

# Changes in End-of-Life Practices in European Intensive Care Units From 1999 to 2016

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**IMPORTANCE** End-of-life decisions occur daily in intensive care units (ICUs) around the world, and these practices could change over time.

**OBJECTIVE** To determine the changes in end-of-life practices in European ICUs after 16 years.

**DESIGN, SETTING, AND PARTICIPANTS** Ethicus-2 was a prospective observational study of 22 European ICUs previously included in the Ethicus-1 study (1999-2000). During a self-selected continuous 6-month period at each ICU, consecutive patients who died or had any limitation of life-sustaining therapy from September 2015 until October 2016 were included. Patients were followed up until death or until 2 months after the first treatment limitation decision.

**EXPOSURES** Comparison between the 1999-2000 cohort vs 2015-2016 cohort.

**MAIN OUTCOMES AND MEASURES** End-of-life outcomes were classified into 5 mutually exclusive categories (withholding of life-prolonging therapy, withdrawing of life-prolonging therapy, active shortening of the dying process, failed cardiopulmonary resuscitation [CPR], brain death). The primary outcome was whether patients received any treatment limitations (withholding or withdrawing of life-prolonging therapy or shortening of the dying process). Outcomes were determined by senior intensivists.

**RESULTS** Of 13 625 patients admitted to participating ICUs during the 2015-2016 study period, 1785 (13.1%) died or had limitations of life-prolonging therapies and were included in the study. Compared with patients included in the 1999-2000 cohort (n = 2807), patients in the 2015-2016 cohort were significantly older (median age, 70 years [IQR, 59-79] vs 67 years [IQR, 54-75];  $P < .001$ ) and the proportion of female patients was similar (39.6% vs 38.7%;  $P = .58$ ). Significantly more treatment limitations occurred in the 2015-2016 cohort compared with the 1999-2000 cohort (1601 [89.7%] vs 1918 [68.3%]; difference, 21.4% [95% CI, 19.2%-23.6%];  $P < .001$ ).

Limitation	2015-2016, No. (%)	1999-2000, No. (%)	Difference, % (95% CI)	P Value
Withholding of life-prolonging therapy	892 (50)	1143 (40.7)	9.3 (6.4 to 12.3)	<.001
Withdrawing of life-prolonging therapy	692 (38.8)	695 (24.8)	14.0 (11.2 to 16.8)	<.001
Failed CPR	110 (6.2)	628 (22.4)	-16.2 (-18.1 to -14.3)	<.001
Brain death	74 (4.1)	261 (9.3)	-5.2 (-6.6 to -3.8)	<.001
Active shortening of the dying process	17 (1.0)	80 (2.9)	-1.9 (-2.7 to -1.1)	<.001

**CONCLUSIONS AND RELEVANCE** Among patients who had treatment limitations or died in 22 European ICUs in 2015-2016, compared with data reported from the same ICUs in 1999-2000, limitations in life-prolonging therapies occurred significantly more frequently and death without limitations in life-prolonging therapies occurred significantly less frequently. These findings suggest a shift in end-of-life practices in European ICUs, but the study is limited in that it excluded patients who survived ICU hospitalization without treatment limitations.

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**D**eath in intensive care units (ICUs) frequently occurs after a decision to limit life-sustaining interventions. Despite international consensus for many ethical principles underlying ICU end-of-life care,<sup>1</sup> there are considerable variations in actual practice within and between countries and regions.<sup>2</sup> For example, in the Ethicus-1 study conducted from January 1999 until July 2000 in 37 European ICUs, the frequency of withholding life-prolonging therapies ranged from 16% to 70%, withdrawing life-prolonging therapies from 5% to 69%, active shortening of the dying process from 0% to 19%, and failed cardiopulmonary resuscitation (CPR) from 5% to 48%.<sup>3</sup>

Over the past decade, there have been changes in European attitudes,<sup>1,4</sup> laws,<sup>5</sup> recommendations<sup>6,7</sup> and guidelines<sup>8,9</sup> regarding end-of-life practices. Although paternalism persists among some European caregivers,<sup>4</sup> more shared decision making has been advocated.<sup>10</sup> Recently, European public support for euthanasia and physician-assisted suicide has increased, resulting in more deaths from these practices.<sup>11</sup> The actual extent of end-of-life practice changes across European ICUs remains unknown. The present Ethicus-2 study was designed to assess whether there has been a change in end-of-life practices in European ICUs from 1999-2000 to 2015-2016.

## Methods

### Centers

All 37 centers that initially participated in the Ethicus-1 study (1999-2000 cohort)<sup>3</sup> were invited to participate in the Ethicus-2 study (2015-2016 cohort). Several ICUs no longer existed, and some others declined participation, resulting in the inclusion of 22 of the original 37 ICUs in the present study. The contributing regions and countries included Northern Europe (Denmark, Ireland, The Netherlands, and the United Kingdom), Central Europe (Belgium, Czech Republic, Germany, and Switzerland), and Southern Europe (Greece, Israel, Italy, Portugal, Spain, and Turkey). These ICUs represent 14 of the original 17 countries. Data from ICUs that participated in the 1999-2000 study but not the 2015-2016 study (ICUs in Austria, Finland, and Sweden) were not included in this comparison study. Institutional ethics committee approval, with a waiver of informed consent, was obtained from each participating center. Countries and centers were coded anonymously and study patients were numbered consecutively to ensure confidentiality and to enable clinicians to report practices without risk of legal liability.

### Patients

This study used the same study population definitions, ethical and legal considerations, and data collection methods as were used in the 1999-2000-cohort.<sup>3</sup> Consecutive adult patients admitted to participating ICUs who died or had any limitation of life-saving interventions over a 6-month period were selected by each ICU between September 1, 2015, and September 30, 2016, and were prospectively included in the study. Patients were followed up until discharge from

## Key Points

**Question** Have end-of-life practices in European intensive care units (ICUs) changed from 1999-2000 to 2015-2016?

**Findings** In this prospective observational study of 1785 patients who had limitations in life-prolonging therapies or died in 22 European ICUs in 2015-2016, compared with data previously reported from the same ICUs in 1999-2000 (2807 patients), treatment limitations (withholding or withdrawing life-sustaining treatment or active shortening of the dying process) occurred significantly more frequently (89.7% vs 68.3%), whereas death without any limitations in life-prolonging therapies occurred significantly less frequently (10.3% vs 31.7%).

**Meaning** These findings suggest that end-of-life care practices in European ICUs changed from 1999-2000 to 2015-2016 with more limitations in life-prolonging therapies and fewer deaths without treatment limitations.

the ICU, death, or 2 months from the first decision to limit life-prolonging therapies.

### Outcomes

End-of-life outcomes were classified into 5 mutually exclusive categories: withholding of life-prolonging therapy, withdrawing of life-prolonging therapy, active shortening of the dying process, failed CPR, and brain death. The primary outcome was whether patients received any limitations in life-prolonging therapy (withholding or withdrawing of life-prolonging therapy, or shortening of the dying process).

### Study Definitions for End-of-Life Categories

- Withholding treatment—a decision was made not to start or increase a life-sustaining intervention, such as not to perform CPR if a patient had a cardiac arrest.
- Withdrawing treatment—a decision was made to actively stop a life-sustaining intervention presently being given, such as stopping a norepinephrine infusion being given for shock.
- Active shortening of the dying process—a circumstance in which someone performed an act with the specific intent of shortening the dying process; these acts did not include withholding or withdrawing although withholding or withdrawing could occur prior to active shortening of the dying process.
- Failed CPR—death despite ventilation and cardiac massage.
- Brain death—documented cessation of cerebral function and meeting criteria for brain death.

A hierarchical categorization was used for the most active limitation if more than one occurred (active shortening of the dying process > withdrawing > withholding). Secondary outcomes included hospital survival or death; specific limitations of therapies including failed CPR, intubation, ventilation, vasopressors, and renal replacement therapy; ICU length of stay; time until initiating the first life-sustaining limitation; time after initiating the first life-sustaining limitation until death; time until withholding or withdrawing life-sustaining therapies or active shortening of the dying

process; patient and institutional characteristics and probabilities of death. Post hoc outcomes included ICU characteristics and ethical practices (see following section for further explanation).

### Study Procedures and Data Collection

No interventions or treatments were given, withheld, or withdrawn from patients for study purposes. At each institution, the senior intensivist responsible for end-of-life decisions determined which end-of-life practice occurred and was responsible for completing the study data form including outcomes.

Similar data forms to those used for the 1999-2000 cohort were used, and data were entered using a dedicated and secured website. Patient data collected included sex, age, religious affiliation, ICU admission diagnosis, chronic disorders, end-of-life category, specific therapy limitations, dates and times of hospital and ICU admission, death or discharge, decisions to limit interventions, and hospital survival or mortality.

Additional procedures to improve validity and consistency included adherence to the study protocol (Supplement 1), following specific instructions for study performance and data form completion, providing concurrent audit and feedback, having immediate answers to frequently asked questions, and having a quality assurance program that evaluated 5% of all patients (crosschecking accuracy of data entry was 8841/9249 [96%]).

To evaluate changes in the ICUs from 1999-2000 to 2015-2016, investigators from the participating centers provided data on ICU variables for both time periods including ICU type, ICU and hospital number of beds, ICU mean admissions per month, and ICU physician and nursing staffing. Yearly ICU mortality was calculated from each ICU's total admission number and mortality.

In an attempt to understand study results in relation to possible changes in ethical practice between 1999-2000 and 2015-2016, investigators were surveyed in 2019 to retrospectively provide data regarding 12 variables that represent various aspects of ethical practice. Variable selection was based on a recent worldwide consensus<sup>1</sup> and on current, evidence-based guidelines and policy statements.<sup>8-10,12</sup> Variable data were collected in a binary (yes/no) form and were based on the following items: (1) routine family meetings<sup>1,10,12</sup>; (2) daily deliberation for the appropriate level of care<sup>1</sup>; (3) end-of-life discussions during meetings<sup>1</sup>; (4) written triggers for limitations<sup>9</sup>; (5) written end-of-life guidelines<sup>5</sup>; (6) written protocols<sup>9</sup>; (7) palliative care consultations<sup>10</sup>; (8) ethics consultations<sup>10</sup>; (9) staff taking communications courses<sup>1,10,12</sup>; (10) staff taking bioethics courses<sup>1,8,10,12</sup>; (11) each country's end-of-life guidelines<sup>1</sup>; and (12) each country's legislation.<sup>1</sup> For each of the 12 ethical practice-related variables for the 2 study periods, a positive answer was graded as 1 and a negative answer as 0. The sum was operationalized as an ICU-specific ethical practice score with a range of 0 to 12 points. This score was derived for the purposes of this study.

### Statistical Analyses

The number of ICU admissions per month (turnover) categorized institutions as small ( $\leq 30$ ), intermediate (31-60), or large

( $\geq 61$ ). Institutions were also dichotomized into academic vs nonacademic centers. For each patient, the main outcome variable was the end-of-life category. Continuous variables showing a symmetric and close to normal distribution are expressed as mean (SD) and compared using the *t* test. Percentages were compared using the  $\chi^2$  or Fisher exact test. Numeric asymmetric variables are presented as median interquartile range (IQR) and compared with the nonparametric Mann-Whitney test (independent samples) or the Wilcoxon signed rank test (paired samples). For paired samples, the primary sampling unit was centers participating in 1999-2000 and in 2015-2016. Probabilities of death within 24, 48, and 72 hours of decisions for withholding and withdrawing life-sustaining treatments and active shortening of the dying process were performed for both study periods.

Pairwise exclusion was the method used for missing data. A case that had a missing value for any variable was omitted from the analysis for each table or analysis separately. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. An additional, exploratory, post hoc, multivariable, logistic regression analysis is detailed in Supplement 2. Statistical analyses were performed using IBM SPSS version 24. A test was considered significant if the *P* value was less than .05. *P* values were 2-sided.

## Results

At the 22 centers participating in this study, 13 625 patients (range, 82-1440 patients per center) were admitted over 5.9 months (range, 1-6 months) in 2015-2016. Of these patients, 1785 (13.1%) died or had limitations of life-sustaining treatments and constituted the 2015-2016 study population. In 1999-2000, these 22 centers admitted 22 081 patients (range, 143-3118 patients per center) over 13.7 months (range, 1-18 months), and 2807 (12.7%) died or had limitations of life-sustaining treatments. Patient characteristics in the 2015-2016 and 1999-2000 cohorts are presented in Table 1. The proportion of patients enrolled in the cohort because limitations were placed on life-sustaining therapy (withholding or withdrawing life-sustaining treatment or active shortening of the dying process) was significantly higher in 2015-2016 (1601 [89.7%]) than in 1999-2000 (1918 [68.3%]; difference, 21.4% [95% CI, 19.2% to 23.6%];  $P < .001$ ), while patients who were enrolled because of death occurring without any limitations in life-prolonging therapies (failed CPR and brain death) was significantly less frequent in 2015-2016 (10.3%) than in 1999-2000 (31.7%; difference, -21.4% [95% CI, -23.6% to -19.2%];  $P < .001$ ).

Table 2 details the retrospectively collected ICU characteristics for the 2 study periods. In 2015-2016, there were significant increases in ICU admission rates per month (median, 91.0 [interquartile range {IQR}, 32.5-118.8]) vs in 1999-2000 (median, 81.0 [IQR, 40.8-185.0];  $P = .02$ ), and the number of ICU beds increased in 2015-2016 (median, 18.0 [IQR, 11.5-26.5]) vs in 1999-2000 (median 18.0 [IQR, 14.0-29.0];  $P = .02$ ). Also, there were significant improvements in ICU

Table 1. Study Population of the 22 European Centers, 1999-2000 and 2015-2016

Patient Characteristics	1999-2000 (n = 2807) <sup>a</sup>	2015-2016 (n = 1785) <sup>a</sup>	Difference (95% CI) <sup>b</sup>
Age, median (IQR), y <sup>c</sup>	67 (54 to 75)	70 (59 to 79)	4.8 (3.8 to 5.8)
Age, decades <sup>d</sup>			
13-29	190 (6.8)	43 (2.4)	-4.4 (-5.5 to -3.2)
30-49	377 (13.4)	166 (9.3)	-4.1 (-6.0 to -2.3)
50-69	1020 (36.3)	656 (36.8)	0.4 (-2.4 to 3.3)
70-96	1220 (43.5)	920 (51.5)	8.1 (5.1 to 11.1)
Male sex <sup>d</sup>	1719 (61.3)	1079 (60.4)	-0.8 (-3.7 to 2.1)
Female sex <sup>d</sup>	1085 (38.7)	706 (39.6)	0.9 (-2.0 to 3.8)
Patients by region <sup>d</sup>			
Northern Europe	587 (20.9)	424 (23.8)	2.8 (0.4 to 5.3)
Central Europe	906 (32.3)	893 (50.0)	17.8 (14.9 to 20.6)
Southern Europe	1314 (46.8)	468 (26.2)	-20.6 (-23.3 to -17.8)
ICU admission (acute) diagnoses <sup>d</sup>			
Respiratory	539 (19.2)	431 (24.1)	4.9 (2.5 to 7.4)
Cardiovascular	478 (17.0)	322 (18.0)	1.0 (-1.3 to 3.3)
Neurologic	472 (16.8)	277 (15.5)	-1.3 (-3.5 to 0.9)
Gastrointestinal	388 (13.8)	98 (5.5)	-8.3 (-10.0 to -6.7)
Surgery	348 (12.4)	339 (19.0)	6.6 (4.4 to 8.8)
Sepsis	248 (8.8)	194 (10.9)	2.0 (0.2 to 3.8)
Trauma	196 (7.0)	28 (1.6)	-5.4 (-6.5 to -4.3)
Metabolic	57 (2.0)	44 (2.5)	0.4 (-0.5 to 1.3)
Miscellaneous	53 (1.9)	38 (2.1)	0.2 (-0.6 to 1.1)
Hematologic	28 (1.0)	14 (0.8)	-0.2 (-0.8 to 0.3)
Chronic diseases <sup>d</sup>			
Cardiovascular	942 (33.6)	758 (42.5)	8.9 (6.0 to 11.8)
None	624 (22.2)	140 (7.8)	-14.4 (-16.4 to -12.4)
Chest	313 (11.2)	180 (10.1)	-1.1 (-2.9 to -0.8)
Other diseases	275 (9.8)	175 (9.8)	0.0 (-1.8 to 1.8)
Cancer	253 (9.0)	179 (10.0)	1.0 (-0.7 to 1.8)
Neurological, cognitive, muscular <sup>e</sup>	135 (4.8)	141 (7.9)	3.1 (1.6 to 4.6)
Digestive	130 (4.6)	99 (5.5)	0.9 (-0.4 to 2.2)
Kidney and urinary system	71 (2.5)	64 (3.6)	1.1 (0.0 to 2.1)
Immunologic	64 (2.3)	34 (1.9)	-0.4 (-1.2 to 0.5)
Missing data	0	15 (0.8)	0.8 (0.4 to 1.3)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

<sup>a</sup> Data are reported as No (%) unless otherwise indicated.

<sup>b</sup> For all variables except age, the difference (95% CI) indicates difference in percentages.

<sup>c</sup> Age was compared using the Mann-Whitney test.

<sup>d</sup> Comparisons were determined using a  $\chi^2$  test and were not corrected for multiplicity; these exploratory analyses were aimed at detecting differences between study periods, also for the purpose of appropriate adjustments in the subsequent multivariable analyses (see Supplement 2).

<sup>e</sup> Indicates 3 disease categories counted as 1.

mortality in 2015-2016 vs in 1999-2000 (10.7% vs 12.2%;  $P < .001$ ) and in mean (SD) ethical practice scores (in 2015-2016, 5.6 [2.7] vs in 1999-2000, 2.9 [1.7];  $P < .001$ ). Results of a post hoc, logistic regression analysis are presented in the eTables 1-4 (Supplement 2).

The distribution of patients, according to the types of end-of-life categories, is shown in the Figure and in Table 3. Overall in 2015-2016, there was significantly less failed CPR (6.2% [110]) than in 1999-2000 (22.4% [628]; difference, -16.2% [95% CI, -18.1% to -14.3%];  $P < .001$ ), significantly more withholding of life-prolonging therapies in 2015-2016 (50.0% [892]) than in 1999-2000 (40.7% [1143]; difference, 9.3% [95% CI, 6.4% to 12.3%];  $P < .001$ ), and significantly more withdrawing of life-prolonging therapies in 2015-2016 (692 [38.8%]) than in 1999-2000 (695 [24.8%], difference, 14.0% [95% CI, 11.2% to 16.8%];  $P < .001$ ). Active shortening of the dying process was significantly less frequent in 2015-2016 (17 [1.0%]) than in 1999-2000 (80 [2.9%]; difference, -1.9% [95% CI, -2.7% to -1.1%];

$P < .001$ ). Brain death was also significantly less frequent in 2015-2016 (74 [4.1%]) than in 1999-2000 (261 [9.3%]; difference, -5.2% [95% CI, -6.6% to -3.8%];  $P < .001$ ).

End-of-life categories are also presented by region in the Figure and Table 3. In 2015-2016 vs 1999-2000, the significant decrease in failed CPR was prominent in the south (difference, -21.3% [95% CI, -24.6% to -18.0%];  $P < .001$ ). Withholding life-sustaining treatment exhibited a significant increase in the south (difference, 16.8% [95% CI, 11.6% to 22.0%];  $P < .001$ ), whereas withdrawing life-sustaining treatment significantly increased in all regions and was highest in the central region (difference, 15.7%, [95% CI, 11.3% to 20.1%];  $P < .001$ ).

Among all patients admitted to the study ICUs during the study periods, hospital mortality was significantly lower in 2015-2016 (10.7% [1458/13 625]) than in 1999-2000 (12.2% [2701/22 081]; difference, -1.5% [95% CI, -2.2% to -0.8%];  $P < .001$ ). No patients survived to hospital discharge after brain

death, failed CPR, or active shortening of the dying process in either study period; whereas survival was significantly higher in 2015-2016 after withholding life-sustaining therapy (34.9% [311] than in 1999-2000 (8.9% [102]; difference, 26.0% [95% CI, 22.5% to 29.5%];  $P < .001$ ) and after withdrawing life-sustaining therapy (2.3% [16] than in 1999-2000 (0.6% [4]; difference, 1.7% [95% CI, 0.4% to 3.0%];  $P < .001$ ). Mortalities after specific limitations in life-prolonging therapies are presented in **Table 4**.

Survival after any therapy limitation was significantly higher in 2015-2016 (20.4% [327] than in 1999-2000 (5.5% [106]; difference, 14.9% [95% CI, 12.7% to 17.1%];  $P < .001$ ). The improved 2015-2016 survival was present in all 3 regions and higher after withholding mechanical ventilation (36.9% [110] than in 1999-2000 (11.5% [15]; difference, 25.5% [95% CI, 22.9% to 28.0%];  $P < .001$ ), higher after withholding vasopressors (89 [20.7%] than in 1999-2000 (19 [4.6%]; difference, 16.1% [95% CI, 14.1% to 18.2%];  $P < .001$ ), and higher after withholding renal replacement therapy (146 [26.9%] than in 1999-2000 (8 [1.8%]; difference, 25.1% [95% CI, 23.0% to 27.2%];  $P < .001$ ) (Table 4).

In 2015-2016, the probability of death following the decision to withhold life-prolonging therapy (adjusted for age, sex, diagnosis, practice, turnover, and region) was 93% within 24 hours, 98% within 48 hours, and 99% within 72 hours; following the decision to withdraw life-prolonging therapy, the probability of death was 98% within 24 hours, 99% within 48 hours, and 100% within 72 hours; and following the decision for active shortening of the dying process, the probability of death was 100% at all 3 time points. In 1999-2000, the probability of death following the decision to withhold life-prolonging therapy (adjusted for age, sex, diagnosis, practice, turnover, and region) was 92% within 24 hours, 94% within 48 hours, and 96% within 72 hours; following the decision to withdraw life-prolonging therapy, the probability of death was 99% within 24 hours, 100% within 48 hours, and 100% within 72 hours; and following the decision for active shortening of the dying process, the probability of death was 99% within 24 hours, 100% within 48 hours, and 100% within 72 hours.

For all study patients, the median time from ICU admission until the first limitation of life-sustaining therapy was shorter in 2015-2016 compared with 1999-2000 (2.1 vs 4.0 days;  $P < .001$ ), and the ICU length of stay was shorter in 2015-2016 compared with 1999-2000 (4.0 vs 5.0 days;  $P < .001$ ) (Table 5). The median time from withdrawing life-sustaining therapy until death was shorter in 2015-2016 compared with 1999-2000 (11.5 vs 17.1 hours;  $P < .02$ ) and shorter than the median time from withholding life-sustaining therapy until death, which was longer in 2015-2016 compared with 1999-2000 (29.0 vs 14.1 hours;  $P < .001$ ) (Table 5).

By region, the median time from ICU admission until the first limitation of life-sustaining therapy was 1.9 days in northern Europe, 1.2 days in central Europe, and 5.0 days in southern Europe in 2015-2016, compared with 2.6 days in northern Europe, 3.9 days in central Europe, and 5.6 days in southern Europe in 1999-2000 (Table 5). The median length of stay in the ICU was 4.0 days in northern Europe, 3.0 days in central

Table 2. ICU and Hospital Variables for 22 European Centers, 1999-2000 and 2015-2016<sup>a</sup>

ICU Characteristics	Total ICUs		Northern Region		Central Region		Southern Region		Difference (95% CI)	P Value <sup>b</sup>
	1999-2000 (N = 22)	2015-2016 (N = 22)	1999-2000 (n = 4)	2015-2016 (n = 4)	1999-2000 (n = 6)	2015-2016 (n = 6)	1999-2000 (n = 12)	2015-2016 (n = 12)		
ICU type										
General	18	18	3	3	3	3	12	12		
Surgical	3	3	1	1	2	2	0	0		
Medical	1	1			1	1	0	0		
Closed ICU, No. (%) <sup>c</sup>	22 (100.0)	21 (95.5)	4 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	12 (100.0)	11 (91.7)	-4.5 (-13.2 to 4.2)	>.99
ICU No. of beds, median (IQR)	18.0 (11.5 to 26.5)	18.0 (14.0 to 29.0)	18.0 (14.3 to 31.5)	19.5 (15.8 to 31.5)	27.0 (19.5 to 40.5)	34.0 (26.0 to 54.3)	13.0 (8.5 to 18.8)	14.0 (10.3 to 17.5)	0.0 (0.0 to 3.0)	.02
ICU admissions/mo, median (IQR)	91.0 (32.5 to 118.8)	81.0 (40.8 to 185.0)	115.0 (55.0 to 141.3)	108.5 (51.8 to 167.5)	155.0 (103.8 to 191.3)	213.0 (178.8 to 296.0)	37.0 (25.0 to 75.5)	46.0 (32.3 to 75.0)	8.0 (2.0 to 27.0)	.02
Institution hospital beds, median (IQR)	800 (595 to 1225)	850 (600 to 1238)	600 (585 to 825)	600 (585 to 825)	1113 (788 to 1678)	1163 (788 to 1940)	725 (487 to 1150)	833 (593 to 1150)	0.0 (0.0 to 350.0)	.31
ICU physician staffing per bed, median (IQR)	0.33 (0.20 to 0.50)	0.40 (0.25 to 0.56)	0.19 (0.15 to 0.43)	0.21 (0.15 to 0.44)	0.28 (0.23 to 0.39)	0.36 (0.22 to 0.68)	0.50 (0.25 to 0.65)	0.50 (0.26 to 0.59)	0.0 (0.0 to 0.1)	.88
ICU nursing staffing per bed, median (IQR)	0.50 (0.40 to 0.68)	0.50 (0.40 to 0.68)	1.00 (0.75 to 1.15)	1.00 (0.75 to 1.15)	0.50 (0.40 to 0.63)	0.50 (0.40 to 0.63)	0.50 (0.40 to 0.50)	0.50 (0.40 to 0.50)	0.0 (0.0 to 0.0)	>.99
ICU mortality, yearly average %	12.2	10.7	11.6	13.1	8.5	9.2	17.4	11.7	-1.5 (-2.2 to -0.8)	<.001
Institution, academic, No., Yes (%)	19 (86.4)	20 (90.9)	4 (100.0)	4 (100.0)	5 (83.3)	5 (83.3)	10 (83.3)	11 (91.7)	4.5 (-14.2 to 23.2)	>.99

(continued)

Table 2. ICU and Hospital Variables for 22 European Centers, 1999-2000 and 2015-2016<sup>a</sup> (continued)

ICU Characteristics	Total ICUs		Northern Region		Central Region		Southern Region		Difference (95% CI)	P Value <sup>b</sup>
	1999-2000 (N = 22)	2015-2016 (N = 22)	1999-2000 (n = 4)	2015-2016 (n = 4)	1999-2000 (n = 6)	2015-2016 (n = 6)	1999-2000 (n = 12)	2015-2016 (n = 12)		
ICU ethical practice variables, No. yes (%)										
Routine family meetings	15 (68.2)	17 (77.3)	2 (50.0)	2 (50.0)	4 (66.7)	5 (83.3)	9 (75.0)	10 (83.3)	9.1 (-17.1 to 35.3)	.74
Daily deliberation for appropriate level of care for each patient	10 (45.5)	17 (77.3)	2 (50.0)	2 (50.0)	1 (16.7)	6 (100.0)	7 (58.3)	9 (75.0)	31.8 (4.6 to 59.0)	.06
End-of-life discussions during weekly meetings	10 (45.5)	14 (63.6)	2 (50.0)	3 (75.0)	2 (33.3)	4 (66.7)	6 (50.0)	7 (58.3)	18.1 (-10.8 to 47.0)	.36
Written triggers for limitations	4 (18.2)	8 (36.4)	1 (25.0)	2 (50.0)	1 (16.7)	2 (33.3)	2 (16.7)	4 (33.3)	18.2 (-7.6 to 44.0)	.31
Written end-of-life guidelines	5 (22.7)	10 (45.5)	2 (50.0)	3 (75.0)	1 (16.7)	2 (33.3)	2 (16.7)	5 (41.7)	22.8 (-4.4 to 50.0)	.20
Written end-of-life protocols	1 (4.8)	5 (22.7)	0	2 (50.0)	0	1 (16.7)	1 (8.3)	2 (16.7)	17.9 (-1.8 to 37.6)	.19
Palliative care consultations	1 (4.8)	7 (31.8)	0	1 (25.0)	0	3 (50.0)	1 (8.3)	3 (25.0)	27.0 (5.6 to 48.4)	.046
Ethics consultations	3 (13.6)	4 (18.2)	0	0	3 (50.0)	3 (50.0)	0	1 (8.3)	4.6 (-17.0 to 26.2)	>.99
Staff taking communication courses	3 (13.6)	12 (54.5)	1 (25.0)	4 (100.0)	0	3 (50.0)	2 (16.7)	5 (41.7)	40.9 (15.6 to 66.2)	.01
Staff taking bioethics courses	2 (9.6)	5 (22.7)	1 (25.0)	2 (50.0)	0	1 (16.7)	1 (8.3)	2 (16.7)	13.1 (-8.3 to 34.5)	.41
Country end-of-life guidelines	3 (13.6)	10 (45.5)	1 (25.0)	4 (100.0)	2 (33.3)	3 (50.0)	0	3 (25.0)	31.9 (6.6 to 57.2)	.045
Country end-of-life legislation	6 (27.2)	12 (54.5)	3 (75.0)	3 (75.0)	3 (50.0)	3 (50.0)	0	6 (50.0)	27.3 (-0.6 to 55.2)	.12
Ethical practice score, mean (SD) <sup>d</sup>	2.9 (1.7)	5.6 (2.7)	3.8 (0.4)	7.0 (2.1)	2.8 (1.6)	6.2 (2.7)	2.6 (1.9)	4.8 (2.8)	2.7 (1.6 to 3.7)	<.001

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

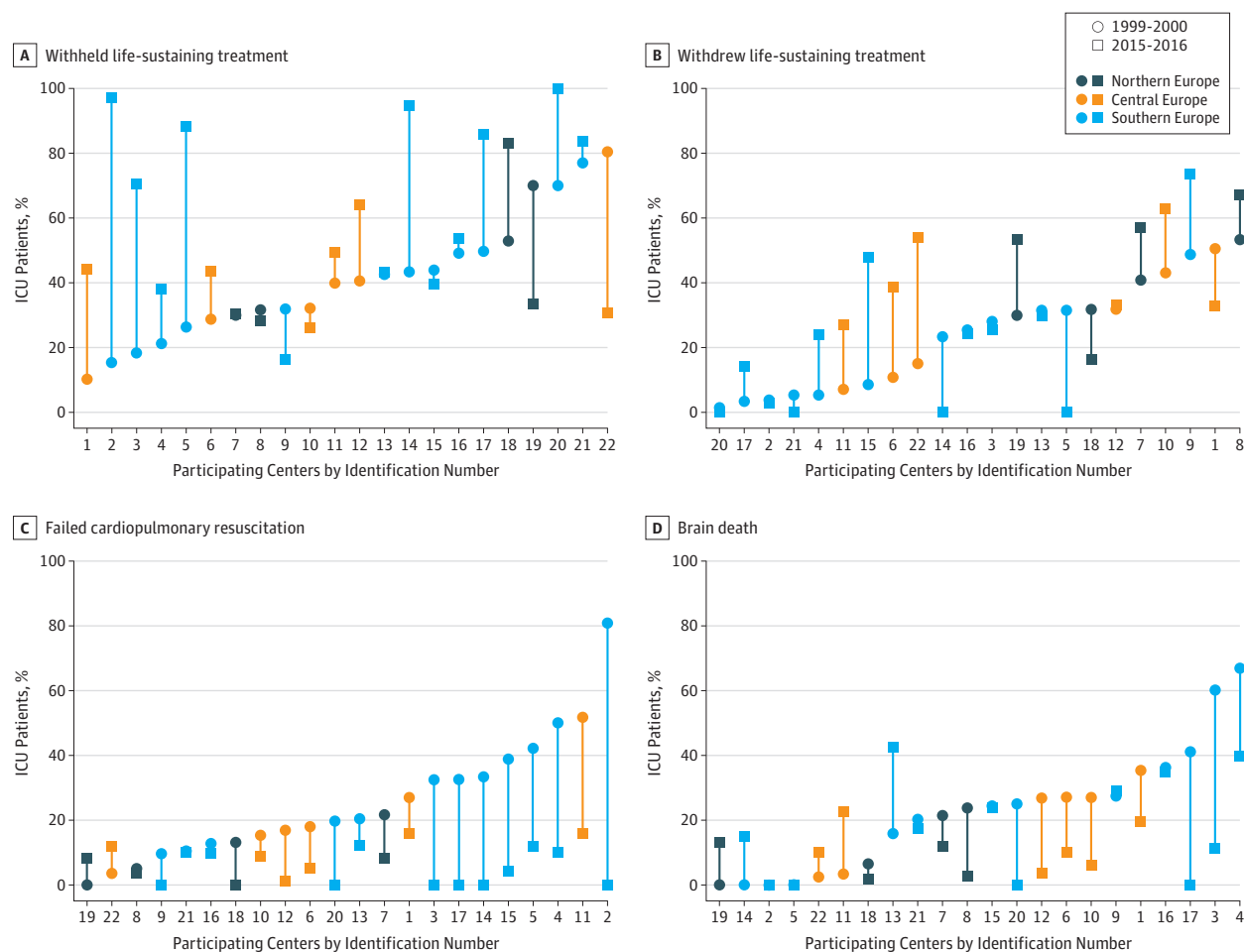
<sup>a</sup> Comparisons of ICU and hospital variables and of the ethical practice score were aimed at detecting differences between the study periods that could support further consideration for variable inclusion in the subsequent multivariable analyses (see Supplement 2); therefore, these comparisons can be considered as exploratory. These exploratory analyses were aimed at detecting subcomponents exhibiting the greatest changes between study periods, thereby driving the overall change in the ethical practice score.

<sup>b</sup> P values of compared, continuous variables were determined by a paired t test (if normally distributed) or by the Wilcoxon signed rank test (if exhibiting skewed distributions); P values of compared percentages were determined using the Fisher exact test. All P values correspond to comparisons of total ICU 2015-2016 vs total ICU 1999-2000. P values of comparisons of subcomponents of the ethical practice score were not corrected for multiplicity.

<sup>c</sup> An open ICU means that the physician who is responsible for the patient admits the patient into the ICU and maintains formal responsibility for the patient and the patient's treatment, while the intensivist is a consultant without primary responsibility for the patient. A closed ICU means that after the patient is admitted into the ICU, responsibility for the patient and the patient's treatment is transferred to the intensivist.

<sup>d</sup> Determined as the sum of the immediately preceding, 12 ethical practice variables and having a score range of 0-12 points (with each point corresponding to an answer of "yes"; a higher score [ie, ≥6 points] as compared with a lower score [ie, ≤3 points] reflects ICU ethical practice that is more organized according to current guidelines and policy statements (see also references<sup>5,8-10,12</sup>).

Figure. Changes in End-of-Life Practices From 1999-2000 to 2015-2016 in 22 ICUs by European Region



Presented are percentages of end-of-life practices in 22 centers with randomization of center numbers. Circles indicate 1999-2000 data and squares indicate the 2015-2016 data. The intensive care units (ICUs) have been sorted by the 1999-2000 prevalences across all ICUs in ascending order. The same ICU

number has been kept throughout. All graphs have varying orders depending on the sort (based from left to right on lowest to highest percentage of patients in 1999-2000). Two centers had 17 patients with active shortening of the dying process (data not shown).

Europe, and 6.0 days in southern Europe in 2015-2016, compared with 3.0 days in northern Europe, 5.0 days in central Europe, and 6.0 days in southern Europe in 1999-2000 (Table 5).

## Discussion

In this prospective observational study of 22 European ICUs, limitations in life-prolonging therapies occurred significantly more frequently, and death without limitations in life-prolonging therapies occurred significantly less frequently in 2015-2016 compared with 1999-2000.

Recent developments may account for the increase in limiting life-prolonging treatment and the decrease in failed CPR. During the time interval between the 2 studies, new laws,<sup>5,13,14</sup> governmental statements,<sup>15-17</sup> recommendations,<sup>6,7,18</sup> guidelines,<sup>8,9</sup> consensus statements by international organizations,<sup>10,19,20</sup> education,<sup>21</sup> and research<sup>1,3,4,22-24</sup> regarding end-of-life practices have been developed. These

frameworks help guide, support, and protect physicians when decisions about life-prolonging treatment are made. Moreover, do not resuscitate orders have become commonplace and provide a formal framework for decision making and communication.<sup>25</sup> Public debates and social media have led to greater awareness and openness to discuss these issues among those in professional and lay communities.

Furthermore, palliative care has improved in Europe<sup>7</sup> and worldwide. Integration of palliative care into ICUs has been shown to result in earlier family meetings, shorter hospital lengths of stay,<sup>26</sup> an increase in advance directives, and a decrease in the use of nonbeneficial life-prolonging treatments.<sup>27</sup> Randomized trials demonstrated that family-support interventions<sup>28</sup> and communication facilitators<sup>29</sup> reduce the length of stay in ICUs.<sup>28,29</sup>

In recent years, physicians have gained greater knowledge about ICU prognoses<sup>30</sup> and subsequent long-term outcomes.<sup>31</sup> Religious,<sup>3,22,32</sup> cultural,<sup>1</sup> legal,<sup>32</sup> and socioeconomic factors<sup>33</sup> may also play a role. Regional differences may

**Table 3. Changes in End-of-life Practices From 1999-2000 to 2015-2016 in 22 Intensive Care Units by European Region**

	2015-2016, %	1999-2000, %	Difference (95% CI), %	P Value
<b>Overall</b>				
Failed CPR	6.2	22.4	-16.2 (-18.1 to -14.3)	<.001
Withheld life-sustaining treatment	50.0	40.7	9.3 (6.4 to 12.3)	<.001
Withdrew life-sustaining treatment	38.8	24.8	14.0 (11.2 to 16.8)	<.001
Active shortening of the dying process	1.0	2.9	-1.9 (-2.7 to -1.1)	<.001
Brain death	4.1	9.3	-5.2 (-6.6 to -3.8)	<.001
<b>Northern region</b>				
Failed CPR	4.0	13.8	-9.8 (-13.2 to -6.4)	<.001
Withheld life-sustaining treatment	49.5	46.3	3.2 (-3.0 to 9.4)	.34
Withdrew life-sustaining treatment	44.3	35.8	8.5 (2.4 to 14.6)	<.006
Active shortening of the dying process	0.0	0.2	-0.2 (-0.6 to 0.2)	>.99
Brain death	2.1	3.9	-1.8 (-3.9 to 0.3)	.14
<b>Central region</b>				
Failed CPR	7.2	20.5	-13.3 (-16.4 to -10.2)	<.001
Withheld life-sustaining treatment	45.6	35.2	10.4 (5.9 to 14.9)	<.001
Withdrew life-sustaining treatment	43.1	27.4	15.7 (11.3 to 20.1)	<.001
Active shortening of the dying process	1.1	8.7	-7.6 (-9.6 to -5.6)	<.001
Brain death	3.0	8.2	-5.2 (-7.3 to -3.1)	<.001
<b>Southern region</b>				
Failed CPR	6.2	27.5	-21.3 (-24.6 to -18.0)	<.001
Withheld life-sustaining treatment	58.8	42.0	16.8 (11.6 to 22.0)	<.001
Withdrew life-sustaining treatment	25.4	18.0	7.4 (2.9 to 11.9)	<.001
Active shortening of the dying process	1.5	0.0	1.5 (0.4 to 2.6)	<.001
Brain death	8.1	12.5	-4.4 (-7.5 to -1.3)	.01
<b>Central vs Northern Region 1999-2000<sup>a</sup></b>				
Failed CPR	20.5	13.8	-6.7 (-10.5 to -2.9)	.001
Withheld life-sustaining treatment	35.2	46.3	11.1 (6.0 to 16.2)	<.001
Withdrew life-sustaining treatment	27.4	35.8	8.4 (3.6 to 13.2)	.001
Active shortening of the dying process	8.7	0.2	-8.5 (-10.4 to -6.6)	<.001
Brain death	8.2	3.9	-4.3 (-6.7 to -1.9)	.001
<b>Southern vs Northern Region 1999-2000<sup>a</sup></b>				
Failed CPR	27.5	13.8	-13.7 (-17.4 to -10.0)	<.001
Withheld life-sustaining treatment	42.0	46.3	4.3 (-0.5 to 9.1)	.08
Withdrew life-sustaining treatment	18.0	35.8	17.8 (13.4 to 22.2)	<.001
Active shortening of the dying process	0.0	0.2	0.2 (-0.2 to 0.6)	.31
Brain death	12.5	3.9	-8.6 (-11.0 to -6.2)	<.001
<b>Southern vs Central Region 1999-2000<sup>a</sup></b>				
Failed CPR	27.5	20.5	-7.0 (-10.6 to -3.4)	<.001
Withheld life-sustaining treatment	42.0	35.2	-6.8 (-10.9 to -2.7)	.001
Withdrew life-sustaining treatment	18.0	27.4	9.4 (5.8 to 13.0)	<.001
Active shortening of the dying process	0.0	8.7	8.7 (6.9 to 10.5)	<.001
Brain death	12.5	8.2	-4.3 (-6.8 to -1.8)	.001
<b>Central vs Northern Region 2015-2016<sup>a</sup></b>				
Failed CPR	7.2	4.0	-3.2 (-5.7 to -0.7)	.03
Withheld life-sustaining treatment	45.6	49.5	3.9 (-1.9 to 9.7)	.19
Withdrew life-sustaining treatment	43.1	44.3	1.2 (-4.5 to 6.9)	.68
Active shortening of the dying process	1.1	0.0	-1.1 (-1.8 to -0.4)	.04
Brain death	3.0	2.1	-0.9 (-2.7 to 0.9)	.45

(continued)



**Table 3. Changes in End-of-life Practices From 1999-2000 to 2015-2016 in 22 Intensive Care Units by European Region (continued)**

	2015-2016, %	1999-2000, %	Difference (95% CI), %	P Value
<b>Southern vs Northern Region 2015-2016<sup>a</sup></b>				
Failed CPR	6.2	4.0	-2.2 (-5.1 to 0.7)	.17
Withheld life-sustaining treatment	58.8	49.5	-9.3 (-15.8 to -2.8)	.006
Withdrew life-sustaining treatment	25.4	44.3	18.9 (12.7 to 25.1)	<.001
Active shortening of the dying process	1.5	0.0	-1.5 (-2.6 to -0.4)	.02
Brain death	8.1	2.1	-6.0 (-8.8 to -3.2)	<.001
<b>Southern vs Central Region 2015-2016<sup>a</sup></b>				
Failed CPR	6.2	7.2	1.0 (-1.8 to 3.8)	.57
Withheld life-sustaining treatment	58.8	45.6	-13.2 (-18.7 to -7.7)	<.001
Withdrew life-sustaining treatment	25.4	43.1	17.7 (12.6 to 22.8)	<.001
Active shortening of the dying process	1.5	1.1	-0.4 (-1.7 to 0.9)	.61
Brain death	8.1	3.0	-5.1 (-7.8 to -2.4)	<.001

Abbreviation: CPR, cardiopulmonary resuscitation.

<sup>a</sup> Column 2 displays the percentage value for the first-mentioned region, and column 3 displays the value for the second-mentioned region.

**Table 4. Outcome of Patients With and Without Limitations of Life-Sustaining Treatments and First Limitations (Withholding or Withdrawing of Life-Sustaining Treatments) for CPR, Endotracheal Tube, Mechanical Ventilation, Vasopressor, and Renal Replacement Therapy in 22 European Centers, 1999-2000 vs 2015-2016**

Characteristics	No. of Patients Who Died/Total No. (%)		Difference (95% CI), %	P Value <sup>a</sup>
	1999-2000 (n = 2807)	2015-2016 (n = 1785)		
Died without limitation of therapy <sup>b</sup>	889/889 (100.0)	184/184 (100.0)		
Died with limitation of therapy	1812/1918 (94.5)	1274/1601 (79.6)	-14.9 (-17.0 to -12.8)	<.001
First limitation in patients with withholding of life-sustaining treatment <sup>c</sup>				
CPR	1635/1736 (94.2)	1151/1469 (78.4)	-15.8 (-17.9 to -13.7)	<.001
Endotracheal tube	120/168 (71.4)	205/349 (58.7)	-12.7 (-15.5 to -9.9)	.006
Mechanical ventilation	116/131 (88.5)	188/298 (63.1)	-25.5 (-28.0 to -22.9)	<.001
Vasopressor	393/412 (95.4)	340/429 (79.3)	-16.1 (-18.2 to -14.1)	<.001
Renal replacement therapy	432/440 (98.2)	397/543 (73.1)	-25.1 (-27.2 to -23.0)	<.001
First limitation in patients with withdrawing of life-sustaining treatment <sup>c</sup>				
CPR	45/46 (97.8)	18/18 (100.0)	2.2 (1.6 to 2.7)	>.99
Endotracheal tube	30/30 (100)	130/137 (94.9)	-5.1 (-6.1 to -4.1)	.35
Mechanical ventilation	73/74 (98.6)	188/196 (95.9)	-2.7 (-3.7 to -1.7)	.45
Vasopressor	232/232 (100.0)	259/263 (98.5)	-1.5 (-2.1 to -1.0)	.13
Renal replacement therapy	97/97 (100.0)	81/81 (100.0)		

Abbreviation: CPR, cardiopulmonary resuscitation.

<sup>a</sup> P values were determined using a  $\chi^2$  or Fisher exact test.

<sup>b</sup> The Table presents study patients who lived or died with or without limitations. There were no patients who survived in the failed CPR or brain death categories (without limitations of therapies.)

<sup>c</sup> The first limitation could, and not infrequently did, involve withholding or withdrawing more than one life-sustaining treatment. Thus, the sum of the total of the first limitations may exceed the number of patients in whom life-sustaining treatment was withheld or withdrawn.

be decreasing due to increasing secularism in parts of Europe<sup>34</sup> and greater international consensus for end-of-life practices.<sup>1</sup>

Many of the centers included in this study reported numerical or statistically significant increases in country end-of-life legislation and guidelines, ICU written end-of-life guidelines, protocols and triggers for limitations, communication and bioethics courses, end-of-life discussions and deliberations about levels of care, palliative care and ethics consultations, and family meetings since 1999-2000. These changes resulted in significant, overall improvements in the ethical practice score. Other factors associated with treatment limitation included physician religion,<sup>3,22</sup> patient age, and chronic disease. The latter 2 factors were previously shown to contribute to decisions to withhold ICU support.<sup>35</sup>

An important finding of this study was the higher survival rates after limitations in life-prolonging therapies. Limitations occur not only at the end-of-life but also earlier to respect patient wishes and to avoid invasive therapies likely to prolong the dying process or result in poor quality of life. Death occurred more often after the actual withdrawal of life-sustaining treatments than after withholding potential future or present life-prolonging therapies. In 2015-2016, more patients survived after withholding mechanical ventilation, vasopressor use, and renal replacement therapy, which may reflect improved ICU practices with more patients surviving acute illnesses.

Previous end-of-life practice comparison studies show contradictory results. Between 1987 and 1993 Prendergast

**Table 5. Time Frames for Length of Stay to First Limitation, to Death After First Limitation, and for Withholding and Withdrawing of Life-Sustaining Therapy in Patients With End-of-Life Decisions, by Region and by Type of Limitation in 22 European Centers, 1999-2000 (n = 2807) and 2015-2016 (n = 1785)**

Years of Cohort	Median (IQR)		Difference (95% CI) <sup>a</sup>	P Value <sup>b</sup>
	1999-2000	2015-2016		
<b>Overall</b>				
Length of stay in the ICU, d	5.0 (1.0 to 13.0)	4.0 (1.0 to 11.0)	-1.8 (-2.8 to -0.9)	<.001
No. of patients	2799 <sup>c</sup>	1785		
Time from ICU admission to first limitation, d	4.0 (1.0 to 12.3)	2.1 (0.3 to 7.5)	-3.5 (-4.5 to -2.5)	<.001
No. of patients	1891	1538		
Time from first limitation of treatment until death, h	16.2 (3.6 to 57.0)	20.0 (3.0 to 87.9)	-32.4 (-50.2 to 14.7)	.08
No. of patients	1817	1274		
Time from withholding life-sustaining therapy until death, h	14.1 (2.8 to 63.5)	29.0 (4.5 to 134.8)	54.2 (24.3 to 84.2)	<.001
No. of patients	1034	581		
Time from withdrawing life-sustaining therapy until death, h	17.1 (4.5 to 49.8)	11.5 (2.3 to 54.6)	26.7 (7.5 to 45.9)	.02
No. of patients	686	676		
<b>Northern region</b>				
Length of stay in the ICU, d	3.0 (1.0 to 11.0)	4.0 (1.0 to 10.0)	-0.99 (-2.64 to 0.66)	.68
No. of patients	586	424		
Time from ICU admission to first limitation, d	2.6 (0.6 to 9.9)	1.9 (0.4 to 6.9)	-2.3 (-3.9 to -0.7)	<.01
No. of patients	474	376		
Time from first limitation of treatment until death, h	12.7 (3.6 to 41.5)	20.9 (3.5 to 69.7)	-56.3 (-87.5 to -25.1)	.04
No. of patients	471	335		
Time from withholding life-sustaining therapy until death, h	9.6 (3.0 to 41.2)	35.0 (5.1 to 147.4)	79.9 (39.3 to 120.5)	<.001
No. of patients	260	147		
Time from withdrawing life-sustaining therapy until death, h	15.0 (4.6 to 43.0)	13.0 (3.3 to 30.9)	39.3 (-9.1 to 87.8)	.22
No. of patients	206	188		
<b>Central region</b>				
Length of stay in the ICU, d	5.0 (2.0 to 15.0)	3.0 (1.0 to 9.0)	-4.5 (-6.1 to 3.0)	<.001
No. of patients	903	893		
Time from ICU admission to first limitation, d	3.9 (0.8 to 14.0)	1.2 (0.1 to 5.1)	6.8 (-8.4 to -5.2)	<.001
No. of patients	640	763		
Time from first limitation of treatment until death, h	26.6 (5.8 to 92.6)	23.5 (2.7 to 115.4)	-17.4 (-52.6 to 17.9)	.13
No. of patients	578	569		
Time from withholding life-sustaining therapy until death, h	32.7 (6.3 to 160.9)	57.0 (8.6 to 286.5)	39.7 (-42.8 to 122.2)	.11
No. of patients	243	187		
Time from withdrawing life-sustaining therapy until death, h	15.6 (5.0 to 51.6)	12.9 (1.9 to 75.7)	32.1 (4.7 to 59.6)	.12
No. of patients	246	372		
<b>Southern region</b>				
Length of stay in the ICU, d	6.0 (2.0 to 14.0)	6.0 (2.0 to 18.0)	1.9 (0.1 to 3.7)	.10
No. of patients	1310	468		
Time from ICU admission to first limitation, d	5.6 (1.5 to 12.7)	5.0 (1.3 to 15.9)	1.0 (-0.9 to 2.8)	.84
No. of patients	777	399		
Time from first limitation of treatment until death, h	12.5 (2.0 to 50.5)	16.2 (3.0 to 62.1)	-11.7 (-35.6 to 12.1)	.14
No. of patients	768	370		
Time from withholding life-sustaining therapy until death, h	11.0 (1.5 to 54.5)	18.5 (3.4 to 74.2)	23.9 (-9.8 to 57.6)	.01
No. of patients	531	247		
Time from withdrawing life-sustaining therapy until death, h	20.8 (4.0 to 50.1)	10.3 (2.5 to 32.7)	-11.2 (-31.9 to 9.6)	.12
No. of patients	234	116		

<sup>a</sup> Difference (95% CI) indicates difference of means, 2015-2016 minus 1999-2000 values.

<sup>c</sup> Cell reports 2799 patients instead of 2807 because there were 8 patients with missing data.

<sup>b</sup> P values were determined by Mann-Whitney test.

and Luce demonstrated a 39% decrease in failed CPR and a 39% increase in withdrawing and withholding treatments in 2 US ICUs.<sup>36</sup> McLean et al compared the mode of dying between 1988 and 1993 in 2 Canadian ICUs and found 23% and 34% increases in the withdrawal of life-sustaining treatments in the 2 ICUs.<sup>37</sup> Jakobson et al found no significant differences in CPR or withholding of life-prolonging therapies in an Israeli ICU between 1994 and 1999.<sup>38</sup> The authors suggested that the lack of change was due to the already low CPR rate and high withholding rate. In a French single-center study by Lesieur et al, limitations increased by 16% from 2012 to 2016, while failed CPR decreased 36%.<sup>39</sup> The present study found an increase from 1999 to 2016 of withholding (9%) and withdrawing (14%) life-sustaining therapies, whereas failed CPR decreased (-16%).

The present study demonstrated that active shortening of the dying process is uncommon in the ICU. Despite increasing public approval, more countries permitting euthanasia, and euthanasia increasing as the cause of death in the Netherlands and Belgium,<sup>11,40</sup> there was a slight decrease in active shortening of the dying process in the study. This may be related to physician reluctance to actively shorten the dying process because ICU patients cannot express their wishes and provide an explicit request, making this action illegal even in Belgium and the Netherlands where euthanasia is permitted. Euthanasia and active shortening of the dying process are not needed in the ICU because once caregivers and surrogates conclude that ongoing interventions are not in the patient's best interest, death typically ensues rather quickly after withdrawing life-prolonging treatment.

Although some changes were statistically significant because of the large numbers of patients, they were not clinically relevant, such as the decrease in active shortening of the dying process and ICU length of stay. Despite the fact that more ICUs in the southern region admitted patients, there were fewer patients admitted in the southern region in 2015-2016 than in 1999-2000 compared with the northern and central regions. This was most likely related to the much lower number of ICU beds and monthly admissions to ICUs in the southern region compared with ICUs in the northern and central regions.

Strengths of the study include its multinational nature, the large number of patients, use of the same centers and definitions, the same physicians being responsible for end-of-life decisions and data collection, methods to improve quality, the long time interval between studies, and the evaluation of changes in the study ICUs (especially ethical practices) in relation to end-of-life outcomes.

### Limitations

This study has several limitations. First, this follow-up study includes only 59% of previous centers, different percentages of patients from the regions, and different physicians treating many of the patients. Second, the majority of the ICUs were academically affiliated and may not be representative of European ICUs more generally. Third, while secular trends, changing ethical views, and public awareness may be responsible for many of the changes observed, the study design did not allow for direct assessment of how ethical principles and laws affect outcomes. Fourth, the data used to calculate the ethical practice score were collected retrospectively and may be subject to recall bias and social desirability bias. Fifth, it remains possible that changes in admission case mix not adjusted for in the analyses, or substantial changes in survival rates related to changes in organizational factors and quality of care, may be confounders responsible for some of the observed changes. Sixth, the number of patients not receiving indicated treatment limitations could not be determined.

### Conclusions

Among patients who had treatment limitations or died in 22 European ICUs in 2015-2016, compared with data previously reported from the same ICUs in 1999-2000, limitations in life-prolonging therapies occurred significantly more frequently and death without limitations in life-prolonging therapies occurred significantly less frequently. Although these findings suggest a shift in end-of-life practices in European ICUs, the study is limited in that patients who survived ICU hospitalization without treatment limitations were not included.

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## REFERENCES

1. Sprung CL, Truog RD, Curtis JR, et al. Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill: the Consensus for Worldwide End-of-Life Practice for Patients in

Intensive Care Units (WELPICUS) study. *Am J Respir Crit Care Med.* 2014;190(8):855-866. doi:10.1164/rccm.201403-0593CC

2. Mark NM, Rayner SG, Lee NJ, Curtis JR. Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: a systematic review. *Intensive Care Med.* 2015;41(9):1572-1585. doi:10.1007/s00134-015-3810-5

3. Sprung CL, Cohen SL, Sjøkvist P, et al; Ethicus Study Group. End-of-life practices in European intensive care units: the Ethicus Study. *JAMA.* 2003;290(6):790-797. doi:10.1001/jama.290.6.790

4. Devictor DJ, Tissieres P, Gillis J, Truog R; WFPICCS Task Force on Ethics. Intercontinental differences in end-of-life attitudes in the pediatric intensive care unit: results of a worldwide survey. *Pediatr Crit Care Med.* 2008;9(6):560-566. doi:10.1097/PCC.0b013e31818d3581

5. Council of Europe. Guide on the decision-making process regarding medical treatment in end-of-life situations. [https://www.coe.int/t/dg3/healthbioethic/conferences\\_and\\_symposia/Guide%20FDV%20E.pdf](https://www.coe.int/t/dg3/healthbioethic/conferences_and_symposia/Guide%20FDV%20E.pdf). Accessed August 30, 2018.

6. Truog RD, Campbell ML, Curtis JR, et al; American Academy of Critical Care Medicine. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College [corrected] of Critical Care Medicine. *Crit Care Med.* 2008;36(3):953-963. doi:10.1097/CCM.0B013E3181659096

7. Cherny NI, Radbruch L; Board of the European Association for Palliative Care. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med.* 2009;23(7):581-593. doi:10.1177/0269216309107024

8. Bossaert LL, Perkins GD, Askitopoulou H, et al; Ethics of Resuscitation and End-of-Life Decisions Section Collaborators. European Resuscitation Council Guidelines for Resuscitation 2015: section 11, the ethics of resuscitation and end-of-life decisions. *Resuscitation.* 2015;95:302-311. doi:10.1016/j.resuscitation.2015.07.033

9. Downar J, Delaney JW, Hawryluk L, Kenny L. Guidelines for the withdrawal of life-sustaining measures. *Intensive Care Med.* 2016;42(6):1003-1017. doi:10.1007/s00134-016-4330-7

10. Davidson JE, Aslaskar RA, Long AC, et al. Guidelines for family-centered care in the neonatal, pediatric, and adult ICU. *Crit Care Med.* 2017;45(1):103-128. doi:10.1097/CCM.0000000000002169

11. Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, Cohen J. Attitudes and practices of euthanasia and physician-assisted suicide in the United States, Canada, and Europe. *JAMA.* 2016;316(1):79-90. doi:10.1001/jama.2016.8499

12. Kon AA, Davidson JE, Morrison W, Danis M, White DB; American College of Critical Care Medicine; American Thoracic Society. Shared decision making in ICUs: an American College of Critical Care Medicine and American Thoracic Society Policy Statement. *Crit Care Med.* 2016;44(1):188-201. doi:10.1097/CCM.0000000000001396

13. Steinberg A, Sprung CL. The dying patient: new Israeli legislation. *Intensive Care Med.* 2006;32(8):1234-1237. doi:10.1007/s00134-006-0186-6

14. Sulmasy DP. Italy's New advance directive law: when in Rome.... *JAMA Intern Med.* 2018;178(5):607-608. doi:10.1001/jamainternmed.2018.0462

15. Socialstyrelsen. To give or not to give life support. Sweden: The National Board on health and Welfare 2011. <https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2011-6-39.pdf>. Accessed September 22, 2019.
16. Danish Patient Safety Authority. A guide on withholding life support, resuscitation and withdrawing of treatment. <https://stps.dk/da/udgivelser/2012/vejledning-om-forudgaaende-fravalg-af-livsforlaengende-behandling,-herunder-genoplivningsforsog,-og-om-afbrydelse-af-behandling>. Accessed August 30, 2018.
17. The Norwegian Directorate of Health. Decision-making process when limiting life-sustaining treatment. <https://helsedirektoratet.no/retningslinjer/beslutningsprosesser-ved-begrensning-av-livsforlengende-behandling>. Accessed August 30, 2018.
18. Valentin A, Druml W, Steltzer H, Wiedermann CJ. Recommendations on therapy limitation and therapy discontinuation in intensive care units: consensus paper of the Austrian Associations of Intensive Care Medicine. *Intensive Care Med*. 2008;34(4):771-776. doi:10.1007/s00134-007-0975-6
19. Bosslet GT, Pope TM, Rubenfeld GD, et al; American Thoracic Society ad hoc Committee on Futile and Potentially Inappropriate Treatment; American Thoracic Society; American Association for Critical Care Nurses; American College of Chest Physicians; European Society for Intensive Care Medicine; Society of Critical Care. An official ATS/AACN/ACCP/ESICM/SCCM policy statement: responding to requests for potentially inappropriate treatments in intensive care units. *Am J Respir Crit Care Med*. 2015;191(11):1318-1330. doi:10.1164/rccm.201505-0924ST
20. Myburgh J, Abillama F, Chiumello D, et al; Council of the World Federation of Societies of Intensive and Critical Care Medicine. End-of-life care in the intensive care unit: report from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine. *J Crit Care*. 2016;34:125-130. doi:10.1016/j.jcrc.2016.04.017
21. Sullivan AM, Lakoma MD, Billings JA, Peters AS, Block SD; PCEP Core Faculty. Teaching and learning end-of-life care: evaluation of a faculty development program in palliative care. *Acad Med*. 2005;80(7):657-668. doi:10.1097/00001888-200507000-00008
22. Bülow HH, Sprung CL, Baras M, et al. Are religion and religiosity important to end-of-life decisions and patient autonomy in the ICU? the Ethicatt study. *Intensive Care Med*. 2012;38(7):1126-1133. doi:10.1007/s00134-012-2554-8
23. Kranidiotis G, Ropa J, Mprianas J, Kyprianou T, Nanas S. Attitudes towards euthanasia among Greek intensive care unit physicians and nurses. *Heart Lung*. 2015;44(3):260-263. doi:10.1016/j.hrtlng.2015.03.001
24. Lobo SM, De Simoni FHB, Jakob SM, et al; ICON investigators. Decision-making on withholding or withdrawing life support in the ICU: a worldwide perspective. *Chest*. 2017;152(2):321-329. doi:10.1016/j.chest.2017.04.176
25. Burns JP, Truog RD. The DNR order after 40 years. *N Engl J Med*. 2016;375(6):504-506. doi:10.1056/NEJMp1605597
26. Braus N, Campbell TC, Kwekkeboom KL, et al. Prospective study of a proactive palliative care rounding intervention in a medical ICU. *Intensive Care Med*. 2016;42(1):54-62. doi:10.1007/s00134-015-4098-1
27. O'Mahony S, McHenry J, Blank AE, et al. Preliminary report of the integration of a palliative care team into an intensive care unit. *Palliat Med*. 2010;24(2):154-165. doi:10.1177/0269216309346540
28. White DB, Angus DC, Shields A-M, et al; PARTNER Investigators. A randomized trial of a family-support intervention in intensive care units. *N Engl J Med*. 2018;378(25):2365-2375. doi:10.1056/NEJMoa1802637
29. Curtis JR, Treece PD, Nielsen EL, et al. Randomized trial of communication facilitators to reduce family distress and intensity of end-of-life care. *Am J Respir Crit Care Med*. 2016;193(2):154-162. doi:10.1164/rccm.201505-09000C
30. Johnson RF Jr, Gustin J. Acute lung injury and acute respiratory distress syndrome requiring tracheal intubation and mechanical ventilation in the intensive care unit: impact on managing uncertainty for patient-centered communication. *Am J Hosp Palliat Care*. 2013;30(6):569-575. doi:10.1177/1049909112460566
31. Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304. doi:10.1056/NEJMoa1011802
32. Ntantana A, Matamis D, Savvidou S, et al. The impact of healthcare professionals' personality and religious beliefs on the decisions to forego life sustaining treatments: an observational, multicentre, cross-sectional study in Greek intensive care units. *BMJ Open*. 2017;7(7):e013916. doi:10.1136/bmjopen-2016-013916
33. Phua J, Joynt GM, Nishimura M, et al; ACME Study Investigators; Asian Critical Care Clinical Trials Group. Withholding and withdrawal of life-sustaining treatments in low-middle-income versus high-income Asian countries and regions. *Intensive Care Med*. 2016;42(7):1118-1127. doi:10.1007/s00134-016-4347-y
34. Norris P, Inglehart R. *Sacred and Secular: Religion and Politics Worldwide*. Cambridge, England: Cambridge University Press; 2004. doi:10.1017/CBO9780511791017
35. Gopalan PD, Pershad S. Decision-making in ICU—a systematic review of factors considered important by ICU clinician decision makers with regard to ICU triage decisions. *J Crit Care*. 2019;50:99-110. doi:10.1016/j.jcrc.2018.11.027
36. Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. *Am J Respir Crit Care Med*. 1997;155(1):15-20. doi:10.1164/ajrccm.155.1.9001282
37. McLean RF, Tarshis J, Mazer CD, Szalai JP. Death in two Canadian intensive care units: institutional difference and changes over time. *Crit Care Med*. 2000;28(1):100-103. doi:10.1097/00003246-200001000-00016
38. Jakobson DJ, Eidelman LA, Worner TM, Oppenheim AE, Pizov R, Sprung CL. Evaluation of changes in forgoing life-sustaining treatment in Israeli ICU patients. *Chest*. 2004;126(6):1969-1973. doi:10.1378/chest.126.6.1969
39. Lesieur O, Herblant A, Cabasson S, Hoppe MA, Guillaume F, Leloup M. Changes in limitations of life-sustaining treatments over time in a French intensive care unit: a prospective observational study. *J Crit Care*. 2018;47:21-29. doi:10.1016/j.jcrc.2018.05.018
40. Sprung CL, Somerville MA, Radbruch L, et al. Physician-assisted suicide and euthanasia: emerging issues from a global perspective. *J Palliat Care*. 2018;33(4):197-203. doi:10.1177/0825859718777325