# Causes and Characteristics of Death in Intensive Care Units: A Prospective Multicenter Study

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## *A Prospective Multicenter Study*

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## ABSTRACT

**Background:** Different modes of death are described in selected populations, but few data report the characteristics of death in a general intensive care unit population. This study analyzed the causes and characteristics of death of critically ill patients and compared anticipated death patients to unexpected death counterparts.

**Methods:** An observational multicenter cohort study was performed in 96 intensive care units. During 1 yr, each intensive care unit was randomized to participate during a 1-month period. Demographic data, characteristics of organ failures (Sequential Organ Failure Assessment subscore greater than or equal to 3), and organ supports were collected on all patients who died in the intensive care unit. Modes of death were defined as anticipated (after withdrawal or withholding of treatment or brain death) or unexpected (despite engagement of full-level care or sudden refractory cardiac arrest).

**Results:** A total of 698 patients were included during the study period. At the time of death, 84% had one or more organ failures (mainly hemodynamic) and 89% required at least one organ support (mainly mechanical ventilation). Deaths were considered unexpected and anticipated in 225 and 473 cases, respectively. Compared to its anticipated counterpart, unexpected death occurred earlier (1 day *vs.* 5 days; $P < 0.001$) and had fewer organ failures (1 [1 to 2] *vs.* 1 [1 to 3]; $P < 0.01$) and more organ supports (2 [2 to 3] *vs.* 1 [1 to 2]; $P < 0.01$). Withdrawal or withholding of treatments accounted for half of the deaths.

**Conclusions:** In a general intensive care unit population, the majority of patients present with at least one organ failure at the time of death. Anticipated and unexpected deaths represent two different modes of dying and exhibit profiles reflecting the different pathophysiologic underlying mechanisms.

DESPITE medical advances in patient management, intensive care unit (ICU) mortality remains high with large variations according to patient case mix and organization of care.[1] Mortality is a major end point in epidemiologic and interventional studies in the ICU. However, the causes of death are poorly reported. In adult surgical patients, the mortality rate is largely attributed to multiorgan dysfunction,[2] while withholding and withdrawal of treatments are reported as the main cause of death in the ICU in pediatric patients.[3]

Factors leading to death likely differ according to the time elapsed since the initial insult prompting ICU admission. Early fatalities occurring after cardiac arrest may result from

- Despite medical advances in patient management, intensive care unit mortality remains high with large variations according to patient case mix and organization of care.
- This study determined the characteristics of anticipated and unexpected deaths in critically ill patients.
- In a general intensive care unit population, the majority of patients present at least one organ failure at the time of death. Compared to its anticipated counterpart, unexpected death occurred earlier and had fewer organ failures.

refractory shock and intractable multiorgan failure, whereas postanoxic encephalopathy is responsible for late death.[4] Similarly, in septic shock patients, the causes of death change over time.[5] Multiorgan failure represents the main cause of death in the early phase of sepsis. Later on, death may be related to end-of-life decisions, ICU-acquired infections, mesenteric ischemia, or healthcare-related complications. This emphasizes the growing influence of ethical considerations in the processes and decisions of care, leading to withholding and withdrawal of treatments.[6] Thus, anticipated and unexpected death should be clearly differentiated. To our knowledge, there are no data quantifying and evaluating the characteristics of these two types of deaths in ICU patients.

The primary aim of the study was to describe the characteristics of death of critically ill patients. As we hypothesized that anticipated and unexpected deaths of patients present different characteristics, the secondary aim of the study was to compare these populations.

## Materials and Methods

### Study Design and Participants

This prospective multicenter observational cohort study was performed from July 1, 2013, to June 30, 2014. All French adult ICUs were contacted by e-mail. ICUs agreeing to participate were randomized by cluster for 1 calendar month in the year of study. All adult patients aged older than 18 yr who died in the ICU were included. The characteristics of each ICU, including its structure, patient populations, and mortality rates, were also recorded. An electronic case report form (eCRF) was completed for each patient who died during the 1-month inclusion period regardless of the time elapsed from his or her ICU admission.

The study was approved by the Ethics Committee of Nîmes University Hospital, Nîmes, France (Internal Review Board number 12/12-01). Authorization to collect and manage computerized data was granted by the Commission Nationale Informatique Liberté (Paris, France; decision number DR-2013–213). All data were entered into a database using secure Web server-based software (LimeSurvey, Version 2.00+, Build 130611; LimeSurvey Project, Germany; http://www.limesurvey.org).

### Data Collection

Patient data collection included the following: (1) demographic and comorbidity characteristics; (2) illness severity at ICU admission evaluated by the Simplified Acute Physiological II (SAPS II) and Sequential Organ Failure Assessment (SOFA) scores; (3) reason for ICU admission and cause of death; and (4) dates of admission and death.

For analysis, the ICU admission diagnoses were grouped into broad categories (hemodynamic, respiratory, renal, hepatic, neurologic, digestive, hematologic, and miscellaneous). At the time of death, the presence of organ failure was defined by a SOFA subscore greater than or equal to 3 for each organ (cardiovascular, respiratory, renal, nervous, hepatic, and hematologic), as previously reported.[7] Organ supports were defined by the use of catecholamines, mechanical ventilation, renal replacement therapy, or liver dialysis.

Deaths were dichotomized as anticipated and unexpected. Anticipated deaths were defined as those occurring after withholding or withdrawal of a treatment procedure due to perceived futility of care or fulfilling brain death criteria. Death was considered as unexpected for patients receiving a full engagement level of therapy or those with a sudden refractory cardiac arrest. In this latter category, an increase in intensity of treatment and the occurrence of major adverse events in the previous 48 h were recorded. An increase in intensity of treatments was defined by one or more of the following interventions in the 48 h before death: initiation or increase in catecholamine dose, initiation of mechanical ventilation or increase in inspired fraction of oxygen more than 20%, initiation of renal replacement therapy or liver dialysis, blood transfusion, and initiation of antibiotics. A major adverse event consisted of cardiac arrest, hypotension (systolic blood pressure less than 70 mmHg), desaturation (oxygen saturation measured by pulse oximetry less than 70%), severe hypoglycemia (less than 40 mg/dl), unplanned extubation, reintubation, ICU readmission, complications of care, reoperation, and drug-related adverse effect.

Réanimations Chirurgicales, Hôpitaux Universitaires Henri Mondor, Assistance Publique–Hôpitaux de Paris, Créteil, France (N.M., G.D.); Département d'Anesthésie-Réanimation, Hôpital Edouard-Herriot, Hospices Civils de Lyon, Lyon, France (B.A.); Réanimation Médicale, Hôpital Edouard-Herriot, Hospices Civils de Lyon, Lyon, France (L.A.); Réanimation Chirurgicale, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France (F.A.); Réanimation, Centre Hospitalier Interrégional de Compiègne Noyon, Compiègne, France (G.B.); Réanimation Adultes et Unité de Soins Intensifs, Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France (J.-M.C.); Réanimation Polyvalente, Hôpital Sainte-Musse, Centre Hospitalier Interrégional de Toulon-La Seyne sur mer, Toulon, France (J.D.-G., C.G.); Réanimations, Centre Hospitalier Universitaire de Amiens Picardie-Site Sud, Amiens, France (H.D.); Anesthésie et Réanimation Adulte, Hôpital Purpan, Centre Hospitalier Universitaire de Toulouse, Toulouse, France (M.G.); Service de Réanimation, Hôpital Inter-Armées Sainte-Anne, Toulon, France (P.G.); Réanimation Médicale, Hôpital Saint-Antoine, Assistance Publique–Hôpitaux de Paris, Paris, France (B.G.); Réanimation Médicale, Hôpital l'Archet 2, Centre Hospitalier Universitaire de Nice, Nice, France (H.H.); Département d'Anesthésie et de Réanimation B, Centre Hospitalier Universitaire de Montpellier, Montpellier, France (S.J.); Division Anesthésie Réanimation Douleur Urgences, Centre Hospitalier Universitaire de Nîmes, Nîmes, France (J.-Y.L.); Réanimation Chirurgicale, Centre Hospitalier Universitaire de Rennes, Rennes, France (Y.M.); Réanimation Polyvalente B, Hôpital Nord, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Priest En Jarez, France (J.M.); Service d'Anesthésie-Réanimation II, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France (A.O.); Service de Réanimation Polyvalente, Centre Hospitalier Universitaire Dupuytren, Limoges, France (N.P.); Réanimation Polyvalente, Centre Hospitalier de Beauvais, Beauvais, France (A.-M.G.R.); Réanimation et Surveillance Continue, Centre Hospitalier de Annecy Genevois, Epagny Metz-Tessy, France (M.S.); Service de Réanimation Polyvalente, Centre Hospitalier Princesse Grace, Monaco City, Monaco (A.T.); and Service d'Anesthésie Réanimation, Hôpital de la Conception (S.W.) and Service Anesthésie et Réanimation, Hôpital Nord (L.Z., M.L.), Assistance Publique–Hôpitaux de Marseille, Marseille, France.

*Members of the AzuRéa Network are listed in the appendix.

### Statistical Analysis

Due to the lack of data on this specific topic, we did not perform a power calculation before the study. Thus, the sample size was based on available data.

Quantitative data are expressed as median and interquartile range. Qualitative data were reported as absolute values and percentages. Mann–Whitney U tests were used for univariate comparisons for continuous variables and chi-square tests or Fisher exact tests for univariate comparisons of categorical variables. Statistical analysis was performed on XLSTAT (version 2013.2.01; Addinsoft, USA). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

## Results

This article reports the primary analysis of these data.

### ICU Characteristics

One hundred twenty-nine of 360 ICUs agreed to participate in the study. From these participating ICUs, 96 actually included patients. Academic and nonacademic hospitals were equally represented. The median (interquartile range) size was 12 (10 to 15) beds. In 2012, the median number of admissions was 497 (353 to 721) with a median SAPS II score of 44 (38 to 47) and a mortality rate of 20% (15 to 23). A total of 702 eCRF were filled in during the study period. Four forms were excluded from analysis because two patients were included twice and an ICU generated two eCRF by mistake. A total of 698 patients died during their ICU stay. The median number of deaths per ICU during the month of inclusion was 6 (4 to 9), ranging from 1 to 23. Deaths occurred in mixed medical-surgical (73%), surgical (16%), and medical (11%) ICUs.

### Clinical Characteristics of Patients Who Died

Patient characteristics are reported in table 1. Death occurred on day 3 (1 to 10) after ICU admission and at night or weekends for 405 (58%) patients. At the time of death, 586 (84%) patients had one or more organ failures as defined by a specific SOFA subscore greater than or equal to 3. These organ failures consisted of hemodynamic (405 [58%]), respiratory (216 [31%]), renal (230 [33%]), neurologic (209 [30%]), hepatic (56 [8%]), and hematologic (56 [8%]). At the time of death, at least one organ support was required in 621 (89%) patients, including catecholamine infusion (440 [63%]), mechanical ventilation (593 [85%]), renal replacement therapy (195 [28%]), and extracorporeal liver support (2 [1%]).

Demographic data were compared according to the following ICU characteristics: type (surgical, medical, or mixed), university affiliation (academic or nonacademic),

**Table 1.** Demographic Admission Data of the Overall Study Population and in the Anticipated and Unexpected Death Subsets

| Variable | Overall Population (n = 698) | Anticipated Deaths (n = 473) | Unexpected Deaths (n = 225) | *P* Value |
|---|---|---|---|---|
| Age, yr | 69 (57–78) | 69 (57–78) | 68 (56–77) | 0.32 |
| Male sex | 465 (67) | 319 (67) | 146 (65) | 0.53 |
| Cancer | 202 (29) | 139 (29) | 63 (28) | 0.70 |
| Smoking | 181 (26) | 114 (24) | 63 (28) | 0.24 |
| Chronic alcoholism | 126 (18) | 85 (18) | 38 (17) | 0.73 |
| Chronic organ dysfunction | 267 (38) | 183 (39) | 84 (37) | 0.73 |
| No. of chronic organ dysfunctions | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0.80 |
| SAPS II | 63 (48–83) | 60 (47–76) | 77 (52–93) | <0.001 |
| SOFA | 11 (7–13) | 10 (7–13) | 12 (9–15) | <0.001 |
| Type of admission | | | | 0.039 |
| Medical | 503 (72) | 351 (74) | 152 (68) | 0.07 |
| Emergency surgery | 145 (21) | 96 (20) | 49 (22) | 0.64 |
| Scheduled surgery | 48 (7) | 25 (5) | 23 (10) | 0.016 |
| Cause of admission | | | | <0.001 |
| Cardiovascular | 193 (28) | 103 (22) | 90 (40) | <0.001 |
| Respiratory | 182 (26) | 127 (27) | 55 (24) | 0.52 |
| Neurologic | 169 (24) | 149 (32) | 20 (9) | <0.001 |
| Digestive | 135 (16) | 93 (15) | 42 (19) | 0.28 |
| Renal | 13 (2) | 7 (2) | 6 (3) | 0.37 |
| Hematologic | 11 (2) | 6 (1) | 5 (2) | 0.35 |
| Miscellaneous | 15 (2) | 8 (2) | 7 (3) | 0.27 |
| Death during night shift and weekend | 403 (58) | 259 (55) | 144 (64) | 0.021 |
| Duration of stay, days | 3 (1–10) | 5 (2–12) | 1 (0–8) | <0.001 |
| Presence of sepsis at time of admission | 197 (28) | 121 (26) | 76 (34) | 0.27 |

Results are expressed as the absolute number and percentage or median and interquartile. Chronic organ dysfunctions: cardiovascular (high blood pressure, cardiac failure, arrhythmia, and coronary disease); respiratory (chronic respiratory failure and chronic obstructive pulmonary disease); kidney (chronic kidney disease needing renal replacement therapy or not); neurologic (dementia and ischemic or hemorrhagic stroke); hepatic (cirrhosis); metabolic (diabetes and obesity). Data were missing for the type of admission for two patients.

SAPS II = Simplified Acute Physiological II; SOFA = Sequential Organ Failure Assessment.

and size (less than or equal to 12 *vs.* more than 12 beds). Only the SAPS II score differed by type of ICU: 56 (43 to 69) in surgical ICU, 67 (49 to 87) in medical ICU, and 65 (49 to 84) in mixed medical-surgical ICU; $P = 0.001$. The duration of ICU stay, the number of organ failures, and the proportions of anticipated to unexpected deaths were similar.

### *Comparison of Anticipated* versus *Unexpected Death*

There were 473 (68%) anticipated and 225 (32%) unexpected deaths. The latter group had higher severity scores and shorter ICU stays (1 [0 to 8] day *vs.* 5 [2 to 12] days; $P < 0.001$; table 1). Unexpected and anticipated death patients were admitted to the ICU for a cardiovascular reason in 40 and 22% of cases, respectively ($P < 0.001$). In contrast, a neurologic cause for admission was more frequent in anticipated death patients (32 *vs.* 9%; $P < 0.001$). The type of organ failures differed with hemodynamic and renal failures being more prominent in the unexpected death group (fig. 1).

The numbers of organ failures were unequally distributed between the two groups ($P < 0.001$; fig. 2), with a higher number of organ failures in the anticipated death group (1 [1 to 3] *vs.* 1 [1 to 2]; $P = 0.003$). A higher number of organ supports was provided to unexpected death patients (2 [2 to 3] *vs.* 1 [1 to 2]; $P < 0.001$). The provision of organ support was greater in the unexpected death patient group (fig. 3).

In anticipated death patients, a formalized procedure of withdrawal or withholding of treatments was recorded in 326 (69%) patients. In the unexpected death group, an increase in intensity of therapy was noted in 191 (85%) patients, including catecholamine infusion (181 [80%]), mechanical ventilation (148 [66%]), antibiotics (92 [41%]), blood transfusion (59 [26%]), and renal replacement therapy (54 [24%]). Major adverse events occurred in 141 (63%) patients (table 2).

## Discussion

This multicenter prospective study reports the characteristics of patients dying in French ICUs. To our knowledge, this is the first study examining the cause, timing, and characteristics of death of critically ill patients admitted to intensive care.

Our approach differs from previous analyses investigating risk factors of death in general or selected ICU populations.[1,7,8] Only a few of the demographic characteristics, such as age, sex ratio, and percentage of patients with sepsis, are similar to those reported in large cohort studies.[1,7,9] As expected, illness severity scores and the need for organ support were high. Thus, the majority of patients presented with at least one organ failure at the time of death. This result is consistent with studies showing an association between organ failure and outcome.[2,7]

Our study reports an apparent discrepancy between the percentages of organ failure and corresponding organ support. It is important to note the absence of a linear relationship between failed and supported organs for all systems. For example, neurologic and hematologic failures do not result in a specific support. Conversely, mechanical ventilation is provided not only for respiratory reasons but also for unstable and comatose patients. Thus, 31% of the population of the study presented respiratory failure (SOFA subscore greater than 2), whereas 90% of them received mechanical ventilation. Similar results were reported in septic and cardiac arrest patients.[10,11]

Our second finding reveals the different profiles of patients with anticipated and unexpected death. Thus, the SOFA score was higher in unexpected death patients, but in contrast, the number of organ failures was higher among anticipated death patients. Although these results appear somewhat conflicting, the SOFA score was collected at

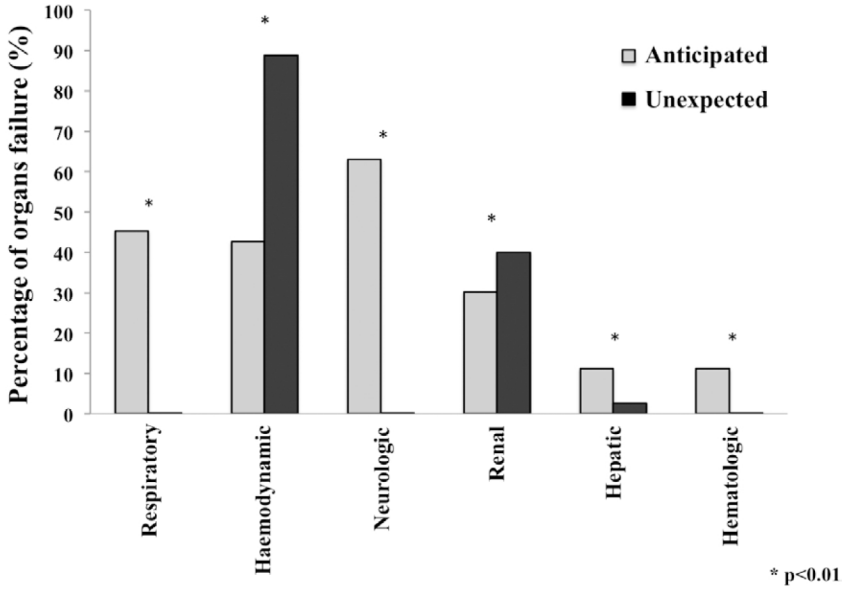


**Fig. 1.** Types of organ failures in anticipated and unexpected death groups. *$P < 0.01$ for comparisons between anticipated and unexpected death groups.

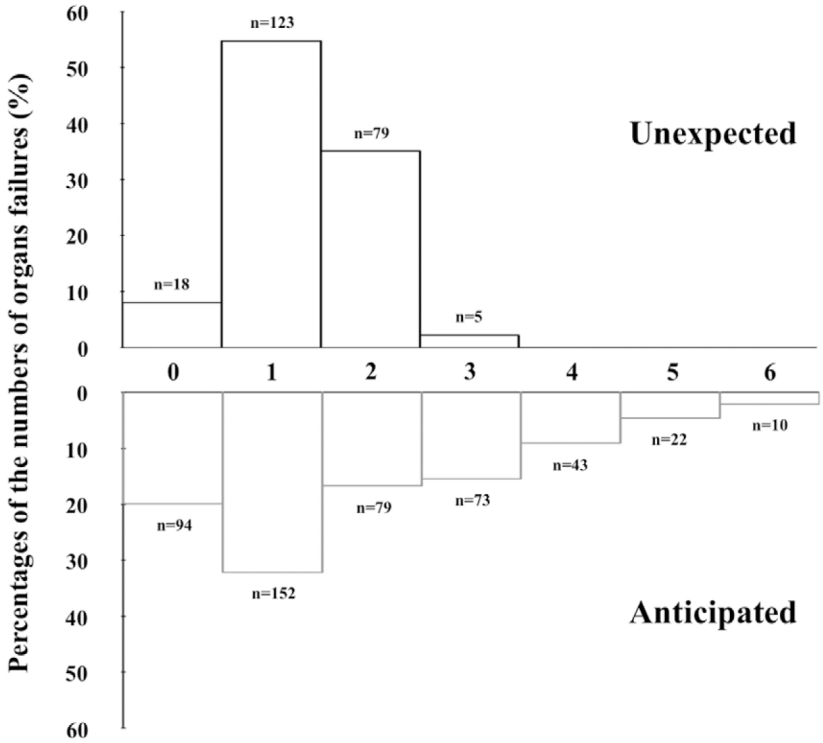


**Fig. 2.** Numbers of organ failures per patient in the unexpected and anticipated death groups (*horizontal axis*) and percentage of organ failures in the two groups (*vertical axis*). In the unexpected death group (*upper part of the graph*), most of the patients presented with one or two organ failures. In the anticipated death group (*lower part of the graph*), the proportions of organ failures per patient showed a homogenous distribution between zero and six organ failures. The sum of all the percentages is 100% in the unexpected and anticipated groups.

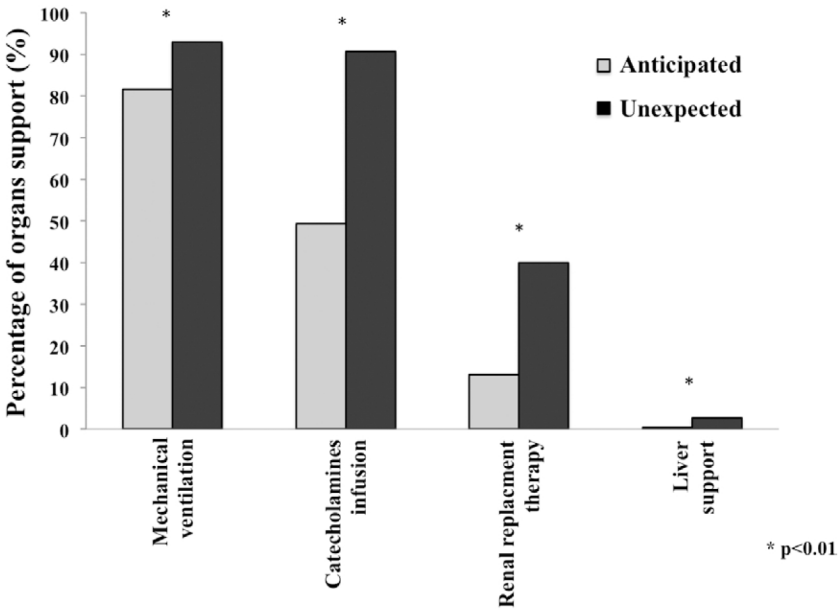


**Fig. 3.** Organ supports given to the anticipated and unexpected death groups at the time of death. *$P < 0.01$ for comparisons between anticipated and unexpected death groups.

ICU admission and the organ failures on the day of death. Between these two moments, the clinical course of the disease may have led to a development or a worsening of multiorgan failure, especially in the anticipated death patients. Second, the SOFA score may, to some extent, provide an imprecise reflection of actual illness severity. For instance, a cardiovascular subscore of 4 can be obtained in a patient receiving either 0.2 or 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ norepinephrine. A

**Table 2.** Major Adverse Events Reported in the 48 h before Death in Patients Having Unexpected Deaths

| Type of Adverse Events | No. of Patients (%) Total: 161 (63) |
|---|---|
| Hypotension | 97 (43) |
| Cardiac arrest | 46 (20) |
| Desaturation | 44 (20) |
| Reoperation | 16 (7) |
| Severe hypoglycemia | 13 (6) |
| Complications of diagnostic and treatment procedures | 11 (5) |
| Reintubation | 3 (1) |
| Drug-related adverse effect | 3 (1) |
| ICU readmission | 1 (0) |
| Unplanned extubation | 0 (0) |

The total of events is greater than 100% as several events occurred in some patients.

ICU = intensive care unit.

recent study showed that the mortality rate varied according to norepinephrine dose, being less than 40% for norepinephrine less than 0.2 and more than 90% for norepinephrine doses greater than 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[12] Third, the parameter used to assess organ failure in the SOFA score may reflect imperfectly the function of the organs. Thus, bilirubin level is used to assess hepatic function, whereas coagulopathy is not taken into account in the score.

Contrary to our unselected cohort, most previous studies focused on subgroup populations. In trauma patients, a triphasic mode of death was reported: hemorrhage in the first hours, brain injury in the first days, and multiorgan failure or treatment withdrawal in the first weeks.[13] Cardiac arrest patients present a biphasic mode of death: early fatalities are related to an initial state of persisting shock, whereas neurologic injuries lead to the majority of late deaths.[4] By contrast, intractable multiorgan failure explains early deaths in septic[14] and adult respiratory distress syndrome[15] patients. Taken together, these studies underline the interaction between cause and time of death. A recent study showed that early and late survival after ICU admission relied on different determinants.[16] Thus, the acute illness characteristics were responsible for mortality in the 30 days after ICU admission. In contrast, age and comorbid condition determined mainly death occurring after 90 days of ICU admission. In our study, unexpected and anticipated death occurred at different times, days 1 and 5, respectively. Consequently, multiorgan failure exhibited different patterns in the two populations. Hemodynamic failure was the primary cause of early death, whereas neurologic and respiratory failures were prominent in late death. Possibly, a rapid death due to intractable hemodynamic failure may prevent the apparition of multiorgan failure in the unexpected death population. In contrast, a longer time of evolution of the initial insult left enough time for the development of multiorgan failure in the unexpected death patients. Thus, prognosis related to the primary insult outweighs any subsequent nonneurologic organ failures. Neurologic status is probably a critical determinant for withdrawal or withholding of treatment decisions.[17]

The importance of ethical concerns in the ICU practice has increased considerably in recent years. The end-of-life process was reported in different populations including adult, pediatric, neurocritical, and cancer patients.[3,18] Forty-seven percent of our patients died with a formalized procedure in place. In a landmark French article, Ferrand *et al.*[6] reported that half of the deaths occurring in the ICU followed withdrawal of or withholding treatments. A similar figure was reported more recently in a further study.[19] Interestingly, the rates of cancer and sepsis did not differ between the two groups. However, nearly one third of anticipated deaths was not associated with a written report of the multidisciplinary decision to withdraw or withhold treatment, contrary to recommendations and French law.[20]

Our study reinforces the need to differentiate the causes of ICU death, whereas most studies simply provide the overall mortality rate. Indeed, this figure may be similar in the anticipated and unexpected death groups; however, timing, pathophysiologic causes, and other factors may markedly differ.

While offering novel insights, some aspects of our study have to be interpreted with caution. The first limitation is a selection bias. There is possibly a discrepancy between what is reported and what is done in real life. An audit conducted by trained staff in the different units could diminish this potential bias. The second limitation lies in the definition of the modes of death of our population; however, a similar discrimination has been used in a pediatric population.[3] Although the casemix appears to represent a general ICU population, our results cannot be applied to different healthcare settings where withdrawal of treatment is not permitted. Last, our study was not designed to find parameters predicting the type of death. Such factors could be interesting for the communication with relatives. Further studies could meet this objective in the near future.

## Conclusions

In a general ICU population, the majority of patients present with at least one organ failure at the time of death. Anticipated and unexpected deaths represent two different modes of death and exhibit different profiles. Unexpected death occurs early and is mainly associated with hemodynamic and, to a lesser extent, renal failures. Anticipated death intervenes later and presents with more organ failure, of which neurologic dysfunction is prominent. Withdrawal of and withholding treatments account for about half of the deaths in this French ICU cohort.

## Acknowledgment

The authors are grateful to Mervyn Singer, M.D., Ph.D., Bloomsbury Institute of Intensive Care Medicine, Wolfson Institute for Biomedical Research, and Department of Medi-

cine, University College London, London, United Kingdom, for critical review of the manuscript.

## Research Support

Support was provided solely from institutional and/or departmental sources.

## Competing Interests

The authors declare no competing interests.

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