmed widespread use of NBTs at the EOL in acute hospitals. While a certain level of NBT is inevitable, its extent, variation and justification need further scrutiny.

Key words: non-beneficial, hospital care, inappropriate, end of life, systematic review, patient safety

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Introduction

The lack of agreed definitions of terms such as treatment futility, inappropriate and non-beneficial treatment (NBT) makes a global dialog difficult and perpetuates the practice of aggressive, and costly, care at the end of life (EOL) [1]. The concept of 'futility' can be seen as a subjective perception of lack of treatment benefit when patients or healthcare providers attach varying weights to the clinical, social or economic perspectives. But perceived and qualitative descriptions of futility cannot easily be measured or replicated for monitoring in routine practice, especially if the patient wishes are not incorporated [2, 3]. A previous review has examined the moral and clinical meaning of futility in the context of proposed guidelines for initiating the EOL dialog [4]. A more recent systematic review investigated the criteria used to justify claims of futility in limitations of treatment for people who had experienced a cardiac arrest. They found that definitions of futility lacked explicit thresholds and that estimates were based on insufficient variables to provide statistical confidence for decision-making [5].

The term 'inappropriate' treatment may be interpreted as interventions that are ineffective in achieving the desired goals, or are 'a disservice to patients who are subjected to ongoing and likely uncomfortable conditions with no benefit' [6]. In other words, the nature of the illness would not be influenced by the resources used in an acute hospital.

Following peer feedback on the implications of value-laden words such as 'too much', 'futile', 'inappropriate' or 'disproportionate' care, the expression NBT appeared to be more acceptable as it indicates a treatment that was administered with little or no hope of it having any effect, largely because of the underlying state of the patient's health and the known or expected poor prognosis regardless of treatment. The term NBT therefore reflects an objective inverse correlation between intensity of treatment and the expected degree of improvement in a patient's health status, ability for survival to hospital discharge [7], or improvement in quality of life [8]. Our focus is on aggressive active management beyond comfort care in the last 6 months of life when the clinical presentation should have signaled the time for transition from aggressive to palliative or comfort care [9]. In turn, palliative care is understood as interventions to prevent and relief physical and spiritual suffering for patients and families facing life-threatening illness [10].

As part of the review, we will use objective parameters to determine NBT in the last 6 months of life to adopt or adapt as operational and measurable concepts in routine care. This is for the purpose of further enhancing awareness and reducing non-beneficial EOL treatment that is ineffective [9], unethical, costly [11] and not in line with patients wishes [12].

The concept of 'non-beneficial' due to 'insufficient' treatment [13] is beyond the scope of this review, as our focus is on use of the term 'non-beneficial' implying 'too much', 'unnecessary' or 'excessive'.

Purpose

The objectives of this review were to examine:

1. the variety of definitions of NBTs and assess the ability to measure them in practice;
2. the extent of measured 'non-beneficial' hospital treatments at the EOL.

Study selection

Eligible studies had a target population (P) of older patients. The scope of the search for interventions (I) considered non-beneficial covered objective definitions of aggressive management such as invasive procedures, operations, complex medications and costly actions commencing or occurring in the last 6 months of life. This covers the last 6 months to the last days of life, a period that qualifies 'terminal illness'. That is, a progressive disease where death as a consequence of that condition can reasonably be expected within 6 months [14]. Comparator (C) interventions were not an eligibility criterion in this review examining the extent of the problem. Outcomes (O) of interest measuring NBT in terminal illness included chemotherapy in the last two weeks, parenteral hydration, artificial nutrition, dialysis, intensive care admission in the last few days of life, mechanical ventilation (MV) in the last days, cardiopulmonary resuscitation (CPR) in terminal patients, intravenous (IV) antibiotics in terminal care, transfusion and any invasive non-palliative treatments which were either administered against patient wishes, delivered due to clinician's uncertainty of prognosis, personal beliefs, sense of duty to cure or moral obligation, or considered unwarranted by treating staff but were administered due to family demands or health system accountability pressures. Eligible study (S) methods included randomized controlled trials, retrospective data reviews (audits), clinical staff surveys, descriptive studies, qualitative studies and observational studies.

Descriptive studies were included as the concept of NBT is still the subject of debate and objective #1 was to examine definitions and the ability to measure them in practice. Descriptive studies were only excluded if they did not address at least one of our study objectives. Quantitative studies were given more weight as objective #2 was to assess the extent of the problem.

Methods

Data sources

We conducted a review of the English language medical literature in Ovid SP (Medline, EMBASE), PubMed, Cochrane library, and the grey literature for publications between January 1995 and April 2015. Our focus was on elderly patients with terminal illness hospitalized at the EOL. Advanced chronic illness was included but was limited to cancer, chronic heart failure, chronic kidney disease, chronic liver disease, stroke and chronic obstructive pulmonary disease.

Search strategy

We used the following combination of terms in the abstract, title or as keyword, limiting the search to English language and years 1995–2015: inappropriate or disproportionate or non-beneficial or costly or futility AND hospital or hospitalization AND cancer, or chronic heart failure, chronic kidney disease, chronic liver disease, stroke, chronic obstructive pulmonary disease AND advanced or terminal or life-limiting or death or dying (Online Appendix 1). Literature searches were mainly conducted by one author (J.C.H.K.) with single database cross-searching of appropriateness by another (M.C.M.); manual searches of the reference lists of papers eligible for inclusion were conducted by several co-authors (J.C.H.K., M.A., K.H., M.C.M.).

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Data extraction

Articles were imported into EndNote and subgroups of eligible vs. excluded were compiled. Title and abstract eligibility assessments were conducted independently by two authors (J.C.H.K. and M.C.M.) using the agreed protocol with inclusion criteria specified in the 'Study selection' section. Exclusions with reasons were documented in an excel spreadsheet (J.C.H.K.) and double checked by a second author (M.C.M.). Discrepancies about eligibility assessments between the two authors were resolved by an external third academic colleague who was not an author of this manuscript but experienced in systematic reviews. Quality assessment conducted by one author (M.C.M.) using an agreed and purpose-designed suitability score comprising objective items (see below). This was developed by the authors using modified domains from existing bias assessment tools for non-randomized studies [15, 16] and scores cross-checked by another author (J.C.H.K.) for potential discrepancies of opinion. A suitability score was calculated to assess quality of the study design and analysis. Assignment of 1 point for each item out of 13 items effectively gave higher weight to quantitative studies with replicable measurements of NBT. The suitability score assessed whether the study:

1. had quantitative design to answer the research question;
2. had clear description of objectives;
3. had sample size of >100 or justifiable sample size calculation;
4. had clearly stated subject selection criteria;
5. included random selection of participants;
6. reported response rate $\geq$80% and a denominator;
7. included a comparison group;
8. reported quantitative indicators;
9. used validated outcome measures or defined them;
10. reported on all intended outcomes;
11. did not exclude important cases from analysis;
12. had $\leq$20% incomplete outcome ascertainment;
13. incorporated potential confounders in the analysis.

This review is not registered with PROSPERO because of the ongoing considerations about search terms and definitions between authors. This enriching process meant the protocol had to be dynamic until late in the review. PROSPERO requires registration of the protocol before the critical assessment commences.

Analyses

A descriptive compilation of definitions and extent of NBT was summarized in tables, using the reported measurements. In deciding on the relevance and feasibility of monitoring measured outcomes, we examined the indicators against the following criteria: objective or subjective, use of an expert panel, items routinely available in the clinical setting, whether social or system factors were incorporated and whether there was a need for additional resources to document the outcomes.

Actual prevalence of indicators of NBT was generally presented without any attempt to pool results across studies as the purpose of the review was to examine the variety of definitions and assess the ability to measure them in practice. Therefore, for most measures, the mean across studies and range was presented. No contact with authors of eligible studies was made to find any additional information. Meta-analysis was only attempted (by RMT) for the indicators where definitions were homogeneous/replicable and there were more than three studies reporting them, so they were not pre-specified. A random effects meta-analysis was conducted to obtain a pooled prevalence (proportion), with studies weighted to account for the standard error and heterogeneity [17]. Forest plots were created to show the study specific and pooled proportions, and ordered by year of study publication. Heterogeneity was assessed using the I-squared statistic, an intuitive expression of inconsistency of study results expressed as a percentage of variation across studies due to clinical and methodological diversity rather than to chance [18, 19]. All analyses were conducted in Stata version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

Results of data synthesis

Thirty-eight studies met the criteria for inclusion in the review of NBT among patients who have been hospitalized (Online Appendix 2, Fig. 1).

The eligible studies included 1 213 171 subjects in 10 countries: USA 18 studies, Europe/UK 7 studies, Canada 5 studies, Brazil 3 studies, Taiwan/South Korea 3 studies and Australia 2 studies (Table 1). Most of the studies (24/38 eligible) were exclusively retrospective data reviews, seven were cross-sectional surveys, four descriptive qualitative studies and three prospective data collections, with two of these using mixed methods. Target groups for the measurement of NBT were mixed and covered: critically ill hospitalized patients (20 studies), healthcare provider or relatives of deceased patients with malignancies or dementia (13 studies), and healthcare providers or surrogates of hospitalized patients with advanced illness (10 studies).

The quality scores for addressing our research question were generally high (mean and median score of 9 out of 13), with 10 studies scoring 11 or higher and only 4 studies scoring <6.

Of the 38 eligible studies, 29 reported objective NBT estimates based on the definition adopted by each study (Table 2). The most commonly reported estimates were ICU admission, administration of CPR, in-hospital mortality and use of chemotherapy in the last 6 months of life. Despite high heterogeneity of study designs and outcomes, most markers of NBT used items that are routinely collected or readily available in hospital records and can be used to compare definitions. The few exceptions were cost of care, cost savings from ICU avoidance, imminent death and judgment that patient would be unable to survive outside ICU [27, 32, 47].

The prevalence of objectively measured NBT using the definitions with the most homogeneous denominators or timeframes varied by type of intervention (Table 3). For example, ICU admission among incurable patients in the period between the last 6 months and the last 7 days of life ranged from 2.0% to 90% (mean 33.3%). However, the seven studies meta-analyzed selected on the basis of uniformity of definition of ICU admission in the last 6 weeks of life, i.e. similar numerator/denominator measurements and similar timeframes. For these, the pooled average estimate of non-beneficial ICU admission was 10% (95% CI 0–33%; Fig. 1). Sensitivity analysis excluding the largest, dominant study made the remaining studies more homogeneous and the estimate dropped to 7% (95% CI 3–10%).

Likewise, studies reporting either newly initiated chemotherapy at the EOL or ongoing chemotherapy for patients with or without previous limitation of treatment administered in the period ranged from 3% to 76% (mean 25.1%; Table 3). Meta-analyses of the five studies reporting comparable timeframes for new or ongoing use of chemotherapy in the last 6 weeks of life indicated that the overall prevalence was 33% (95% CI 24–41%; Fig. 2).

Resuscitation attempts for terminal patients including those with pre-existing limitations of care ranged from 11.0% to 90.0% (mean

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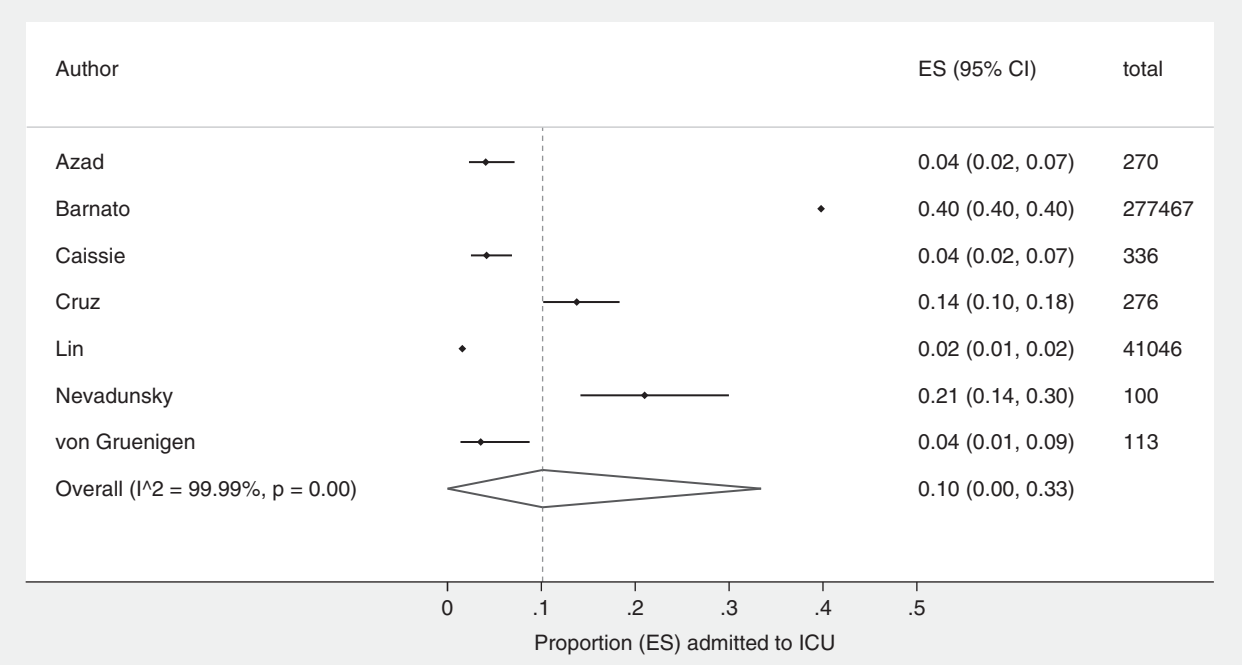


Figure 1 Pooled estimates of non-beneficial intensive care unit (ICU) admission at the EOL.

28.1%). Death in ICU or a hospital ward or post-discharge within a few months of initiation of aggressive treatment also varied widely from 11.0% to 96.4% (mean 58.0%). Non-beneficial tests were undertaken in a third to half of patients with DNR orders and in a quarter of those in the last 3 months of life (Table 3).

Other active management interventions included dialysis, radiotherapy, transfusions and life support treatment and these were administered on average to a third of terminal patients (mean 29.9% and range 7.0–77%). Non-beneficial medicines including antibiotics, cardiovascular, digestive and endocrine treatments were also administered to over a third of terminal patients (mean 38%, range 10.7–75.0%). Other measurable NBT less commonly used was expressed in terms of unnecessary use of hospitals, emergency services and rapid response systems, duration of treatment and length of stay and cost of ICU treatment.

In six studies of objective indicators, expert skill was required to decide on the non-beneficial nature of some of the markers of care chosen [24, 27, 29, 32, 37, 48]. These markers included anticipated cardiac arrest, unnecessary medication, low ECOG performance scores, treatment never reaching the patient's goals and treatment unable to improve patient's survival or quality of life. Markers incorporating health system factors were measured in eight studies: underutilization of hospice care [41, 46, 53], absence of palliative care consultation before ICU admission [54], delayed documentation of code blue status [38], cost savings from ICU avoidance [27], cost of hospitalization with/without ICU admission [47] and delayed decision to forgo life-sustaining treatment [34].

Unnecessary imaging were performed in at least a quarter of all terminal patients in a large study [22] and unwarranted blood tests at higher rates (37.0–49.0%) in a smaller study [26]. These could be regarded as 'low-value' care and are distinct from invasive, life-prolonging treatments that are non-beneficial.

Subjective definitions

Eleven studies included subjective definitions based on clinicians' expertize to determine the non-beneficial nature of the treatment, and where indicators were neither routinely collected nor amenable to replication [6, 8, 13, 28, 32, 33, 36, 39, 42, 44, 51]. Examples of these definitions include: procedures 'when there is no evidence that will prolong survival beyond a few days' [4]; 'perceived imbalance between the amount or intensity of treatments being provided and the patient's expected survival, quality of life or wishes' [13]; and 'treatments that (1) would almost certainly result in a quality of life that the patient has previously stated that he/she would not want, or (2) are not consistent with the goals of care (as indicated by the patient) [8]. In light of the inability to reliably measure or routinely collect these definitions, the focus of this manuscript was then confined to indicators that could help us operationalize and monitor the concepts in the real world. The use of subjective definitions of non-beneficial care will be the subject of a separate manuscript.

Discussion

This review has gathered a comprehensive list of objective indicators of NBT measurable routinely in practice confirming widespread hospital practice of non-beneficial patient management at the end of life. We found a wide range of timeframes and intensity of interventions and diagnostic procedures defined as NBT. While the prevalence varies by patient condition, health system and type of aggressive treatment, overall the findings strongly indicate the persistence of ambiguity about what is deemed non-beneficial, and a culture of 'doing everything possible' even if it is against expressed patients' wishes. These behaviors have repercussions not only on the capacity and financial sustainability of the health services, and perpetuate the unrealistic high social expectation of survival at all costs,

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Table 1 Relevant studies, methods and study populations—1995 to 2015 (38 studies)

Authors and publication year	Country	Sample size	Study type				Suitability score[a]	Study population		
			Record review	Survey	Prospective	Qualitative/ descriptive		Deceased patient, provider or relative of deceased	Critically or terminally ill patient	Healthcare providers or relatives of ill patients
Cruz *et al.*, 2015 [20]	Brazil	347	✓				8	Patients who died in a tertiary cancer hospital		
Downar *et al.*, 2015 [8]	Canada	688		✓			6			Health professionals working in ICUs and acute care wards
Anstey *et al.*, 2015 [13]	USA	1363		✓			11			ICU doctors and nurses
Hart *et al.*, 2015 [21]	USA	13 405	✓				9	Deceased patients in ICU who had limitations of treatment	Survivors of ICU who had limitations of treatment	
Kaushik *et al.*, 2014 [22]	UK	71 269	✓				9	Patients who died of gynecological cancer from 2000 to 2012		
Singal *et al.*, 2014 [6]	Canada	294		✓	✓		7		Prospective collection from patients admitted to the medical-surgical trauma ICU	Health care providers of patients admitted to the medical-surgical trauma ICU
Elsayem *et al.*, 2014 [23]	USA	5326	✓				10		Cancer patients admitted through emergency departments	
Weir *et al.*, 2014 [54]	USA	52	✓				5	Advanced incurable cancer patients who died in ICU		
Kim *et al.*, [24] 2014	South Korea	95	✓				11	Lung cancer patients admitted to ICU who died	Lung cancer patients admitted to ICU who survived	
Frickhofen, [25] 2014	Germany	N/R				✓	4		Cancer patients from a Medicare database	
Azad *et al.*, 2014 [26]	Australia	270	✓				11		Oncology patients admitted to hospital with a DNR	
Portman *et al.*, 2014 [27]	USA	N/R	✓				5		Critical care patients at bone marrow transplant clinic	
Marck *et al.*, 2014 [28]	Australia	681		✓			5		Nurses and doctors managing ICUs	
Lee *et al.*, 2013 [29]	South Korea	196	✓				9	Terminally ill cancer patients admitted to the hemato-oncology Dept who died in hospital		
Nevadunsky *et al.*, 2013 [30]	USA	100	✓				11	Patients who died from cancer and were treated by oncologist in last year of death		
Lopez-Acevedo M *et al.*, 2013 [53]	USA	169	✓				7	Women who died of ovarian cancer		
Lin and Hsieh, 2013 [31]	Taiwan	74 039	✓				10		Cancer patients in the last 3 months of life	Expert from academic, clinical, legal and social fields

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Huynh *et al.*, 2013 [32]	USA	1136		✓			8			Critical care specialists working in ICUs
Jox *et al.*, 2012 [33]	Germany	29				✓	6			Clinicians involved in palliative care consultations
Azoulay *et al.*, 2012 [34]	France	1265	✓				12		Patients in several ICUs	
Bouleuc *et al.*, 2011 [35]	France	138	✓				6		Patients admitted to palliative care	
Piers *et al.*, 2011 [36]	Europe and Israel	1651		✓			6			ICU nurses and physicians providing bedside care in 82 adult ICUs
Fede *et al.*, 2011 [37]	Brazil	87		✓			7		Terminally ill ambulatory cancer patients	
Caissie *et al.*, 2014 [38]	Canada	336	✓				9	Patients with recurrent or spread cancer who died in oncology ward		
Riechelmann *et al.*, 2009 [39]	Brazil	372	✓				7		Ambulatory patients with advanced cancer receiving palliative care	
von Gruenigen *et al.*, 2008 [40]	USA	113	✓				8	Deceased ovarian cancer patients		Families of cancer patients at the EOL
Earle *et al.*, 2008 [41]	USA	215 484	✓				11		Terminally ill cancer patients from Medicare database	
Sibbald *et al.*, 2007 [42]	Canada	44				✓	4			Key medical and nursing informants from ICU
Cornet *et al.*, 2005 [43]	Holland	58	✓		✓		12		Haemato-oncological patients admitted to ICU	
Palda *et al.*, 2005 [44]	Canada	255		✓			7			Medical and nursing unit directors of all Canadian ICUs
Barnato *et al.*, 2004 [45]	USA	277 467	✓				9	20% sample of Medicare decedents over 65 years of age	5% sample of hospital survivors	
Rady *et al.*, 2004 [46]	USA	252				✓	10	Admitted patients who subsequently died		
Angus *et al.*, 2004 [47]	USA	540 200	✓				10		Terminal patients using ICU services at EOL	
Ewer *et al.*, 2001 [48]	USA	243	✓				13		Cancer inpatients who experienced cardiac arrest and received CPR	
Wallace *et al.*, 2002 [49]	USA	5196	✓				11		Patients who received CPR in ICU	
Varon *et al.*, 1998 [50]	USA	83	✓				10		Cancer patients who suffered cardiac arrest	
Hamel *et al.*, 1997 [51]	USA	490			✓		8		Hospitalized patients with 9 advanced illnesses	
	USA	164	✓				12			

Table continued

Table 1 Continued

Authors and publication year	Country	Sample size	Study type				Suitability score[a]	Study population		
			Record review	Survey	Prospective	Qualitative/ descriptive		Deceased patient, provider or relative of deceased	Critically or terminally ill patient	Healthcare providers or relatives of ill patients
Ahronheim *et al.*, 1996 [52]								Elderly patients with advanced dementia or metastatic solid tumor malignancy who died in acute teaching hospital		

[a]Quality score out of 13 points. DNR, do-not-resuscitate; N/R, not reported.

but also more importantly reflect a disregard for human dignity and quality end of life.

Admission to an acute hospital and prevention of death through clinical interventions are often the default position whether a patient has a reversible component to their disease or whether they are at their natural end of life [55]. As the elderly and frail population increases, the number attendances to emergency rooms and admissions to acute hospitals are rapidly expanding [56, 57]. Achieving a balance between doing everything that is technically feasible but ethically and clinically appropriate to improve quality of care at the end of life is difficult [11, 58]. Clinical judgment alone does not always accurately predict patients who may not benefit from further active treatment [59].

Objective indicators of NBT

The most commonly reported measurable outcomes across studies in this review were admissions to ICU for patients with either advanced incurable disease or pre-existing limitations of treatment; administration of CPR for terminal patients with or without prior limitation of treatment orders; and initiation or continuation of chemotherapy in the last 14 days to 1 month of life. In addition to inflicting unnecessary patient suffering, these aggressive management approaches have substantial resource implications for hospitals. These indicators could be easily adopted as markers of non-beneficial care and monitored routinely to inform hospital practice. Other forms of life support treatment for patients with DNR are also clearly non-beneficial and the variety of interventions may be too heterogeneous to aggregate them into a single indicator. Death in ICU or death in hospital are available indicators but their specificity to mark them as 'non-beneficial' cannot be established from routine data unless detailed audits are undertaken.

For instance, linking with additional clinical EOL flags could turn this indicator into a relevant, actionable and internationally comparable quality performance measure useful for health policy-making, monitoring and development of interventions [60]. Non-beneficial medicines cannot be easily ascertained without expert input and are not always available in clinical databases. 'Underuse' of hospice care (i.e. short LOS or late admission to hospice) cannot always be assumed to be non-beneficial care if there is no choice to use them earlier in health systems with insufficient hospices to refer terminal patients, or if their location is unsuitable for people in remote areas; or if the health insurance does not cover the services. The portion of 'overuse' of emergency and intensive care services in the last months of life that is driven by patients or families rather than by physicians can only be changed through a public education campaign [6]. The 'non-beneficial' nature of long hospital length of stays hemodialysis, MV, central line insertions, administration of vasoactive agents and blood products may still be debatable and difficult to monitor in light of uncertainty of time to death. The recognition of the dying as someone with multi-morbidity and in advanced illness refractory to conventional treatment with no hope of recovery within a few months could minimize prognostic uncertainty. Finally, failure to reach agreement on the definitions, timeframes for interventions and inclusion of the patient perspective makes it challenging to determine their undesirability as NBT.

System factors are known contributors to the perpetuation of NBT although most studies in our review did not address the reasons and omitted health system factors. They include lack of opportunity for EOL discussions or communication failures between

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Table 2 Objective measurement and relevance of parameters for operational definition of NBT (29 studies)

Authors and publication year	Routinely collected or readily available	Expert panel or skill required	Health system factors incorporated	Markers of 'non-beneficial' care: how measured and measurable
Da Cruz *et al.*, 2015	✓			Terminal patient transferred to ICU and ≥1 advanced life support measure initiated and maintained (MV, vasopressor or hemodialysis)
Hart *et al.*, 2015	✓			Patients with documented limitations of treatment or DNR admitted to ICU and receiving either: CPR, MV, vasoactive medications or initiation of renal replacement therapies among patients
Kaushik *et al.*, 2014	✓			Emergency admissions in last year of life, ongoing or first chemotherapy cycle, emergency imaging and urological procedures in last 3 months of life
Elsayem *et al.*, 2014	✓			Admission to ICU, proportion of patients dying in ICU/hospital with symptoms of respiratory distress and altered mental status
Weir *et al.*, 2014	✓		✓	Death in ICU, mean time from admission to death in ICU, proportions of advanced cancer patients on MV, proportion without palliative care consult before ICU admission
Azad *et al.*, 2014	✓			Oncology patient with DNR commencing CPR or continuing: ICU admission, MET calls, ventilation, parenteral nutrition invasive procedures, chemotherapy, radiotherapy, IV antimicrobials, blood products, blood draws, imaging
Frickhofen 2014	✓			Chemotherapy within 14 days of death, repeat hospitalizations, emergency room visits and, intensive care admissions within the last month of life
Kim *et al.*, 2014	✓	✓		Cancer patients beyond third-line chemotherapy (refractory) or bedridden or with poor performance status or DNR order admitted to ICU; receiving CPR, MV, vasoactive agents or hemodialysis
Portman *et al.*, 2014		✓	✓	Chemotherapy within 14 days of death; number of days of hospice care before death; interventions in patients with low performance score (ECOG 3-4); cost savings form ICU avoidance
Caissie *et al.*, 2014	✓		✓	Attempts at CPR or ICU admission with untimely (>48 hours post admission) or absent documentation of code blue status/DNR
Lee *et al.*, 2013	✓	✓		Prescription of medications that had no short-term benefit to patient survival or quality of life for people with <6-month expected survival
Nevadunsky *et al.*, 2013	✓			Chemotherapy in last 6 months, intubation, CPR and admissions to ICU
Lopez-Acevedo M *et al.*, 2013	✓		✓	Chemotherapy in last 14 days of life; >1 admission or ED visit in last 30 days of life; death in ICU; admitted to hospice in <3 days before death; and not admitted to hospice.
Lin and Hsieh, 2013	✓			Treatment in ICU after 7 days following a CPR for cancer patients who die within 3 months is probably futile
Huynh TN *et al.*, 2013		✓		Perceived futile treatment or probably futile treatment according to expert opinion of a panel of specialists if burden outweighed the benefits, death was imminent, treatment will never reach the patient's goals, or patient was unable to survive outside of an ICU.
Azoulay *et al.*, 2012	✓		✓	Treatment intensity: type and duration of LST in ICU; ICU mortality; in-hospital death; time from ICU admission to decision to forgo LST; length of stay in ICU.
Bouleuc *et al.*, 2011	✓			Termination of chemotherapy in the last month of life; number of emergency presentations in the last 3 months of life; death in ICU
Fede *et al.*, 2011	✓	✓		Unnecessary medication prescribed by physician at EOL (based on explicit criteria) and its associated adverse events and economic burden
Earle *et al.*, 2008	✓		✓	Initiation or continuation of chemotherapy within 14 days of death, Emergency room visit in last month of life, hospitalization in last month of life, ICU admission in last month of life, underutilization of hospice services (admission in the last 3 days of life)
von Gruenigen *et al.*, 2008	✓			Last chemotherapy in last 14 days, new chemotherapy course in last 3 months of life, ED visits and ICU admissions in last month of life.
Cornet *et al.*, 2005	✓			Proportion of hemato-oncology patients dying in ICU with high SOFA score on admission
Barnato *et al.*, 2004	✓			Death in acute hospital; ICU during terminal admission; intensive procedures during terminal admission

Table continued

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Table 2 Continued

Authors and publication year	Routinely collected or readily available	Expert panel or skill required	Health system factors incorporated	Markers of 'non-beneficial' care: how measured and measurable
Rady *et al.*, 2004	✓		✓	Invasive non-palliative procedures received in ICU, proportion dying in hospital; DNR or termination of aggressive Rx in last 48 hours; frequency of radiology or lab tests; non-referral to hospice before death
Angus *et al.*, 2004	✓		✓	ICU admission for terminal care, length of stay in ICU for terminal care, cost of hospitalization with and without ICU admission
Wallace *et al.*, 2002	✓			CPR attempted
Ewer *et al.*, 2001	✓	✓		Mortality/survival to discharge after CPR in anticipated cardiac arrest
Varon *et al.*, 1998	✓			CPR outcome
Hamel *et al.*, 1997	✓		✓	Survival, hospital resource use, cost per quality-adjusted life years, functional status
Ahronheim *et al.*, 1996	✓			Invasive non-palliative treatment: CPR, feeding tube; non-invasive but complex diagnostic tests on patients with incurable illness; painful or uncomfortable interventions such as IV lines or blood drawing; systemic antibiotics in the last weeks of life; DNR orders

LST, life-sustaining treatment; DNR, do-not-resuscitate; MV, Mechanical ventilation.

Table 3 Estimates of objectively measured NBT by homogeneous indicator categories (21 studies)

Outcome	Indicator description	Estimate	Total patients
ICU admissions in final days, weeks or months	ICU admission and advanced life support despite orders for limitation of LST [20]	13.8%	276
	ICU admission for cancer patients with DNR orders [26]	2.0%	270
	ICU admissions for patients who had pre-existing DNR or LST limitations [21]	4.5%	277 693
	ICU admission in the last month of life [40]	3.5%	113
	ICU admission for patients refractory to chemotherapy or bedridden [24]	23.0%	95
	ICU admission for patients who had received palliative chemotherapy [24]	84.0%	95
	ICU admission in last 6 months of life for cancer patients on treatment [30]	21.0%	100
	ICU treatment $\geq$7 days after CPR in terminal cancer patients [31]	1.6%	41 046
	ICU admissions during terminal hospitalization [45]	39.8%	277 467
	ICU admission for oncology ward patients who died with late code status [38]	5.0%	336
Chemotherapy in final weeks or months	New chemotherapy in the last month of life [40]	11.5%	113
	Last chemotherapy within 14 days of death [40]	8.8%	113
	Ongoing chemotherapy to cancer patients with DNR [26]	13.0%	270
	Ongoing chemotherapy in last 3 months of life [22]	25.0%	71 269
	Chemotherapy in last 6 months of life for cancer patients [30]	76.0%	100
	Chemotherapy in last 6 weeks of life for cancer patients [30]	30.0%	100
	First chemotherapy cycle in last 3 months of life [22]	3.0%	71 269
	Discontinuation of chemotherapy delayed until last month of life [35]	33.3%	138
CPR attempt	CPR in ICU to patients with advanced refractory cancer [24]	15.0%	95
	CPR to patients with pre-existing limitations of treatment [21]	24.6%	277 693
	CPR to patients who died in ICU [21]	15.0%	277 693
	CPR to terminal cancer patients in last 6 months of life [30]	13.0%	100
	CPR to terminal cancer patients with belated code status [38]	11.0%	336
	Insertion of CVC line in ED in last month of life linked to in-hospital death [22]	OR 3.5	71 269
	MV in ICU to stage IIIB-IV cancer patients [24]	90.0%	95
Objective active management interventions	One or more forms if life support treatment for patients with DNR [21]	40.9%	277 693
	Hemodialysis to refractory cancer patients [24]	14.0%	95
	Vasoactive agents in ICU to refractory cancer patients [24]	77.0%	95
	Blood products to cancer patients with DNR [26]	10.0%	270
	Intensive procedures during terminal admission [45]	30.3%	277 467
	Ongoing radiotherapy to cancer patients with DNR [26]	7.0%	270
Futile medicines	Futile use of gastric protectors in terminal cancer at final admission [29]	51.0%	196
	Unnecessary medications at the EOL [37]	24.0%	87

Table continued

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Table 3 Continued

Outcome	Indicator description	Estimate	Total patients
	IV antibiotics to cancer patients with DNR [26]	22.0%	270
	Futile use of antihypertensive drugs in terminal cancer at final admission [29]	47.3%	196
	Futile use of statins in terminal cancer at final admission [29]	75.0%	196
	Futile use of hypoglycemic agents in terminal cancer at final admission [29]	10.7%	196
Died in ICU, or during hospital admission	Died in acute care hospital (elderly post intensive procedure) [45]	39.0%	1 457 370
	Died in hospital (with altered mental status and respiratory distress) [23]	11.0%	9246
	Died in hospital after CPR (cancer patients) [50]	90.4%	83
	Died in hospital (palliative care patients) [35]	54.0%	138
	Died in hospital (advanced cancer patient) [40]	16.8%	113
	Died in ICU out of those who died in hospital [23]	29.0%	9246
	Death in ICU among patients with SOFA score $\geq$15 [43]	60.0%	58
Mortality post -discharge	Mortality at 12 months post sequential organ failure in ICU [43]	88.0%	58
	Mortality at 12 months post CPR (cancer patients)[50]	96.4%	83
	Mortality at 6 months after initiation of dialysis [51]	73.0%	490
	Mortality 6 months after futile ICU admission [32]	85.0%	1136
Non-beneficial tests	Ongoing blood tests on patients with DNR orders [26]	49.0%	270
	Imaging on patients with DNR orders [26]	37.0%	270
	Emergency imaging in last 3 months of life [22]	25.0%	71 269
Other non-beneficial management	Utilization of rapid response systems [26]	5.0%	270
	Use of emergency consultations in last 3 months of life [35]	50.0%	138
	Hospital admission in the last month of life [40]	8.8%	113
	Use of hospice for LOS shorter than 3 days [40]	3.5%	113
	Median time from ICU admission to decision to forgo LST [34]	19 days	1265
	Median duration of antibiotics for patients spending their birthday in ICU [34]	9 days	1265
	Median duration of MV for patients spending their birthday in ICU [34]	6 days	1265
	Per capita cost of futile care in ICU [31]	USD$13 100	41 046
	Additional cost of ICU care per day above cost of ward care [27]	USD$2000	N/R
	Cost per QALY of dialysis at EOL for patients with worst prognosis [51]	USD $274 100	490

CVC, central venous catheter; ED, emergency department; DNR, do-not-resuscitate; LST, life-sustaining treatment; MV, mechanical ventilation; NBT, non-beneficial-treatment.

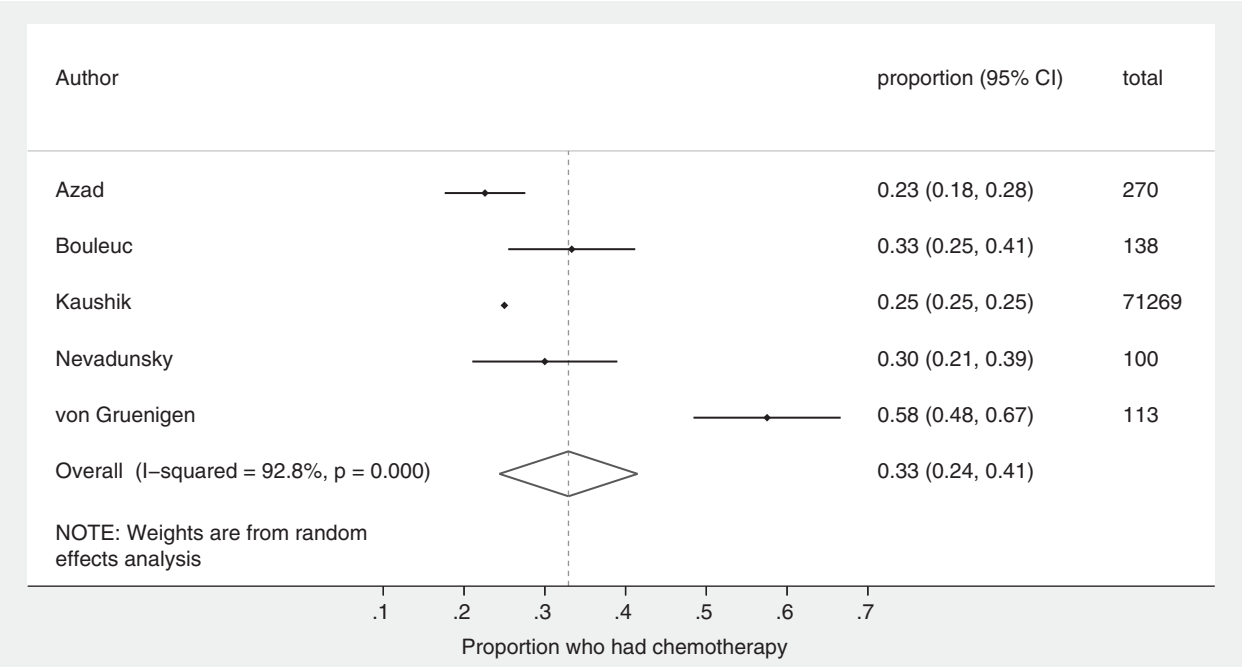


Figure 2 Pooled estimates of non-beneficial chemotherapy use at the EOL.

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health professionals and patients [61], healthcare professionals' suboptimal skills for recognition of illness severity, diagnosis of dying or need for limiting treatment [28, 46]; uncertainty about prognosis [44]; financial incentives to prolong services to insured patients in some health systems [62]; physicians' ethical ambivalence [63], cultural beliefs, spiritual principles, disagreement within the treating team, legal pressures [42, 44]; absence of proper documentation on limitations of care and lack of discussion with patients [28]; or lack of understanding of advance care planning [4, 7, 8, 34]. Further, excess intensity of care can lead to job dissatisfaction and be a surrogate indicator of high workload and inadequate communication within the treating team [36].

Other barriers leading to non-beneficial medical and surgical management at the EOL are multifactorial. Among the causes of NBT reported by the reviewed studies, family pressures (73%), communication issues before or after ICU (19%), medico-legal concerns (5%) and disagreement between specialist teams (2%) were mentioned [6]. Reported causes for non-beneficial ICU admission among oncology patients were clinical trial in intermediate situations (47%), initiation of full-scale first-line treatment in newly diagnosed advanced cases (30%) and lack of communication of limitation of treatment preferences in refractory bedridden patients (23%) [24]. In two studies, the authors argued that continuation of aggressive therapy despite not-for-resuscitation orders [26] and reversal of limitations of treatment [21] was justifiable as it contributed to patient survival until hospital discharge, suggesting that not-for-resuscitation order should signal withdrawal of CPR only.

Chemotherapy overuse close to the time of death and under-referral to hospice services have been suggested as potential indicators of poor quality of care [41]. Importantly, having a 'do-not-resuscitate order' (DNR) does not inevitably imply withdrawal of all management; only cessation of aggressive life-prolonging treatment, which in most cases, has little effect on immediate or medium term survival [26]. Specific examples of reasons for use of chemotherapy in the last 6 months of life include the doctors' inclination to offer clinical trials of aggressive support to newly diagnosed patients [30, 49]; lack of knowledge and competency with EOL care led to non-beneficial ICU admission regardless of prognosis [46]; doctors' uncertainty about disease course in cases of leukemia where multiple disease relapses can be followed by many remissions [49]; or clinical inertia of physicians not considering prognosis as they are trained to cure [20].

It is worth noting that some degree of these treatments is likely to be justified depending on whether the death is anticipated (known to be in the last 6 months or last year of life), or unexpected (patient in ICU in the last month or last 14 days of life). Hence, reducing prognostic uncertainty by early consideration and documentation of disease trajectory and estimated patient survival may guide the decision of whether and to what extent to administer NBT.

Addressing non-beneficial treatments

In this review, we aimed to suggest a practical list of indicators for measuring and identifying NBT. While quantification was deemed feasible for many aspects of terminal NBT, two issues may affect the usefulness of the indicators: first, outcome bias when two patients who have the same terminal risk profile receive treatment and one survives and the other dies. Some may argue that this changes what is non-beneficial. Second, making these decisions in the moment, as the direction of the decision may vary depending on factors such as clinician's beliefs that everything should be done [64], whether functional status has been previously assessed, or whether EOL discussions incorporating patient values have not been held [65].

While a standard definition of NBT is not yet agreed, common indicators have been identified and strategies advocated to minimize or prevent NBC have been proposed. They range from health professional education, promotion of early discussion of resuscitation status with patients and guidelines for admission to intensive care unit [42]. Some believe that advance care planning and communication training contribute to lower rates of perceived NBT [8]. Others recommend the use of validated comorbidity (Charlson Score) and geriatric scores (G8 score) [25] or standard assessment of performance status (ECOG 3 or 4) to support the clinical impression of lack of benefit of further anticancer treatment [11]. A decision-making model has also been suggested where a dedicated intensivist coordinates multiple opinions of subspecialists managing different patient organs before determination of ineffectiveness of ICU admission [46]. The feasibility of implementation of these models is yet to be determined.

The perpetuation of false hope, scarcity of healthcare resources, staff dissatisfaction with anticipated poor outcomes and imbalanced utilization of those resources [66] should be sufficient deterrents for excessive, non-beneficial responses to terminal illness. The long-held perception of death as treatment failure [44] still leads to prolongation of treatment and it is seen as 'the default option' for patients presenting to emergency departments [28]. These perceptions continue to drive the medicalization of death, prolongation of patient suffering [67] and prevent high-quality EOL care [68].

Strengths of this review

This review documented extensive quantitative definitions and indicators of NBT used in many countries over two decades. A comprehensive bias assessment tool with 13 items was used to measure quality. We acknowledge that variation in findings across studies may depend on the definition and the measurement used, and tried to aggregate the most homogeneous denominators in the meta-analysis. Meta-analyses were possible for two EOL-specific indicators (chemotherapy and ICU admission) despite some heterogeneity of timeframes. The indicators covered indicators reflecting patient, practice and system issues. Most study designs were of high quality and most reported indicators are collected routinely in hospitals and therefore their ongoing or episodic surveillance is feasible and should be encouraged to monitor trends, investigate locally relevant causes and respond to them accordingly.

Limitations of this review

Only four studies were qualitative, and eight reported perceived NBT. Expert opinion is considered lower-level evidence [69] and indicators are subject to value judgments despite agreed generic definitions. We focused on the interpretation of evidence from the quantitative perspective, where methods and measurements were appropriate to answer our research question.

Eight of the articles were conference abstracts with insufficient details for a complete critical appraisal, which may have biased the quality assessment toward the negative side in half of them [25, 27, 35, 54]. However, we included abstract articles in an effort to prevent publication bias towards favorable outcomes resulting from excluding evidence from research that would otherwise go unreported [70, 71]. In studies published as abstracts, the conclusions

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equated intense interventions with unnecessary care based on authors' perception or personal knowledge rather than evidence from measurable definitions in the studies [23, 25].

Our analysis found high heterogeneity but we believe it is the duty of systematic reviewers to report on all findings from all available eligible studies, however diverse or inconsistent. Clinical and methodological heterogeneity is inevitable in the real world [19] and it indicates that variability is due to differences in study design or target population, and the generalizability is not high. It is expected that as evidence accrues over time and new studies are less heterogeneous in design, the pooled estimate becomes more accurate. We dealt with the problem of heterogeneity by estimating I^2 which 'seeks to determine whether there are genuine differences underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity)' [18]. We used random effects models to allow for this heterogeneity in the pooled estimates. The wide confidence intervals reflect the heterogeneity so that the precision is not overstated and show the wide range of true values that the studies support.

Only English language articles were included although 10 studies were conducted among non-English speaking settings and subjects. Finally, it is possible that our search strategy missed some relevant studies as the automated search failed to find numerous eligible articles which were later found through the manual search of reference lists (see PRISMA diagram). We made an effort to check all references from all eligible articles and included newly identified in this review.

Conclusions

This review confirmed that the practice of NBT at the EOL has been recognized for at least two decades and it remains today despite much literature about its negative repercussions for patients, families, healthcare professionals and the health system.

The emerging conclusion is that given the uncertainty of prognosis on time to death, the social and ethical pressures, and the compassionate recommendation for trial ICU admissions while families come to terms with the inevitable, it appears that a certain level of NBT must always be present, but this does not mean that its prevalence should not be reduced. The debate must continue about the acceptable and affordable extent of NBT and the justifications for it.

Supplementary material

Supplementary material is available at *INTQHC* online.

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Authors' contributions

M.C.M. and K.H. conceived the project idea; M.C.M. and J.C.H.K. developed the protocol, conducted literature searches, abstract eligibility assessment and bias assessment; M.C.M. produced all versions of the manuscript incorporating changes suggested by all others; R.M.T. conducted the meta-analysis and contributed intellectual input into all versions of the manuscript; K.H., M.A. and I.A.M. contributed clinical input into interpretation of results, and contributed manual searches of articles. All authors provided input into all versions of the manuscript.

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