Intensive Care Med (2023) 49:226–229
https://doi.org/10.1007/s00134-022-06917-5

WHAT'S NEW IN INTENSIVE CARE

Close collaboration between pathologists and intensivists to understand (not just) coronavirus disease

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Struggling with an unknown entity—challenge for intensivists

Despite improvements in imaging and diagnostic procedures in critically ill patients presenting with organ failure, uncertainty often exists with regard to the exact diagnosis and a corresponding targeted therapy. Recent studies have demonstrated an error rate of up to 44% in diagnosis after autopsy [1]. The novel coronavirus disease 2019 (COVID-19)—especially the associated severe acute respiratory syndrome—led to a rush of critically ill patients to intensive care units, which were neither prepared in terms of staff and logistic demands nor in terms of specific knowledge of such a new disease.

After a period of uncertainty and overload, more clinical insights into the 'nature' of the COVID-19 were revealed by autopsies. Assisted by pathologists, intensivists learnt to transfer such knowledge into therapeutic improvement. Specifically, the frequency of deep venous thrombosis or pulmonary embolism led to the adoption of an anticoagulation strategy. Autopsies, histopathological analyses, molecular findings, results of immunohistochemistry, and ultrastructural analyses had a direct impact, and, consequently, the pandemic started a new effective interdisciplinary collaboration, which should continue even beyond the pandemic.

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Lightening pathophysiological shadows—crucial demand for clinical autopsies

Autopsy allows transparency by sharing [2] its results, and is crucial for risk mapping, root cause analysis, and identification of adverse events, even if some changes seen in autopsies may be post-mortem effects. Although their practice is decreasing, autopsies can have a significant impact on the quality of healthcare and its cost containment [3]. However, autopsy practice has been too easily relegated to the mere ascertainment for the sole purpose of diagnostic confirmation or matters of justice [4]. What has been overlooked, then, is how pathological changes can impact diagnostic procedures and the efficacy of therapies [5]. Therefore, autopsies play a fundamental role in understanding the pathophysiological mechanisms of diseases and potential therapeutic approaches [6].

An important and instructive example comes from the German experience with the recent pandemic, with the creation of the German Research Network for Autopsies in Pandemics (DEFEAT PANDEMIcs). This network is highly organized at a national level to collect and share data, materials, and results as quickly as possible. Tissue sampling is followed by a diagnostic pathway using an extensive armamentarium of modern technologies. These include ribonucleic acid (RNA) sequencing, in situ hybridization, viral genome sequencing, RNA and proteome-wide gene expression analysis, innovative tissue imaging, and 3D reconstruction [7].

Today, the evidence regarding the thrombo-inflammatory mechanism underlying COVID-19, the diffuse alveolar damage, and the exuberant immune reaction characterized by cytokine production, known as the 'cytokine storm', is the result of observations and answers

to specific questions asked by the clinician to the pathologist [8], which was not immediately possible when COVID-19 spread. However, the performance of clinical and forensic autopsies has revealed important aspects of the disease, clarifying morphological and virological features and promoting unexplored therapeutic approaches and new research frontiers [9].

Nevertheless, post-mortem investigation rates remain so low worldwide that the term 'science blockade' has been used to define the general reluctance towards autopsies. Each country has chosen to respond to this emergency situation with its own decisions. Countries such as Italy have chosen not to perform hospital autopsies, whereas countries like Germany—after initial procrastination—have mandated autopsies for all patients who died with a diagnosis of COVID-19 with a nationwide autopsy register [10]. Tissue collection during autopsy represents an invaluable source for research aimed at better defining controversial aspects of SARS-CoV-2 virulence and influencing potential new therapeutic strategies, even in COVID-19 survivors [11].

Recent studies investigate genetic susceptibility to COVID-19 and the prognostic value of specific loci. For example, the molecular biology of primary lung tissue is essential to undertstand the determinants of mortality in order to develop new precision therapies and to monitor the prognosis of the disease. Whole-transcriptome sequencing of autopsy lung tissue is critical to identify characteristic changes in the host transcriptome and unique microbial diversity in lung parenchyma of patients with severe COVID-19 [12].

As per acute distress respiratory syndrome (ARDS), validation of the vascular phenotype in the different causes represents an opportunity for vessel-targeted therapies, including promising ones like the trial of ANGPT1 supplementation in COVID-19 patients [13]. The study of cellular and molecular mechanisms underlying ineffective alveolar regeneration in ARDS and fibrosis may lead to new therapies to promote physiological regeneration, thereby accelerating restoration of barrier integrity, oedema resolution, ventilatory clearance, and survival in ARDS and prevention of fibrosis in fibroproliferative ARDS and idiopathic lung fibrosis [14]. Histopathological studies from deceased patients with ARDS caused by SARS-CoV-2 help us understand the thrombotic pathophenotype of SARS-CoV-2. ARDS is associated with increased expression of N9P in the pulmonary endothelium and colocalization of N9P-fibrin in the lumen of pulmonary arteries [15]. Furthermore, an association between N9P expression in the pulmonary endothelium and ventilatory ratio was observed, suggesting that a clinically relevant correlation with histopathophenotypic data linking pulmonary vascular endothelial dysfunction to dead space fraction and a novel pathway by which NEDD9 may regulate pulmonary microthrombosis has been described: the formation of a protein complex with the β3 subunit of αvβ3-integrin [16].

Formalizing interdisciplinary exchange—roadmap to optimize outcome in critical ill patients

Certainly, clinical–diagnostic sharing must be extended to biopsy procedures and fine-needle aspirates (FNA)—if appropriate, together with radiologists—with Rapid On-Site Assessment (ROSA) and immediate provisional diagnosis. This collaborative experience should also implement communication with patients and families in order to share diagnostic–therapeutic paths and to develop a consensus aimed at performing autopsies even when there are religious reasons against it, by offering valid alternative autopsy techniques [10].

The findings of autopsies regarding SARS-CoV-2 ushered in clinical improvements, and communication between pathologists and intensivists, which promotes a better understanding of the patho-mechanisms and causes of death. Regular clinical-pathological conferences on cases of critically ill patients, either with unknown diagnosis or delayed therapeutic progress, present an ideal platform to determine further diagnostic possibilities, such as immunohistochemical, molecular pathological, or even electron microscopical analyses in biopsies or cytological specimens. Hence, autopsies should be promoted in fatal cases, followed by interdisciplinary discussion and presentation of the pathological findings. Finally, interdisciplinary clinical science involving pathological findings should be promoted. To provide an appropriate platform for such efforts, a comprehensive database, including clinical, image, laboratory, and pathological findings, as also therapeutic strategy, is one lesson learned by coping with the pandemic (Fig. 1). Data and biomaterial collection over time is mandatory, since an autopsy study demonstrated differences in causes of death after long-term treatment of COVID-19 patients in intensive care [16].

In conclusion, our goal is to improve patient outcome by extrapolation from clinic-pathological autopsy studies. It is, therefore, appropriate to state that in the field of a closer collaboration between pathologists and intensivists, *'mors gaudet succurrere vitae'* ('death delights in helping life') [5].

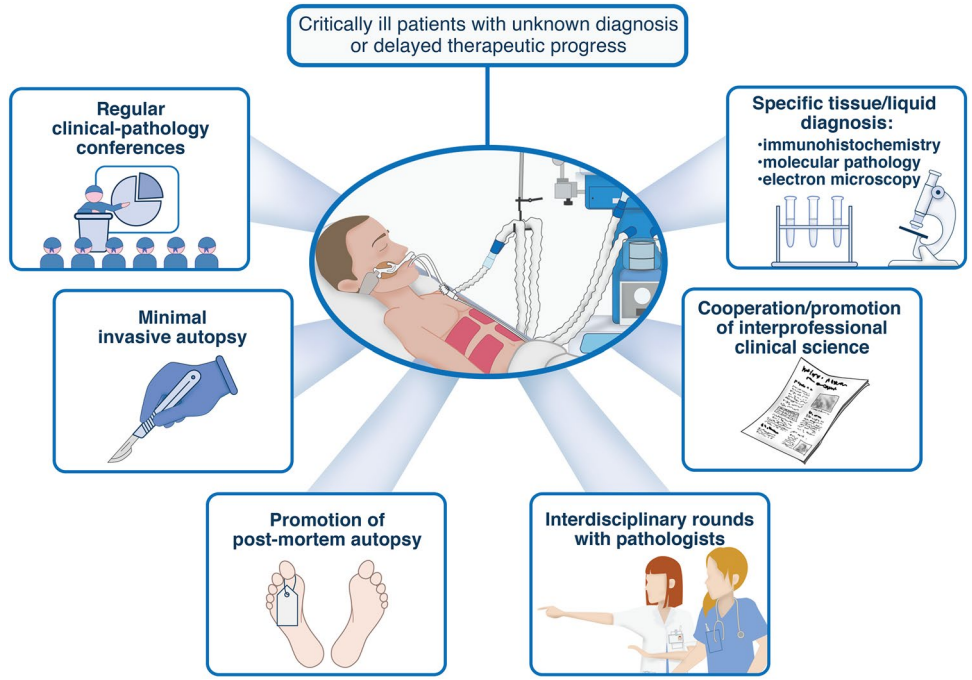

Fig. 1 Pathways for close collaboration between intensivists and pathologists

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Funding
Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflicts of interest
All the authors declare no conflicts of interest.

Publisher's Note

Received: 18 July 2022 Accepted: 13 October 2022
Published: 2 November 2022

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