CRITICAL CARE

REVIEW

Clinical review: What is the role for autopsy in the ICU?

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Abstract

The availability of advanced diagnostic tools has grown in the past decades. Hence, a growing false belief exists that everything is known about the patient before death. Moreover, intensivists may wrongly believe that autopsy findings do not contribute to the understanding of pathophysiological events. The immediate result is that few ICUs nowadays assemble enough autopsy cases with new and interesting clinicopathological features. However, we believe that, at least in tertiary ICUs, autopsies remain a valuable examination, as a tool for quality control, as a way of establishing gold standards for diagnostic examinations and as an aid in developing guidelines for treatment and diagnosis of diseases frequently encountered in the ICU. Finally, due to the ever-expanding armamentarium of immunosuppressive agents, a growing list of opportunistic infections is discovered during autopsy. The present article gives an overview of autopsy studies conducted in the ICU and discusses the pros and cons of performing these.

Introduction

During the past decades, autopsy rates have been declining worldwide. The non-forensic, clinical autopsy rate at large hospitals in the United States dropped from 41% in 1964 to 22% in 1975 [1]. In spite of this decline, the post-mortem examination remains clinically relevant for time-honoured reasons: the information obtained helps to understand diseases; it provides essential feedback for the clinician and leads to quality assessment and education; and data from it are important for epidemiologists [2].

We analyzed reports that compare post-mortem cause of death with clinical diagnosis. The discrepancies between these two were classified into four categories according to Goldman's criteria (Table 1) [3]. This article has the goal of convincing intensivists of the role of autopsy and gives an overview of the studies performed in the ICU.

Reasons for the decline in autopsy rate

Costs

The costs for post-mortem analysis cannot be charged to family members since autopsy findings are irrelevant for the management of their relative. Hospital administrators are not easily convinced to spend money on procedures lacking an immediate impact on patient management and just for teaching purposes [4,5]. In Belgium, the cost of an autopsy is estimated at 473 euros and is carried by the social security system. In London, the cost of one autopsy is 850 euros when the costs for building a mortuary are taken into account.

Judicial factors

In the US, some authors claim that the most important factor explaining the decrease in the autopsy rate is that a minimum number of autopsies is no longer needed for accreditation by the Joint Commission on Accreditation of Hospitals. Some clinicians also seem to be more reluctant to seek consent out of fear of litigation since autopsy can reveal missed diagnoses [4].

Communication with patients' relatives

Because of the growing impact of the opinions of patients and their relatives, physicians are often forced to discuss necropsy with them. As a result, the autopsy rate in France has markedly declined after 1994 (from 15% to 3%), the year that bioethics law impelled physicians to inform relatives about the performance of a post-mortem examination [6]. However, it is not clear what the attitude of relatives is. In a Swedish study, 84% reported accepting an autopsy for themselves and 80% for a next of kin [7]. In a study performed in a surgical ICU, relatives refused 2 of 27 autopsy requests. Nevertheless, the autopsy rate was only 25% [8]. This demonstrates that the low autopsy rate reflects a low autopsy request rate on the part of clinicians more than refusal by relatives.

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Table 1. Classification of discrepancies between pre- and post-mortem diagnoses (according to Goldman and colleagues [3])

Major: important underlying conditions and all primary causes of death
Class I: may have altered therapy or survival
Class II: would not have altered therapy or survival
Minor: unknown preexisting condition not directly related to the cause of death
Class III: would not have altered therapy or survival
Class IV: may have altered therapy or survival
Nondiscrepancy
Class V: complete agreement between clinical and post-mortem diagnosis
Nonclassifiable
Class VI: patients died immediately after admission with no diagnostic procedure or refused any diagnostic procedure. Autopsy was unsatisfactory, with no clear findings and no diagnosis could be established

Autopsies are less likely to be performed when not recommended strongly by the treating physician. In one study based on physician and surrogate responses, the expected autopsy rate was 42%, while the actual autopsy rate was 23% [9]. Training physicians how to recommend autopsies may increase autopsy rates.

Reluctance of pathologists

Another reason for the decline in autopsy rates is the growing reluctance of pathologists to perform autopsies. Several studies analyzing the delay of pathology reports show a long delay (up to 90 days) [6]. This indicates a lack of interest in autopsy findings, both from pathologists and clinicians. The reasons for this are many. First, pathologists are experiencing an increasing workload. Secondly, since infectious diseases are rising, pathologists fear the risk of infection [10]. Finally, autopsies now contribute little to the scientific output of the pathology department, with only 6% of the published articles being based on autopsy findings [6].

Modern technology

It can be argued that the sensitivity of modern diagnostic methods would reduce diagnostic errors to an extent that autopsies would be unnecessary. However, this reasoning was not confirmed by a study by Goldman and colleagues [3], who studied the time course of diagnostic errors during the 1960s, 1970s and 1980s and found no differences among the three periods: in all three eras about 10% of the autopsies revealed a class I missed diagnosis (Table 1).

Analyses of diagnostic error rates, adjusted for case mix, country and autopsy rate, yielded stable figures for major missed diagnoses throughout the past three decades [11]. A possible explanation for the stability of the error rates is increased case selection by clinicians. Since fewer autopsies are performed, clinically challenging cases may be more likely to be selected for autopsy. However, several prospective studies performed in the 1960s, 1970s and 1980s have shown that clinicians have a poor ability to identify cases that will yield 'diagnostic surprises' [12-14]. A study performed by Cameron and colleagues [15] showed that 15% of main diagnoses were not confirmed by autopsy in cases where physicians said they would have requested an autopsy. The rate was similar at 14% in cases where physicians said they would not have requested an autopsy.

The lack of a decrease in the proportion of missed diagnoses during the past decades does not indicate a lack of progress in medical science since the types of missed diagnoses varied in the different eras [16]. Rather, it suggests that our clinical and technical investigations are less sensitive for new disease entities.

Why do autopsies still play an important role in the ICU?

Autopsies can be used to check the accuracy of existing diagnostic tools

The imperfect correlation between pre- and post-mortem findings illustrates that existing diagnostic tools do not always provide 100% certainty about the existence of a specific disease entity [5]. Autopsies yield important information on the rates of discrepancies between clinical diagnosis and histology. A few studies investigating this have been performed in the ICU. Combes and colleagues [17] performed the largest, prospective study, corroborating the results of other studies performed in the ICU; namely, that the overall type I error rate averages 10%. A study performed by Roosen and colleagues [18] with an autopsy rate of 93% revealed that fungal infection, cardiac tamponade, abdominal haemorrhage, and myocardial infarction are the diagnoses most frequently missed in a medical ICU.

Autopsies allow the accuracy of existing diagnostic tools to be checked. One example may clarify this matter. The role of *Candida* spp. in the airways of critically ill patients was examined in a prospective, controlled autopsy study performed in our medical ICU [19]. A

survey by Azoulay and colleagues [20] demonstrated that 24% of French intensivists treat *Candida* spp. when found in the airways of mechanically ventilated patients. However, we did not find *Candida* pneumonia at autopsy despite the frequent pre-mortem occurrence of *Candida* spp. in the respiratory tract of critically ill patients. This finding argues against the use of expensive antifungal treatment in mechanically ventilated patients solely on the basis of isolation of *Candida* spp. from tracheal aspirates and broncho-alveolar lavage fluid. Recent published guidelines of the Infectious Diseases Society of America on the treatment of invasive candidiasis in intensive care reinforce this [21].

Autopsies are useful for understanding pathophysiology

There are several examples of the value of autopsy in elucidating pathophysiological mechanisms of disease in the ICU. Extensive observational data have shown a consistent, almost linear relationship between blood glucose levels in hospitalized patients and adverse clinical outcomes, even in patients without established diabetes [22]. It has never been entirely clear, however, whether glycaemia serves as a mediator of adverse outcomes or merely as a marker of illness. Several early studies suggested a clinical benefit from strict glucose control during critical illness [23]. Recently, a large multicentre study called into question the beneficial findings of tight glycaemic control [24]. Autopsy might be of help in elucidating the potential toxic effects of hyperglycaemia on various organs. Vanhorebeek and colleagues [25] used post-mortem liver samples from the original Leuven study [23] and showed that mitochondrial function in hepatocytes was retained in patients with tight glycaemic control compared to the patients in the conventional treatment group. There was, however, no differential effect on mitochondrial function of myocytes. This autopsy report could encourage clinicians to perform histological and molecular studies in order to clarify the mechanisms of glucose toxicity and to what extent tight glycaemic control should be achieved.

Autopsies are useful in understanding epidemiology and describing new disease entities

An illustrative example of the value of autopsy in explaining certain epidemiological and pathophysiological features of new disease entities is the description of pathology specimens from patients dying of confirmed 2009 influenza A H1N1 infection. Autopsy studies have shown that the main pathological changes associated with 2009 influenza A H1N1 infection are located in the lungs, identifying three distinct histological patterns. Ongoing aberrant immune responses in lung specimens could be identified in patients dying of 2009 influenza A H1N1 infection [26]. Also, concurrent bacterial infection was found in autopsy specimens of 22 of 77 (29%) patients, including 10 *Streptococcus pneumoniae* infections. These autopsy findings underscore both the importance of pneumococcal vaccination for persons at increased risk for pneumococcal pneumonia and the need for early recognition of bacterial pneumonia in persons with influenza [27].

Autopsies continue to serve as an invaluable educational tool

Due to the ever-expanding armamentarium of immunosuppressant and immunomodulating drugs, there is a growing list of potentially lethal and difficult to diagnose opportunistic infections. Patients with these uncommon infections often present in an advanced state of their disease, the conditions of which are often discovered only post-mortem. The autopsy has an educational role in describing the histological features of these advanced disease states and their complications.

Moreover, the autopsy can be an integral part of the safety analysis of new drugs. Due to detailed brain autopsies, natalizumab, a novel antibody directed to the adhesion molecule α_4 integrin, was identified as a risk factor for development of progressive multifocal leukoencephalopathy in patients with Crohn's disease or multiple sclerosis treated with this drug [28].

Shojania and colleagues [11] studied the effect of increasing autopsy rate on the incidence of major diagnostic errors. They found that major errors decreased at a rate of 12.4% for every 10% increase in autopsy rate, and class I errors decreased at a rate of 17.4% for every 10% increase in autopsy rate. This points to the important educational value of post-mortem examination and we believe that the decreasing autopsy rate is contrary to progress in medical diagnostics. We think that medical students should follow at least some autopsies to underline the importance of the necropsy.

However, it needs to be stressed that the procedure needs to be done according to certain criteria and ideally attended by the intensivist that took care of the patient. The autopsy has always been a valid monitor of clinical diagnostic performance if it meets four necessary conditions, according to Saracci [29]: a high necropsy rate (28 to 50%); specified and stable conditions under which necropsies are performed; calculation of sensitivity and specificity rather than overall accuracy; and an estimate of the error in post-mortem diagnoses. Durning and Cation [30] showed that autopsy cases were frequently evaluated as a valuable educational experience by attending physicians.

New, innovative techniques might improve the diagnostic yield of autopsies

A very intriguing field of interest is molecular investigations at autopsy. Even with normal structural findings,

Table 2. Strategies to improve autopsy rate

Efforts by the pathological department
Coordinate autopsies with the schedules of requesting physicians
Faster processing of the autopsy reports
Provision of resources for performing autopsies
Creation of regional autopsy centres
Provides opportunities to improve autopsy quality
Develops strategies for using autopsy results to improve clinical performance
Improvement of training for pathology residents
Better education of medical students
Quality control of performed autopsies (different pathologists interpreting the same autopsy specimens) in order to improve diagnostic value
Provide opportunities to improve autopsy quality by specialization
Efforts by physicians
Allow physicians complete discretion in requesting autopsies (arbitrary sampling as a result will augment the numbers of important misdiagnoses)
Analyse data from regional centres to identify patterns of missed diagnoses and to generate prediction rules that would enhance the process of case selection
Augment autopsy numbers with widespread use of structured death reviews and structured reports of epidemiological statistics on various diseases encountered in the ICU
Communicate the conclusion of the autopsy report to the relatives
Efforts by both departments
Clinicopathological conferences on a monthly basis attended by the treating intensivist, the radiologist and the pathologist
Interesting cases should be published with the aim of education and improving knowledge of epidemiology

molecular analysis of frozen sections can ultimately resolve 'unsolved' cases of sudden death. Ackerman and colleagues [31] report the results of post-mortem molecular testing and the identification of a novel mutation in a young woman who died in the ICU after a near-drowning secondary to what turned out to be a form of congenital long-QT syndrome. Because of this molecular finding at autopsy, an asymptomatic sibling carrying the same mutation was able to receive prophylactic treatment. For sudden cardiac deaths the protocols for autopsy recommend freezing a piece of spleen for molecular analysis.

Autopsies might protect physicians from subsequent malpractice litigation

Among intensivists, the mistaken belief that sophisticated diagnostic tests have rendered the autopsy obsolete combined with reluctance to ask bereaved families to consent to autopsy has substantially reduced interest in the procedure. Moreover, there is a misperception that autopsies increase physicians' exposure to malpractice claims. Educational efforts should overcome these barriers (Table 2) [32]. There must be more attempts to coordinate autopsies with the schedules of requesting physicians.

Clinicopathological conferences should take place on a regular (for example, monthly) basis. This means a joint effort of both intensivists and pathologists. The clinicians need to inform the pathologist about the patient's pre-mortem status, the expected findings and the unsolved questions. The pathologist needs to understand the importance of the results of autopsy in medical development. Autopsies can lead to an increased awareness for rare and emerging diseases and eventually result in better daily clinical practice.

Information for relatives

The information gained by autopsy findings can help relatives to understand the cause of death of their loved ones. Sadly enough, autopsy results are often not communicated to them. In a study performed by Burton and colleagues [9], 78% of relatives reported that autopsy results were not discussed.

Overview of recent studies performed in the ICU

Table 3 lists clinical autopsy studies in the ICU setting. The amount of major missed diagnoses of class I varied between 3 and 16%. There was no significant difference in the type of hospital (referral or general district hospital) or the type of unit (surgical, medical or mixed). Most of the studies were retrospective in design, except for the study by Combes and colleagues [17]. They prospectively analyzed autopsies performed on patients who died in a tertiary care medical-surgical ICU during 3 years. Monthly clinical-pathological meetings were held to compare clinical and autopsy diagnoses. During the study, 1,492 patients were admitted, of whom 315 (21%) died during

Table 3. Overview of recently performed autopsy studies in the ICU setting

Author	Period	Studied population	Type of hospital*	Study design	Autopsy rate (%)	Number of autopsies	Major error† (%)	Class I error (%)
Roosen *et al.* [18]	1996	Medical	Referral, Belgium	Retrospective	93	100	36	16
Combes *et al.* [17]	11/1995 to 10/1998	Mixed	Referral, France	Prospective	53	167	31.7	10.2
Dimopoulos *et al.* [41]	1999	Mixed	Referral, Belgium	Retrospective	45	222	8.5	5.4
Maris *et al.* [42]	1/2004 to 12/2005	Mixed	Referral, Belgium	Retrospective	37	289	19	6
Nadrous *et al.* [33]	1/1998 to 12/2000	Mixed	Referral, USA	Retrospective	33	455	21	4
Tai *et al.* [16]	1/1994 to 12/1995	Medical	Referral, USA	Retrospective	22	91	19.78	8.79
Mort *et al.* [43]	7/1986 to 7/1992	Surgical	Referral, USA	Retrospective	29	149	23	9.5
Podbregar *et al.* [44]	1/1998 to 12/1999	Medical	Referral, Slovenia	Retrospective	46	126	52.4	12
Twigg *et al.* [45]	6/1996 to 5/1999	Mixed	District, UK	Retrospective	40	97	23.71	4.12
Silfvast *et al.* [37]	1/1996 to 12/2000	Mixed	Referral, Finland	Retrospective	89	346	5	2.3
Fernandez-Segoviano *et al.* [46]	5/1983 to 12/1985	Mixed	Referral, Spain	Prospective	51	100	22	7
Pastores *et al.* [34]	1/1999 to 9/2005	Oncologic	Referral, USA	Retrospective	13	86	26	17
Ong *et al.* [47]	1/1997 to 12/1998	Trauma and burns	Referral, USA	Retrospective	97	153	18.95	3
Al-Saidi *et al.* [48]	11/1994 to 6/1999	Bone marrow transplant	Referral, Canada	Retrospective	47	28	10.7	3.6
Gerain *et al.* [36]	11/1985 to 10/1986	Oncologic	Referral, Belgium	Retrospective	69	34	59	Unknown

*Referral: a hospital that is linked to a university, deals with general admissions and with referrals from other hospitals. †Major error: class I or II according to Goldman's criteria of missed diagnoses [3].

their ICU stay and 167 (53%) were autopsied. Clinicians most frequently erroneously overdiagnosed cancer, endocarditis, myocardial infarction and pneumonia. The intensivist missed 171 diagnoses.

In all studies, infections were most frequently missed. Medical development has led to new treatments, such as new cytotoxic agents, and organ and stem cell transplantation, which have led to an increased number of viral and fungal infections with unusual clinical presentations [3,16,33-35]. In a study performed at our medical ICU, fungal infections occurred in 16% of deceased patients. In 30% of all cases, the diagnosis was not considered premortem [18]. Veress and Alufuzoff [2] found a significant increase in infectious diseases in autopsy patients, from 27% in the 1970s to 32% in the 1980s, and an increase in undiagnosed infections of 30%. Gerain and colleagues [36] studied the causes of death in oncology patients who died in an ICU. In 23.5% of all deaths the primary cause was infectious disease, with fungal disease in 87.5%. Cancer itself was the direct cause of death in only 10%. Silfvast and colleagues [37] showed that 62% of class I diagnostic errors were found in patients with pneumonia or other already known infections. This finding emphasises the difficulty of diagnosing unexpected or new pathogens in patients with existing infections.

Pulmonary embolism remains one of the major missed diagnoses throughout the past three decades (8.9%) [38]. In autopsied patients who died from pulmonary embolism, the diagnosis was unsuspected in 14 of 20 (70%). Most of these patients had advanced associated disease [38]. As Goldman postulates, the persistent high rate of missed pulmonary embolism is more a reflection of the high mortality of the pathology when this diagnosis is missed [35]. The availability of new diagnostic techniques can also give misleading information. The frequency of a false-positive diagnosis of pulmonary embolism (when the clinician ascribed the death to pulmonary embolism not confirmed at autopsy) rose from 33% in 1959 to 44% in 1999/2000 [39].

Intra-abdominal and retroperitoneal bleeding and more general acute abdominal complications are underdiagnosed in the ICU. Altered mental status, narcotic medication, immunosuppression and mechanical ventilation make the bedside diagnosis difficult. Angiography or computed tomography are often not an option in these unstable patients and bedside ultrasound is frequently inconclusive. Papadakis and colleagues [40] studied the diagnostic discrepancy in veteran soldiers receiving mechanical ventilation. Thirty-nine percent of the class I errors were potentially treatable abdominal disorders. In two-thirds, the errors arose because clinicians failed to consider the diagnosis, and not because the clinicians had misleading or inconclusive information from diagnostic procedures.

Conclusion

Over the past decades, autopsy rates have been declining and studies on autopsy findings are scarce. We are

convinced that the performance of necropsy is necessary for many reasons. First, studies have shown that despite technical improvements, the frequency of missed disorders has not diminished compared to the 1960s and 1970s. The reason is the advent of several new pathologies with more opportunistic infections in an era of HIV and influenza A H1N1 pandemics, new immunosuppressive treatments for transplant recipients and auto-immune diseases. Second, we argue that the post-mortem examination can be useful for relatives, especially if the cause of death is not clear. We regret the fact that autopsy results are often not reported to the relatives. Moreover, clinicians and pathologists do not communicate well with each other. Input from the clinician can motivate the pathologist to find new, rare or unsuspected diseases.

The costs of post-mortem examination are negligible compared to the overall costs of ICU stay. Since the results may improve our daily practice, we should not consider the costs as a reason to forestall autopsies.

We ask that the importance of post-mortem examinations be reconsidered, since autopsy remains the ultimate tool of accountability for clinical evaluation and management of new and old diseases.

Competing interests
WM reports receiving a grant from Pfizer for investigational research in fungal diseases.

Authors' contributions
GDeV, EM and WM contributed equally in developing the design and concept of the article. GDeV and EM wrote the article and WM critically reviewed the article and made some changes. The authors have no financial interest in this article.

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