Intensive Care Med (2015) 41:1572–1585
DOI 10.1007/s00134-015-3810-5

SYSTEMATIC REVIEW

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Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review

Received: 9 January 2015
Accepted: 7 April 2015
Published online: 23 April 2015

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Take-home message: In this systematic review of end-of-life care in the ICU, we identified substantial variability in the prevalence and pattern of withdrawal and withholding of life-sustaining treatment in ICUs worldwide. This variability was present at multiple levels: between world regions, countries, ICUs within a country, and even individual intensivists in one ICU.

Electronic supplementary material The online version of this article (doi:10.1007/s00134-015-3810-5) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* Prior studies identified high variability in prevalence of withdrawal of life-sustaining treatment in the ICU. Variability in end-of-life decision-making has been reported at many levels: between countries, ICUs, and individual intensivists. We performed a systematic review examining regional, national, inter-hospital, and inter-physician variability in withdrawal of life-sustaining treatment in the ICU. *Methods:* Using a predefined search strategy, we queried three electronic databases for peer-reviewed articles addressing withdrawal of life-sustaining treatment in adult patients in the ICU. Data were analyzed for variability in prevalence of withdrawal of life-sustaining treatment. Withholding of life-sustaining treatment was also examined where information was provided. An assessment tool was developed to quantify the risk of bias in the included articles. *Results:* We identified 1284 studies, with 56 included after review. Most studies had unclear or high risk of bias, primarily due to unclear case definitions or potential confounding. The mean prevalence of withdrawal of life-sustaining treatment for patients who died varied from 0 to 84.1 % between studies, with standard deviation of 23.7 %. Sensitivity analysis of general ICU patients yielded similar results. Withholding also varied between 5.3 and 67.3 % (mean 27.3, SD 18.5 %). Substantial variability was found between world regions, countries, individual ICUs within a country, and individual intensivists within one ICU. *Conclusions:* We identified substantial variability in the withdrawal of life-sustaining treatment across world regions and countries. Similar variability existed between ICUs within countries and even between providers within the same ICU. Further study is necessary, and could lead to interventions to improve end-of-life care in the ICU.

Keywords Critical care · Intensive care · Withdrawal of life-support · Withholding of life-support · Medical decision-making

Introduction

In recent decades, advances in medical technology have afforded intensivists a remarkable ability to extend life, even in the setting of critical illness. This has led to extensive ICU utilization at the end of life, with an estimated one in five Americans admitted to the ICU prior to death [1]. In the face of incurable illness, however, aggressive ICU care can prolong suffering and may not be in the patient's best interest. Consequently, limitation of life-sustaining treatment has become a common practice in much of the world, including measures such as withholding or withdrawing life-sustaining treatment [2].

While the majority of patients in North American and European ICUs have some form of limitation of life-sustaining treatment prior to death, practices in end-of-life care are highly variable. Significant variability in prevalence of limitation of life-sustaining treatment has been reported at many levels: between regions, between individual ICUs, and even between individual intensivists. Several explanations for this variability have been posited. The results of one large European study suggested that physician, geographic, and religious factors were associated with significant regional differences in the prevalence of limitation of life-sustaining treatment [3]. Other studies cite the importance of cultural or statutory factors as well as religious ones [4–7]. Interestingly, even studies in culturally homogenous regions found a high prevalence of inter-ICU variability in end-of-life care [8–18], and a study examining decisions made by individual intensivists within the same ICU also found significant variability [19].

To better characterize the variability seen in end-of-life care in the ICU, we performed a systematic review of English-language observational and interventional studies examining the prevalence of withdrawal of life-sustaining treatment in adult ICU patients. We sought to compare the degree of variability seen at each level (inter-physician, inter-hospital, and between regions/nations) to see if similar variance exists. We chose to focus on withdrawal of life-sustaining treatment as the primary objective of our search strategy because definitions were more uniform across studies, although, when present, we analyzed the prevalence of withholding of life-sustaining treatment as a secondary endpoint. Preliminary results from our review were presented previously as an abstract [20].

Methods

We incorporated the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement for our study [21]. As some components of the PRISMA statement are intended for the review of interventional trials, additional published methodology pertaining to end-of-life research and the review of observational studies was also incorporated [22, 23]. Inclusion and exclusion criteria were prespecified, as were sources for review, planned analyses, and metrics for quality assessment.

Search strategy

We searched three databases (PubMed, Embase, Cochrane Library; from 1990 to 2013) using a predefined search strategy. Given that practice, documentation, and in some cases even legislation, regarding end-of-life care has changed significantly over the last few decades, 1990 was chosen as the start date for our search. Few studies prior to this date met our other search criteria (see publications by year in Supplemental Material). Our review was completed in 2014, with studies through the end of 2013 included. Controlled vocabulary was used in the form of Emtree terms for Embase and MeSH terms for Pubmed and Cochrane Library. We employed a Boolean search strategy combining synonyms for critical care with synonyms for life support, medical decision-making, withdrawal, withholding, or medical futility (Supplemental Material).

We restricted our search to English-language peer-reviewed journal articles involving adult patients. The bibliographies of included articles were searched independently by two investigators (S.R. and N.M.) to identify additional articles for inclusion. When appropriate, article authors were contacted for additional information.

Study selection

All abstracts underwent independent dual review (S.R. and N.M.) with third-party (N.L.) mediation when necessary. Selected articles underwent full-text review in similar fashion (Fig. 1).

We selected studies addressing withdrawal of life-sustaining treatment in adult patients in an ICU setting. Prospective and retrospective observational studies were considered. Controlled trials involving interventions that could affect a provider's likelihood to withdraw life-sustaining treatment (an example of this being a structured palliative care intervention designed to standardize end-of-life care) were also considered if a "usual care" arm were present, with only the usual care arm included, since our goal was to identify variation in usual care. Studies were included only if data quantifying the prevalence of withdrawal of life-sustaining treatment were provided; studies solely addressing provider attitudes or provider recall of past cases were not included.

Data collection and analysis

Each included article was reviewed independently by two authors (S.R. and N.M.). Analysis was then performed using GraphPad Prism® (La Jolla, CA, USA), with a significance threshold of $p < 0.05$ for all analyses.

For each study, the prevalence of withdrawal of life-sustaining treatment among all patients who died was tabulated and analyzed. In order to capture potential "terminal discharges" from the ICU, the prevalence of withdrawal of life-sustaining treatment was calculated out of all ICU patients who died within the ICU or after

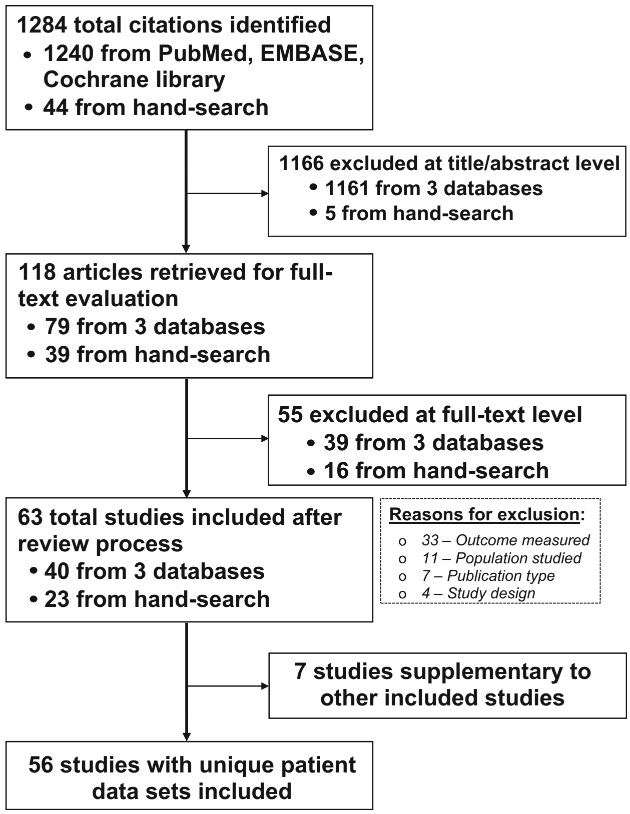

Fig. 1 Flowchart of study identification, review, and inclusion

discharge from the ICU following withdrawal of life-sustaining treatment within the ICU. Careful attention was paid to how each study categorized patients with brain death. When patients with brain death were included in the study being examined, prevalence of withdrawal of life-sustaining treatment was recalculated with these patients excluded when possible. For studies examining multiple ICUs or multiple time-points for the same ICU(s), patients were combined across ICUs and time-points and a single mean prevalence of withdrawal of life-sustaining treatment was calculated. Because many studies looked at specific patient populations or subspecialty ICUs, this analysis was repeated for the subset of general medical and surgical ICUs.

For those studies that gave the prevalence of withholding of life-sustaining treatment, we also examined the combined prevalence of withholding and withdrawal. Withholding of only cardiopulmonary resuscitation (DNR orders) was considered to be full treatment, rather than withholding of life-support, for the purposes of this review. This decision was made as this was the most common approach taken in included studies which provided withholding data. The prevalence of withdrawal of life-sustaining treatment was tabulated by region, for the general ICU population. Studies were classified by geographic region into Africa, Asia, Australia, Europe, Middle East, North America, or South America. A one-way analysis of variance was performed on prevalence of withdrawal of life-sustaining treatment across all regions with at least two studies, followed by analysis using Tukey's multiple-comparisons test (significance cutoff of $p < 0.05$). We next performed linear regression analysis on the prevalence of withdrawal of life-sustaining treatment versus the median year of data collection for each study. Regression analyses were repeated for withholding and combined withholding and withdrawal of life-sustaining treatment, for studies with sufficient data.

For studies providing sufficient data on prevalence of withdrawal of life-sustaining treatment for more than one region, ICU, or individual provider, we quantified the variability found within the individual studies themselves. The range, interquartile range, and sample standard deviation (SD) of prevalence of withdrawal of life-sustaining treatment between regions, ICUs, or providers were calculated. In three cases, studies did not provide all necessary data in numerical form, and some information was estimated from available graphs.

Risk of bias assessment

A risk of bias assessment tool was adapted from prior published methodology [24] and used to assess the risk of selection, attrition, ascertainment, and confounding biases (Supplemental Material). Articles underwent independent dual review (S.R. and N.M.) with each article rated at a "low," "high", or "unclear" risk of bias for prespecified sources of bias. Studies with a low risk of bias in all key domains were considered to have an overall low risk of bias, while those with a high risk of bias in any key domain were considered high risk of bias.

Results

The primary search strategy identified 1284 studies, with 40 included after abstract and full-text review [3–8, 11–13, 16, 17, 19, 25–52]. Searching of bibliographies yielded 23 additional publications [9, 10, 14, 15, 18, 53–70] resulting in a total of 63 studies. Of these 63 studies, 7 [28, 29, 34, 43, 44, 56, 68] were secondary descriptions of previously included studies, leaving 56 studies with unique patient cohorts for data abstraction and analysis (Fig. 1).

Study characteristics

These 56 studies included 31 prospective and 25 retrospective studies (Table 1). Two studies [17, 33] performed a retrospective analysis of a prospectively collected database, and were considered retrospective. Two studies were predominantly prospective with either a retrospective historical control, or a minority of retrospective data points, and were considered prospective [11, 15]. The majority of studies were observational ($n = 51$). Three studies, while technically observational, were explicitly designed to take place following a change in hospital policy or legislation regarding end-of-life care [36, 42, 50]. Four studies [12, 15, 42, 50] provided a prevalence of withdrawal of life-sustaining treatment at two different time-points for the same ICU(s). One study [15] provided data on two time-points, one of which was before the date specified for inclusion in our methods. We excluded that time-point from analyses of overall prevalence of limitation of life-sustaining treatment, but included it in analyses of temporal trends. Two studies [40, 58] involved interventions targeting end-of-life decision-making, and only the usual care arm was included in this review (Fig. 2).

Studies described practices in over 30 countries, with many studies examining ICUs in more than one country and a large number involving ICUs in Europe ($n = 22$) and/or North America ($n = 26$). When combined, these studies describe withdrawal of life-sustaining treatment in 986 ICUs throughout the world, though it is likely that the same ICUs were included in more than one study (making the number of unique ICUs <986). From these 986 ICU reports, 479 were classified as "medicosurgical", "med/surg", "general", or "mixed", 87 were classified as medical ICUs, 56 as surgical or trauma ICUs, 2 as burn ICUs, 7 as neurologic ICUs, and 28 as "other." ICU type was not specified in 327 instances (Fig. 2).

Risk of bias assessment

Most studies had unclear ($n = 8$) or high risk ($n = 39$) of bias, primarily from unclear case definitions or potential confounding bias (Supplemental Fig. 1). Variability in prevalence of withdrawal of life-sustaining treatment remained high, even when a sensitivity analysis was restricted to studies with low or unclear risk of bias (Supplemental Fig. 2).

Prevalence of limitation of life-sustaining treatment

Three studies did not provide a prevalence of withdrawal of life-sustaining treatment out of patient deaths, but rather provided a prevalence of withdrawal of life-sustaining treatment out of all ICU patients (regardless of survival status) without providing explicit mortality data [47, 58, 61]. Since our denominator was ICU deaths, we excluded these studies from analysis of prevalence of withdrawal of life-sustaining treatment.

Across the 53 studies included in this analysis, prevalence of withdrawal of life-sustaining treatment varied from 0 to 84.1 % with a mean of 42.3 % and a sample standard deviation (SD) of 23.7 % (Fig. 3a). The median rate of withdrawal was 44.1 % and the interquartile range was 27.4–61.5 %. Prevalence of withholding life-sustaining treatment, for studies that provided this information [3–7, 9, 11, 13–15, 19, 25, 35, 36, 38, 39, 50, 54, 55, 66], varied from 5.3 to 67.3 % with a mean of 27.3 % and SD 18.5 % (Fig. 3c). Among the studies with information on both withholding and withdrawal, prevalence of limitation of life-sustaining treatment (combined withholding and withdrawal of life-sustaining treatment) ranged from 10.1 to 82.8 % (Fig. 3c), with a mean of 51.5 % and SD of 22.7 %. ICUs with lower prevalence of withdrawal tended to have higher prevalence of withholding (Supplemental Fig. 2), although this did not reach statistical significance.

We performed a sensitivity analysis of "general ICU patients", by excluding studies that restricted their patient populations solely to: oncologic patients [27], mechanically ventilated patients [30, 33], trauma patients [31, 40, 46, 69], brain-injured or neurocritical care patients [16, 32, 63], burn patients [41, 57], patients without a surrogate decision maker [48, 49], patients who were in the ICU for <48 h [38], or patients who either received mechanical ventilation or were in the ICU for >24 h [64]. For the remaining 37 studies, variability in the prevalence of withdrawal of life-sustaining treatment remained high, from 0 to 83.7 % (Fig. 3b) with mean 38.6 % and SD 24.1 %. All the studies which provided both withholding and withdrawal data met the criteria of general ICU studies, with one exception [38].

Regional variability in withdrawal of life-sustaining treatment

General ICU studies were broken down into regions: Africa [13, 70], Asia [7, 9, 53, 54], Australia [26, 52], Europe [3, 8, 17, 18, 25, 35, 37, 39, 42, 45, 53, 55, 62, 65–67, 70], Middle East [3–6, 36], North America [10–12, 14, 15, 19, 50, 51, 53, 59, 60] and South America [53]. Variability in withdrawal of life-sustaining treatment was noted both within and between regions (Fig. 4a). Non-weighted averaging of the mean regional prevalence of withdrawal of life-sustaining treatment provided in each of these studies yielded an average prevalence of 50.8 % for Australia ($n = 2$, SD 5.94 %), 12.8 % for Asia ($n = 4$, SD 12.09 %), 43.3 % for Africa ($n = 2$, SD 48.71 %), 3.1 % for the Middle East ($n = 5$, SD 3.129 %), 8.0 % for South America ($n = 1$), 43.6 % for Europe ($n = 17$, SD 21.27 %), and 50.4 % for North America ($n = 11$, SD 14.2 %). Mean values were significantly different overall between the regions ($p < 0.001$), with significant differences in post hoc

Table 1 Study summary table

Citation (by first author)	Countries, sites	ICU n and type[a]	Patient (pt) characteristics	Design	Outcome measured	Brain death	ICU pt deaths n	WLST (%)	Comments
Aldawood [5]	Saudi Arabia	1, med/SURG	ICU pts with end of life decisions made	P, O	WLST/deaths "in study period"	E	176	2.84	
Azoulay [53]	Multiple, 7 world regions	282, varied	ICU pts with end of life decisions made	P, O	WLST/In-hospital deaths	NS	3050	17.0	
Bertolini [25]	Italy	84, varied	ICU deaths or terminal discharges	P, O	WLST/ICU deaths or terminal discharges	E	3168	17.1	
Brieva [26]	Australia	2, general	Pts who died in the ICU	R, O	WLST/ICU deaths	I	283	46.6	
Buckley [54]	China	1, general	ICU pts who died or had life support limited	P, O	WLST/ICU deaths or terminal discharges	E	490	28.0	
Cesta [27]	USA (Texas)	1, oncology	Adult cancer pts who died in the ICU	R, O	WLST/ICU deaths	NS	267	32.2	
Cook [30]	Sweden, USA, Canada, Australia	15, med/surg	Ventilated ICU pts with expected ICU stay >72 h	P, O	WLST/In-hospital deaths	NS	363	44.1	
Cooper [31]	USA (12 states)	Unclear, general	Trauma ICU pts aged 18-84	P, O	WLST/In-hospital deaths	NS	954	60.9	Unclear ICU *n*; appears to be 69
Cote [32]	Canada	6, trauma	Ventilated trauma pts with severe head injury	R, O	WLST/Deaths (unclear where)	NS	228	70.2	
Diringer [33]	USA (Missouri)	1, neuro	Ventilated, non-elective ICU pts	R, O	WD of ventilator/In-hospital deaths	I	562	49.6[b]	
Eidelman [4]	Israel	1, general	All ICU pts	P, O	WLST/In-hospital deaths	I	57	0	No clear case of WLST
Esteban [8]	Spain	6, med/surg	All ICU pts	P, O	WLST/ICU deaths or terminal discharges	I	582	25.4[b]	
Ferrand [55]	France	113, varied	All ICU admissions except CCU pts	P, O	WLST/ICU deaths	E	471	40.0	
Gajewska [35]	Belgium	1, med/surg	Pts who died in the ICU	P, O	WLST/ICU deaths	I	90	47.8[b]	
Garland [19]	USA (Ohio)	1, MICU	All ICU pts	P, O	WLST/In-hospital deaths	NS	46	27.4	Per author communication
Ismail [57]	UK	1, burn ICU	All ICU pts with burns who died	R, O	WLST/In-hospital deaths	NS	63	60.3	
Jakobsen [36]	Israel	1, general	All ICU pts	P, I	WLST/In-hospital deaths	I	69	0	See "before" group in [4]
Jensen [37]	Denmark	2, general	ICU pts who died or had life support limited	R, O	WLST/ICU deaths	NS	176	66.5	
Kapadia [9]	India	4, med/surg	Pts who died in the ICU	P, O	WLST/ICU deaths	NS	143	2.8	
Keenan [11]	Canada (Ontario)	9, general	Pts who died in the ICU	P, O	WLST/ICU deaths	NS	452	62.6	
Keenan [10]	Canada (Ontario)	3, med/surg	Pts who died in the ICU	R, O	WLST/ICU deaths	I	380	55.5[b]	
Knaus [58]	France	25, med/surg	ICU pts with at least 1 organ failure on admit	P, C	WLST/ALL pts (not deaths)	NS	Not given	7.7	WLST/Deaths unclear
Kollef [59]	USA (Montana)	1, MICU	Pts who died in the ICU	R, O	WLST/ICU deaths	NS	159	43.4	
Kollef [60]	USA (Montana)	1, MICU	Pts who died in the ICU	P, O	WLST/In-hospital deaths	NS	113	41.6	
Kranidiotis [38]	Greece, Cyprus	8, general	All pts in the ICU > 48 h who died	P, O	WLST/deaths (unclear where)	E	306	2.9	
Lee [61]	USA	1, MICU	All ICU pts	R, O	WLST/ALL pts (not deaths)	E	Not given	2.0	WLST/Deaths unclear
Manara [62]	United Kingdom	1, general	All ICU pts	R, O	WLST/In-hospital deaths	E	338	65.1	
Mani [7]	India	1, med/surg	All ICU pts	R, O	WLST/deaths (unclear where)	NS	88	3.4	

Table 1 continued

Citation (by first author)	Countries, sites	ICU n and type[a]	Patient (pt) characteristics	Design	Outcome measured	Brain death	ICU pt deaths n	WLST (%)	Comments
Mayer [63]	USA (New York)	1, neuro	Neuro ICU pts who died in ICU or shortly after	R, O	Terminal extubation/In-hospital deaths	E	74	43.2	Only pts with single attending included
McLean [12]	Canada	2, general	Pts who died in the ICU	R, O	WLST/ICU deaths	NS	439	58.3	
Meissner [39]	Germany	1, surgical	All SICU patients	P, O	WLST/In-hospital deaths	NS	1513	4.8	
Mercer [18]	UK	1, general	Pts who died in the ICU	R, O	WLST/ICU deaths	E	95	72.6	
Miguel [64]	Spain	1, general	All ICU pts	P, O	WLST/Deaths at up to 1 year	I	51	17.6[b]	
Mosenthal [40]	USA (New Jersey)	1, SICU/trauma	All trauma ICU pts	P, I	WLST/In-hospital deaths	NS	42	37	
Nolin [65]	Sweden	1, general	All ICU pts	R, O	WLST/In-hospital deaths	NS	755	39.6	
Ouanes [13]	Tunisia	2, MICU + SICU	Pts who died in the ICU	R, O	WLST/ICU deaths or terminal discharges	NS	326	8.9	
Pham [41]	USA (Washington)	1, burn ICU	Burn ICU Pts who died within 72 h of admit	R, O	WLST/ICU deaths	NS	128	84.1	
Prendergast [14]	USA (38 states)	131, varied	All ICU pts	P, O	WLST/ICU deaths	E	5910	36.2	
Prendergast [15]	USA (California)	2, general	All ICU pts	P, O	WLST/Deaths in ICU or shortly thereafter	I	175	65.7[b]	Excluded historical control (before 1990)
Quenot [42]	France	1, general	All pts who died in the ICU or after discharge	P, C	WLST/In-hospital deaths	NS	773	51.5	Average of two time-periods
Sjokvist [66]	Sweden	1, med/surg	ICU pts except post-op cardiac pts in ICU < 3 days	P, O	WLST/ICU deaths	E	78	30.8	
Spronk [67]	Netherlands	2, med/surg	All pts who died in the ICU or shortly thereafter	R, O	WLST/deaths in ICU or < 7 days after	NS	347	56.2	
Sprung [3]	Europe, 17 countries	37, varied	All ICU pts	P, O	WLST/In-hospital deaths	I	3728	39.5[b]	Per author communication
Trunkey [69]	USA (Oregon)	1, trauma	Trauma ICU pts over 65 years old	R, O	WLST/ICU deaths or terminal discharges	NS	70	67.1	
Turgeon [16]	Canada	6, unclear	Ventilated pts with traumatic brain injury	R, O	WLST/In-hospital deaths	NS	228	70.2	
Turner [70]	UK and South Africa	2, SICU + general	All ICU pts who died or had WLST	P, O	WLST/ICU deaths	I	106	63.2	
Verkade [45]	Netherlands	1, general	All ICU pts	R, O	WLST/ICU deaths	E	208	83.7	
Watch [46]	USA (New Mexico)	1, unclear	Trauma ICU pts over 55 years old who died (Massachussetts)	R, O	WLST/ICU deaths	NS	64	54.7	
White [47]	USA			1,	MICU				Mechanically ventilated MICU pts
R, O	WD ventilator/ ventilated pts	NS	Not Given	19.2	WD ventilator/ventilated pts, no WLST/deaths				
White [48]	USA ("west-coast")	1, MICU	MICU pts without capacity or surrogate	P, O	WLST/ICU deaths	NS	13	61.54	Only pts without surrogate
White [49]	USA (6 states)	7, med/surg	ICU pts without capacity or surrogate	P, O	WLST/ICU deaths	NS	25	60	Only pts without surrogate
Wilson [50]	USA (Minnesota)	1, MICU	Pts who died in the ICU	R, C	WLST/ICU deaths	NS	141	65.2	
Wood [51]	Canada (Ontario)	1, med/surg	Pts who died in the ICU	P, O	WLST/ICU deaths or terminal discharges	E	110	64.5	
Wunsch [17]	UK	127, general	Not specifically stated	R, O	WLST/In-hospital deaths	I	36397	31.8	

Table 1 continued

Citation (by first author)	Countries, sites	ICU *n* and type[a]	Patient (pt) characteristics	Design	Outcome measured	Brain death	ICU pt deaths *n*	WLST (%)	Comments
Yazigi [6]	Lebanon	1, MICU	ICU pts with end of life decisions made	P, O	WLST/In-hospital deaths	E	94	6.4	
Zib [52]	Australia	1, unclear	All ICU pts who had WLST	P, O	WLST/ICU deaths	NS	~85	55.0	WLST only as a percentage of pt deaths

Seven studies performed separate analyses of one of the above studies rather than providing unique data. These studies were considered supplemental and are not shown in the table [28, 29, 34, 43, 44, 56, 68]

WLST withdrawal of life-sustaining treatment, *R* retrospective, *P* prospective, *O* observational, *I* control arm of an interventional trial, *C* observational before and after a change in policy/legislation, *E* brain death excluded from analysis, *I* brain death patients included in analysis, *NS* not specified

[a] *Varied* refers to the presence of multiple ICUs of different types within one study. *Med/surg* refers to medicosurgical ICUs, and *general* to mixed ICUs, or non-specialty ICUs where the specific type is not given in the paper

[b] For publications which did not exclude patients with BD from WLST, we recalculated WLST prevalence excluding BD patients where possible

comparisons between the Middle East and North America, Middle East and Europe, Middle East and Australia, as well as between Asia and North America. Comparisons between all other regions were not significant. Testing with Kruskal–Wallis one-way analysis of variance also showed a significant overall difference between regions ($p = 0.0025$). Regional variability in withholding and overall limitation of life-sustaining treatment for the 19 general ICU studies that provided this data was also analyzed (Supplemental Fig. 4).

One study [53] that combined prevalence of withdrawal of life-sustaining treatment from Australia and Asia as "Australasia" was classified under Asia for this review, as the majority of patients in this cohort were from Asia ([70]; Supplementary materials). Excluding this study did not significantly alter any analyses (data not shown). Israel was classified as "Middle East" for the purposes of this review. For one study [34] that classified Israel within a large cohort of European ICUs, we recalculated the prevalence of withdrawal of life-sustaining treatment for both regions, based on data provided by the authors (personal communication). In another study, Israel was classified as Southern Europe/Mediterranean [53]; however, it contained only a small fraction of the patients within this cohort.

No statistically significant temporal trends in prevalence of withdrawal of life-sustaining treatment were detected, even when looking within geographic regions (Fig. 4b). Examining withholding, withdrawal, and limitation of life-sustaining treatment for the 19 studies that provided the requisite data showed similar results (Supplemental Fig. 5).

Variability in limitation of life-sustaining treatment within studies

Four studies provided prevalence of limitation of life-sustaining treatment for more than one region/country [3, 14, 53, 70], 12 studies provided prevalence of limitation of life-sustaining treatment for more than one ICU within a country [3, 8–17, 25], and 1 study examined limitation of life-sustaining treatment by individual providers within a single ICU [19]. All these studies except for one [16] fit the profile of general ICU patients as defined above. The prevalence of withdrawal of life-sustaining treatment exhibited comparably high variability across regions and countries, as well as for ICUs within a country and physicians within an ICU (Fig. 5). Withholding also varied significantly between ICUs for the studies that included both withholding and withdrawal data (data not shown). For the study examining inter-physician variability [19], withholding varied from 22.2 to 75 % with mean 55.4 % and SD 16.9 % (data via personal communication).

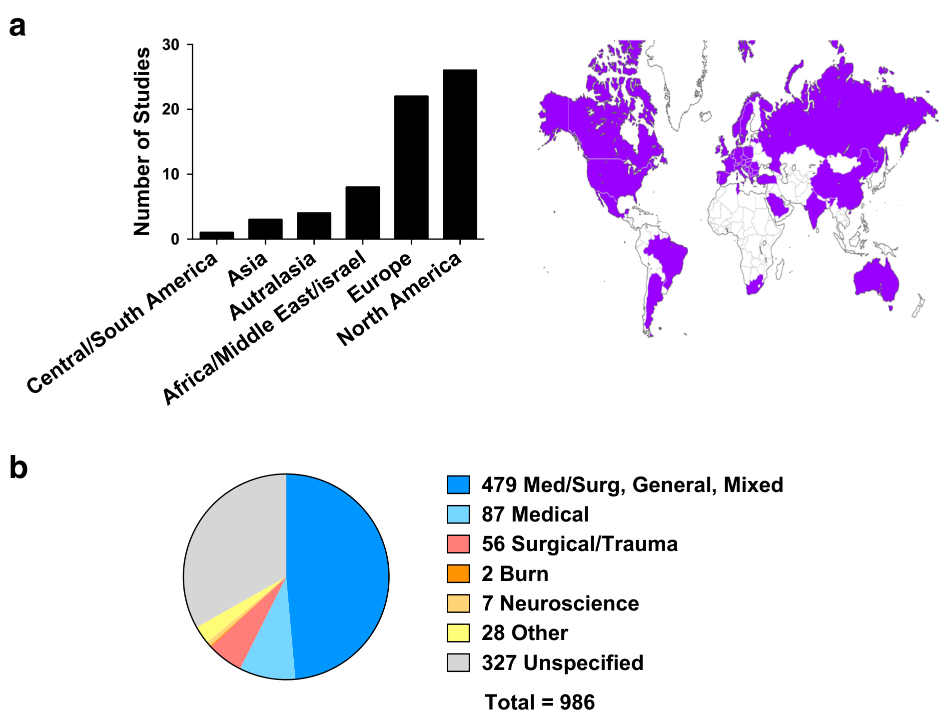

Fig. 2 Study demographics. **a** Countries represented in included studies; shown in *purple* on accompanying map. **b** ICU types represented in included studies

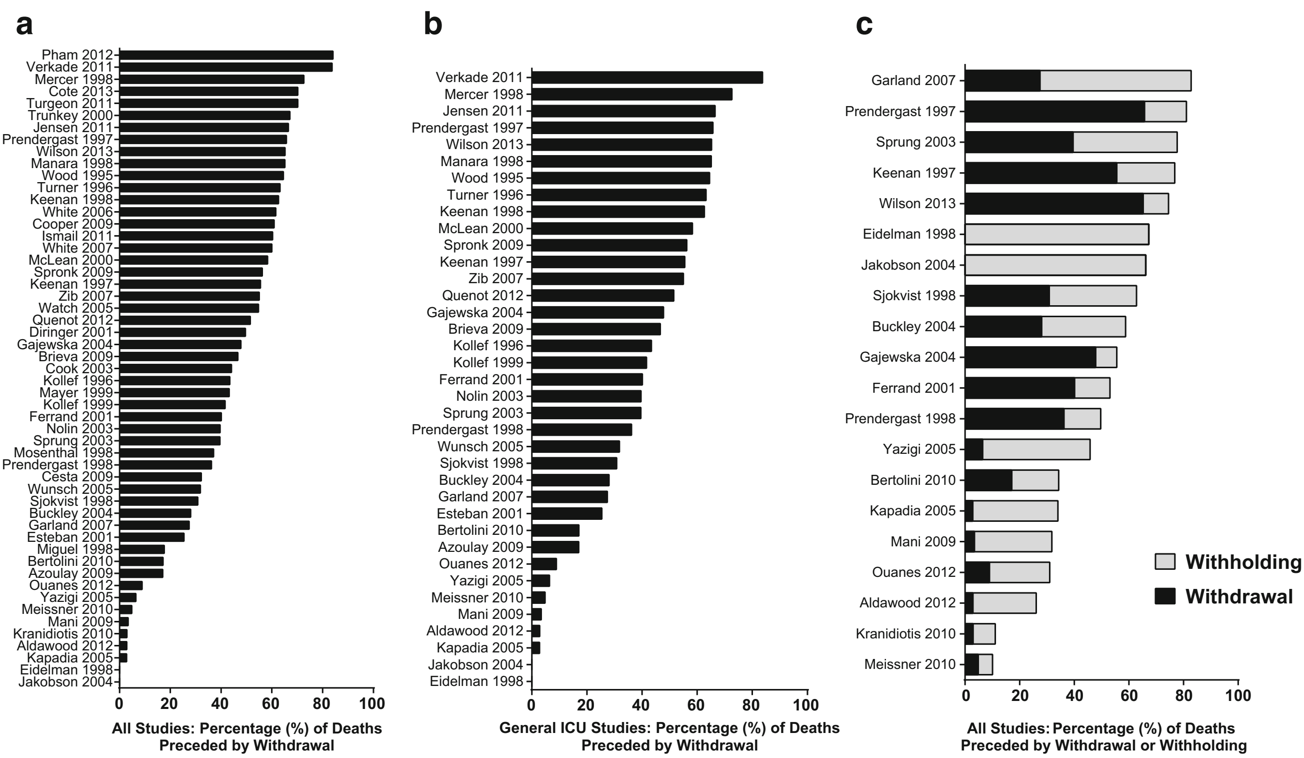

Fig. 3 Mean prevalence of limitation of life-sustaining treatment by study. **a** Mean prevalence of withdrawal of life-sustaining treatment for all studies with sufficient data. **b** Mean prevalence of withdrawal of life-sustaining treatment for studies for a "general ICU" population, excluding specific ICU populations as described in methods. **c** Mean prevalence of withdrawal and withholding for all studies with sufficient information. Note that among these studies, only Kranidiotis 2010 [38] was not considered to examine a "general ICU" population

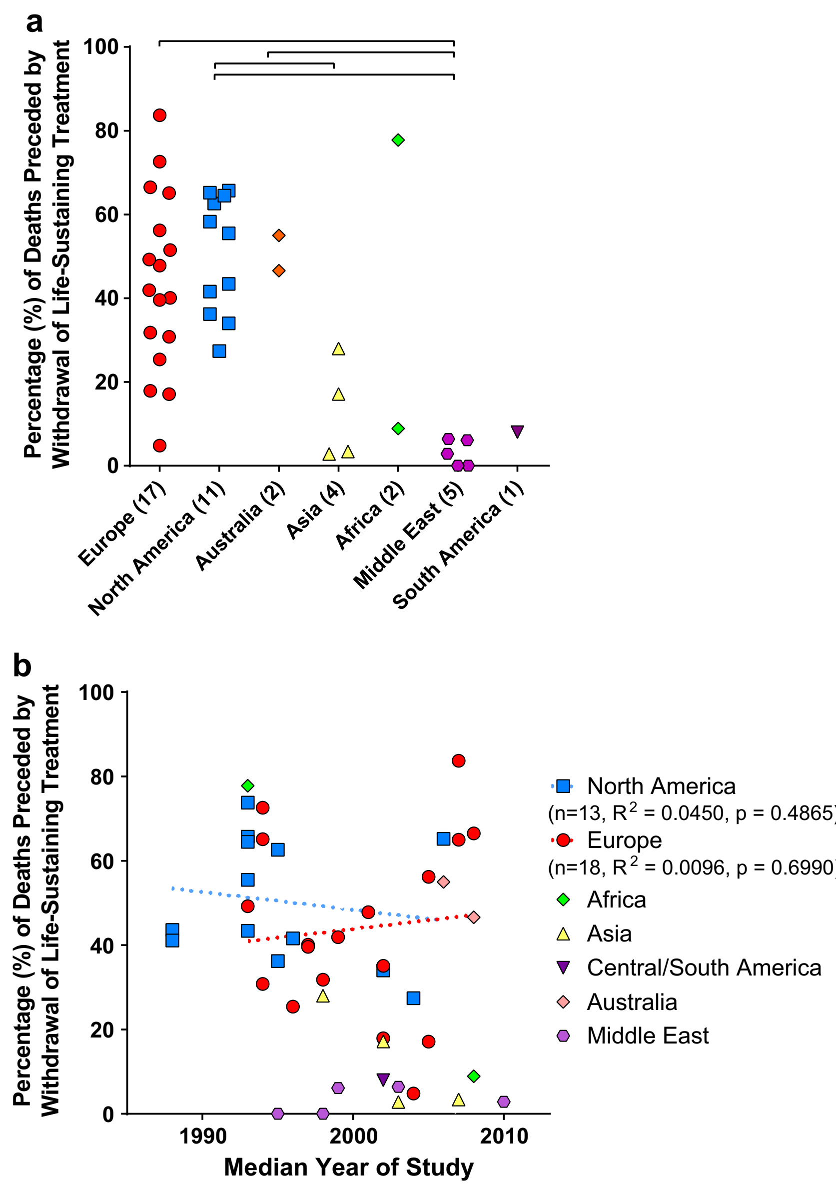

Fig. 4 **a** Regional variability in mean prevalence of withdrawal of life-sustaining treatment, by study. Studies examining more than one region are represented by a data point in each region examined. *Parentheses* indicate a statistically significant difference between regions, as described in "Results". **b** Temporal trends in mean prevalence of withdrawal of life-sustaining treatment, by region. *X-axis* denotes the mean year of patient recruitment or, in the case of retrospective studies, of data reviewed. Regression analysis is shown for North America and Europe. Regression was not run on other regions due to low sample size and the fact that the countries represented over time were not consistent. For three studies examining two time periods for the same ICU population, we included each of the two periods as a distinct data points

Discussion

In this systematic review, we identified publications describing end-of-life practices in almost 1000 ICUs on six continents spanning three decades. We found substantial variability in the prevalence of withdrawal of life-sustaining treatment worldwide and on many levels. The overall percentage of deaths preceded by withdrawal of life-sustaining treatment varied between 0 and 84 % across individual studies, and this variability persisted even when we excluded studies examining specific ICU patient populations. Variability in the prevalence of withholding was similarly substantial. In addition to overall variability, we also identified regional variability in the prevalence of withdrawal and withholding of life-sustaining treatment. We found a similar degree of variation in the prevalence of withdrawal of life-sustaining treatment between world regions, between countries, between individual ICUs within culturally homogenous regions or countries, and, in one study, between individual intensivists in one ICU. While the existence of variability in prevalence of withdrawal of life-sustaining treatment at each of these levels has been reported previously, this is the first systematic exploration of worldwide variability in withdrawal of life-sustaining treatment and the first to compare the degree of variability found at each level of analysis.

While we analyzed withholding where possible, we focused on withdrawal of life-sustaining treatment as the primary objective of our search strategy. Withholding and

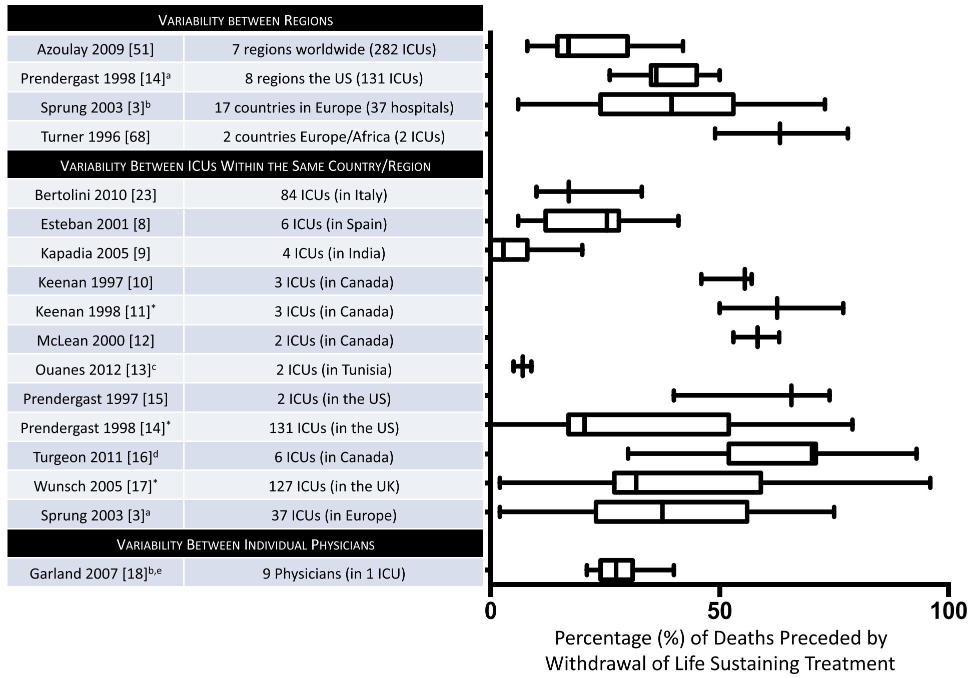

Fig. 5 Whisker plots showing high variability in prevalence of withdrawal of life-sustaining treatment within published studies. Minimum, maximum, interquartile range, and mean are displayed. *a* Compared median (rather than mean) prevalence between regions. *b* Information per personal correspondence with authors. *c* Excludes 10 patients who were discharged "in extremis" to die at home. *d* Prevalence of withdrawal out of deaths within first 3 days of care in patients with traumatic brain injury. *e* One physician had only 4 reported deaths, and was excluded from analysis. *Data abstracted from graphs

withdrawal of life-sustaining treatment are often considered to be ethically equivalent [71], but we believe documentation regarding these actions varies significantly. Withdrawal is an active process that often requires a written order and justification, and the initiation of withdrawal is therefore likely to be documented. Withholding, however, is the absence of an action, in many cases may not require an order, and therefore may be less consistently documented. Providers may not even consider certain aggressive treatments (e.g., surgery, dialysis, extracorporeal membrane oxygenation) when caring for the terminally ill patient, and are therefore unlikely to document these interventions as withheld. Few studies examine this topic, but in one study, while the decision to withdraw life-sustaining treatment was consistently documented, factors relating to withholding of life-sustaining treatment (e.g., advance directives, resuscitation orders) were not [72]. As we included retrospective studies involving chart review, we were concerned that differing documentation practices across institutions could lead to variation in the reported prevalence of withholding that did not reflect true differences in practice.

Several studies included in this review identify specific cultural, geographic, religious, statutory, or physician factors, which may help explain the variability seen in withdrawal of life-sustaining treatment. Prior large studies [3, 53] have identified significant regional variability in withdrawal of life-sustaining treatment, and our review supports this finding. We identified an especially low prevalence of withdrawal of life-sustaining treatment in regions of the Middle East and Asia where the "Western" conception of equivalence between withdrawal and withholding of life-support may not be uniformly accepted [4–7, 9, 36, 54]. In Israel, for example, the prevalence of withdrawal of life-sustaining treatment approaches 0 % in many ICUs [4, 36], and we found that such regions often have higher prevalence of withholding of life-sustaining treatment. Studies have also shown that certain patient and ICU factors are associated with a higher prevalence of withdrawal of life-sustaining treatment, including: presence of a surrogate decision-maker [48, 49], advanced patient age [31], non-surgical specialty of attending physician [33], increased severity of acute or chronic illness [55], and higher ICU census [19]. Prior studies have also identified an increasing prevalence of withdrawal of life-sustaining treatment over recent years [12, 15]. While we did not observe a significant increase in the prevalence of withdrawal of life-sustaining treatment over the years examined in this review, the low sample size in each region and the high variability may have obscured this trend.

It is likely that many factors influence variability in the prevalence of withdrawal of life-sustaining treatment; we identified a degree and pattern of variability that is unlikely to be consistently explained by only regional or religious factors. For example, one study from the United Kingdom found that the prevalence of withdrawal of life-sustaining treatment ranged from 0 to 96 % in 127 ICUs with a nearly uniform distribution across those two extremes [17]. This distribution of prevalence of withdrawal of life-sustaining treatment is similar to that seen in a US study of 131 ICUs [14], a study of 37 ICUs in Europe [3], and the worldwide prevalence of withdrawal of life-sustaining treatment across published studies included in this review. Furthermore, a recent study by Quill and colleagues examining withdrawal of life-sustaining treatment in 153 ICUs in the United States found dramatic variability, even after accounting for individual patient and ICU characteristics [73].

Future research is needed to explore the variability in end-of-life care that our review uncovered. We identified important variability in definitions of withdrawal of life-sustaining treatment, whether DNR orders were considered withholding of life-sustaining treatment, and how and where death was measured. This variability made direct comparison of studies difficult, and achieving consensus on how to report data on end-of-life care will be important for future research. We believe future studies should document the proportion of deaths preceded by a DNR order as a separate category within withholding life support, in order to provide as much information as possible. Our search identified one study that compare the prevalence of limitation of life-sustaining treatment by individual intensivists within a single ICU [19]. The inter-physician variability shown in this study, consistent with the results of a large provider survey [74], is one area for further exploration. There is currently a lack of clear guidelines or consistent training on how best to approach end-of-life care, which is another potential source for variability in care. Each decision made about end-of-life care is unique, and likely to remain subject to factors such as patient demographics, values, and goals of care; and physician background and attitudes. Recent work [75] has shown, however, that worldwide consensus regarding principles of end-of-life care can be reached by providers from different backgrounds and regions. It will be interesting to examine whether development and implementation of guidelines for end-of-life decision-making based upon commonly-accepted principles reduces variability in end-of-life care and improves overall quality of care. Such guidelines may provide a framework for discussion with patients and families, and may reduce variability while simultaneously respecting the individual nature of each end-of-life treatment decision. Guiding and supporting a patient and their family through the process of deciding whether or when to limit or stop life-sustaining measures is one of the more difficult and important tasks facing the critical care practitioner, and optimizing approaches to the limitation of life-sustaining treatment could greatly improve ICU care worldwide.

Limitations

Our study has several limitations. First, we exclusively looked at English-language peer-reviewed publications providing primary data on withdrawal of life-sustaining treatment, and may not have identified all relevant publications. Second, our search strategy was not designed to capture studies that only reported on withholding of life-sustaining treatment, and it is possible that including these studies would affect our results. Third, many included studies had a high or unclear risk of bias, and studies also varied significantly regarding patient populations, ICU types, and study definitions. Fourth, given the pervasive heterogeneity in multiple areas of our data, we did not conduct a pooled analysis and the statistical tests we did perform should be viewed with caution. Even without performing a meta-analysis, however, decisions about how to best categorize and analyze such disparate data necessarily introduce some degree of subjectivity into our analysis. Finally, regions outside North America and Europe were underrepresented, making it difficult to draw definite conclusions about end-of-life practices in many areas of the world.

Conclusions

Our study is the first systematic review to address worldwide variability in the prevalence of withdrawal of life-sustaining treatment in adult ICU patients. In this review, we identified substantial variability in the limitation of life-sustaining treatment between regions, between ICUs within a region, and between physicians within a single ICU. This variability is persistent across many levels of analysis and is unlikely to be completely explained by one predominant geographic, institutional, patient, or physician factor. Efforts to develop a consensus or framework for end-of-life decision-making, while ensuring that individual patient values and goals are respected, offer one potential opportunity to reduce this variability. Future studies are needed to further characterize the variability we observed, to generate consensus guidelines, and to develop interventions to improve end-of-life care in the ICU.

Acknowledgments The authors would like to thank Drs. Charles Sprung, Mario Baras, and Alan Garland for graciously providing additional data and analyses from their studies. We would also like to thank Sherry Dodson and the University of Washington Health Sciences Library staff for their assistance with our literature search.

Conflicts of interest The authors report no conflicts of interest related to this study.

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