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REVIEW

Precision medicine in sepsis and septic shock: From omics to clinical tools

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Abstract

Sepsis is a heterogeneous disease with variable clinical course and several clinical phenotypes. As it is associated with an increased risk of death, patients with this condition are candidates for receipt of a very well-structured and protocolized treatment. All patients should receive the fundamental pillars of sepsis management, which are infection control, initial resuscitation, and multiorgan support. However, specific subgroups of patients may benefit from a personalized approach with interventions targeted towards specific pathophysiological mechanisms. Herein, we will review the framework for identifying subpopulations of patients with sepsis, septic shock, and multiorgan dysfunction who may benefit from specific therapies. Some of these approaches are still in the early stages of research, while others are already in routine use in clinical practice, but together will help in the effective generation and safe implementation of precision medicine in sepsis.

Key Words: Sepsis; Septic shock; Organ dysfunction; Precision medicine; Biomarkers; Phenotype; Endotype

Core Tip: Sepsis is a heterogeneous disease with different clinical courses and several clinical phenotypes. Precision medicine in sepsis allows the identification of specific subgroups of patients who may benefit from a personalized approach with interventions targeted towards specific pathophysiological mechanisms.

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INTRODUCTION

Sepsis requires a structured and protocolized treatment, which have been thoroughly reviewed in the literature[1-3]. The last version of the Surviving Sepsis Campaign (SSC) guidelines was released in 2021[4], and the hour-1 bundle was updated in 2018 [5]. The implementation of the SSC recommendations and bundles[6] is associated with a sustained reduction in the risk of death. Still, mortality from sepsis remains unacceptably high[7].

All patients with sepsis are candidates for receipt of the main pillars of sepsis treatment: Infection control, initial resuscitation, and multiorgan support. However, specific subgroups of patients not responding to conventional therapies may benefit from other therapies, which can be considered therapeutic rescue strategies.

Currently, sepsis is defined as organic dysfunction associated with a dysregulated response of the host to infection[8]. The host response is initiated when bacterial endotoxin or other bacterial structures interacting with the host´s immune system stimulate the production of a cascade of immune mediators that activate and target leukocytes, leading to organ dysfunction.

SEPSIS: A HETEROGENEOUS DISEASE

We have to ask ourselves whether all septic patients' clinical courses are predictable. Does dysregulated host response to infection progress and manifest similarly in all patients? The answer is clear and resounding: No. In sepsis, there is significant heterogeneity between individuals. In a certain way, such heterogeneity is foreseen based on

the existing differences in age, causative microorganisms, types of sepsis foci, and comorbidities. Pathophysiologically, there are also significant differences. The inflammatory response occurs in two distinct stages: The pro-inflammatory and the anti-inflammatory phases. These phases vary among individuals and within the same individual, depending on a particular moment within the clinical course. This could explain the observed heterogeneity in responses to available immunomodulating treatments (*e.g.*, corticosteroids, elimination of cytokines, and anti-cytokine antibodies).

Therefore, patients with a low risk for adverse outcomes are candidates to receive conventional treatments. In contrast, patients with a high risk of clinical deterioration could benefit from specific therapies addressing their particular pathophysiological characteristics. This gives rise to so-called 'precision medicine'. This term comes from oncology and described the adaptation of a treatment to each patient's traits based on the genomic study and the molecular characteristics of tumors.

In this narrative review, we explain the different strategies to create and implement precision medicine for sepsis, with the intent of supporting individualization of patients' management (Figure 1). In the first part of this manuscript, we will review the technologies developed to identify endotypes and phenotypes (omics-based biomarkers, bioinformatics, and biomarkers commonly used in the clinic). In the second part of the manuscript, we will describe the different endotypes with their specific potential treatments (*e.g.*, immunoglobulins, endotoxin- and cytokine-hemadsorption, restoration of immunoparalysis) (Table 1). Omics-based biomarkers research is still in the early stages, while other biomarkers are now available and in use in the clinic.

TECHNOLOGIES DEVELOPED TO IDENTIFY ENDOTYPES AND PHENOTYPES

Omics technologies

Novel technologies have been developed in recent years to detect different evolutionary patterns or other patterns in response to different therapies in sepsis. Omics-based biomarkers and bioinformatics can select various endotypes and phenotypes of sepsis patients indistinguishable from the clinical point of view at the bedside. Therefore, they help in the adaptation of specific therapies to patients according to their individual characteristics[9].

Genomics and epigenomics: Genomics is defined as the study of genes and their functions. The different clinical presentations and prognoses of sepsis patients have already been associated with particular genetic variants. A genetic polymorphism is an allelic variant that exists in an unalterable state in a population, with a frequency (generally > 1%) that cannot be accounted for by new mutations. Various polymorphisms have been described in the genes that encode pro-inflammatory and anti-inflammatory cytokines. This is also true for cytokine receptors, cellular recognition pathways, intracellular signaling pathways, and hemostasis molecules. All these pathways are involved in the severity and risk of mortality in sepsis[10].

Epigenomics studies the additional changes that alter gene expression without changing the DNA sequence. These include DNA methylation, non-coding (nc)RNAs, histone variants, and histone post-translational modifications. Epigenetic modifications can respond to environmental stimuli by activating or inhibiting gene transcription. Lorente-Sorolla *et al*[11] showed that sepsis patients undergoing widespread changes in the methylome of their circulating monocytes had associated aberrant levels of interleukin (IL)-10 (IL-10) and IL-6, and a high occurrence of organ dysfunction. Changes in histone modifications, especially histone acetylation, can lead to abnormal expression of IL-10 mRNA[12]. An ncRNA is a functional RNA molecule transcribed from DNA, though not translated into a protein. ncRNAs regulate gene expression at the transcriptional and post-transcriptional levels. The three major classes of short ncRNAs are known as micro (mi)RNAs, short interfering (si)RNAs, and piwi-interacting (pi)RNAs. Plasma levels of miR-133a are higher in critically ill patients with sepsis than in patients with non-infectious inflammation, and predict intensive care unit (ICU) and long-term mortality[13]. Consequently, epigenetic biomarkers could help detect patients with clinical deterioration and unfavorable evolution[11-14].

Table 1 Clinical applicability of precision medicine strategies

Precision medicine strategy	Target (s)	Clinical application
Genomics and epigenomics	Genetic variants	Prognosis, severity
	Genotypes	Susceptibility to sepsis
Transcriptomics	Gene expression profiles, activity and regulation	Susceptibility to sepsis
	Sepsis response signatures	Severity, prognosis
Metabolomics	Small molecules produced by cells	Prognosis
	Metabolomic profile	Response to treatment
Proteomics	Proteins expressed by the genome under certain conditions	Diagnosis, Prognosis
	Biomarkers	Diagnosis, prognosis
Bioinformatics	Machine learning techniques	Diagnosis
		Prediction of clinical trajectories
		Assessment and treatment of organ dysfunction
		Clinical phenotypes
Biomarkers	Levels of molecules (mostly inflammatory)	Phenotypes
		Antimicrobial stewardship
		Prediction of organ dysfuntion
		Allocation of hospital resources
		Diagnosis
		Severity
Immunoglobulins	Immunoglobulin levels	Detection and treatment of sepsis-associated hypogammaglobulinemia
Endotoxin and hemoadsoption	Endotoxin levels and elimination by hemoadsoption	Rescue therapy
Cytokines and hemoadsoption	Cytokine levels and elimination by hemoadsoption	Rescue therapy
Immunoparalysis	mHLA-DR expression	Immunoparalysis detection
		Immunoadjuvant treatment
		Stratification of patients
		GM-CSF therapy

GM-CSF: Granulocyte-macrophage colony-stimulating factor.

Individualized treatment based on the genetic characteristics of the host has not yet been implemented in clinical practice, even though it is undoubtedly one of the most promising research fields for the future management of patients with sepsis and septic shock.

Transcriptomics: The transcriptome is the set of messenger RNAs and ncRNA molecules in a specific cell or tissue. Transcriptomics is the study of the transcriptome of one particular cell or tissue in a specific circumstance, based on the analysis of gene expression profiles. It aims at monitoring gene activity and regulation. Transcriptomic studies have made possible the characterization of different gene expression profiles in sepsis.

Interindividual transcriptome variation in sepsis has been evaluated in several large cohorts. Maslove *et al*[15] identified two subtypes in septic patients. The subtype 1 gene expression profile is characterized by a significantly increased expression of genes involved in inflammatory and Toll-like receptor (TLR)-mediated signaling pathways. This profile is associated with a higher prevalence of sepsis. Davenport *et al* [16] analyzed peripheral blood leucocyte global gene expression of 265 critically ill

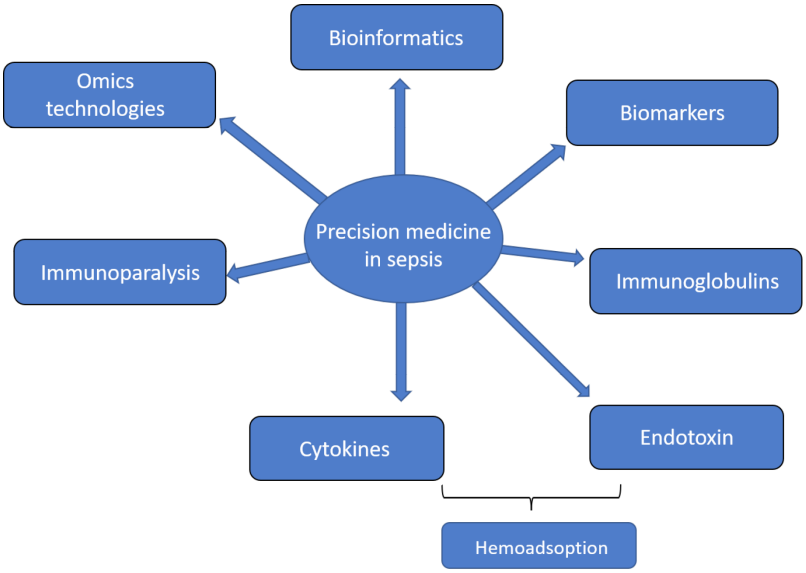

Figure 1 Strategies to create precision medicine in sepsis.

patients with community-acquired pneumonia and organ dysfunction. That transcriptomic study showed two distinct sepsis response signatures: *SRS1* and *SRS2*. *SRS1*, present in 41% of patients, identified patients with an immunosuppression phenotype that included features of endotoxin tolerance, T cell exhaustion, and down-regulation of human leucocyte antigen class II. *SRS1* was associated with higher 14-, 28- and 60-d mortality than *SRS2*. Sweeney *et al*[17] performed an unsupervised clustering analysis on pooled transcriptomic profiles from 14 datasets of sepsis patients (n = 700). The authors described three transcriptomic subtypes based on their functional analysis: the inflammopathic, adaptive, and coagulopathic subtypes. The adaptive subtype was associated with a lower clinical severity and lower mortality rate than the other subtypes. The coagulopathic subtype was associated with higher mortality and occurrence of clinical coagulopathy than either the adaptative or inflammopathic subtypes. Septic shock was more frequent in the inflammopathic subtype. Wong *et al*[18,19] conducted a genome-wide expression profiling using whole blood-derived RNA from 98 children with septic shock, and identified three subclasses of patients, which they designated as A, B, and C. Patients in subclass A were characterized by repression of genes corresponding to adaptive immunity and glucocorticoid receptor signaling. The subclass A patients had higher illness severity and mortality rate than the patients in subclasses B and C.

In the future, transcriptomic studies should help us in the early identification of patients with evolutionary patterns associated with greater severity and mortality, allowing for more personalized treatment.

Metabolomics: Metabolomics is the study of the metabolome, a collection of small molecules produced by cells[20]. This technology has been increasingly used in various investigations, such as the identification of biomarkers, drug activities, or drug-induced toxicity and metabolism. Critical illnesses, such as sepsis, alter the metabolomic profile. Thus, metabolomic studies in sepsis have been aimed at discovering metabolites that discriminate between patients with sepsis and non-infectious systemic inflammatory response syndrome (SIRS), identifying prognostic factors, and recognizing changes in response to treatment[21].

Su *et al*[22] studied a total of 65 patients (35 with sepsis, 15 with SIRS, and 15 healthy subjects). Levels of dimethylisine, 2-phenylacetamide, glyceryl-phosphoryl-ethanolamine, and D-cysteine were associated with the severity of sepsis. In addition, four other metabolites (S-(3-methylbutanoyl)-dihydrolipoamide-E, glycerophosphocholine, and S-succinyl-glutathione) were elevated within 48 h prior to death, indicating their potential use in predicting mortality. Neugenbauer *et al*[23] demonstrated that high levels of putrescine, *lysoPCaC18:0*, and *SM C16: 1* are associated with higher mortality in community-acquired pneumonia and intra-abdominal infections. In a previous study, Mickiewicz *et al*[24] found 20 metabolites significant for discrimination between survivors and non-survivors. The pathways highlighted in this study were related to energy metabolism and branched-chain amino acid processes.

Metabolomic studies have characterized the fundamental role of lysophospholipids, especially lysophosphatidylcholine (LPC), in sepsis prognosis[25-27]. Ferrario *et al*[28] studied the changes in lipid homeostasis that occur during sepsis progression. Plasma samples from 20 patients with septic shock were studied on days 1 and 7 of septic evolution. The authors identified 137 metabolites, many of which were significantly different between survivors and non-survivors. LPC and phosphatidylcholine were found at lower levels in non-survivors than in survivors on day 1 and day 7. Using regression models, the lowest levels of LPC on day 7 were identified as the strongest predictors of mortality. Drobnik *et al*[26] observed that the LPC concentration was markedly reduced in patients with sepsis compared to controls, and a negative correlation between these levels and mortality was found. Instead, Cho *et al*[25] found no association between low LPC levels and severity of the disease in septic patients. They also observed no differences in LPC levels between survivors and non-survivors.

In sum, metabolomics is a tool that allows for predicting the severity and prognosis of sepsis patients. This technology also provides a higher level of biochemical detail and knowledge than other systems biology approaches.

Proteomics: Proteomics is the part of omics that is responsible for the study of the proteome. The proteome comprises the set of all proteins expressed by the genome of a cell, tissue, or organism at a given time and under certain conditions of time and environment[29]. This technology provides an analysis of the expression, location, function, and interaction of proteomes. Compared to other immunological tests, proteomics is a novel method that has the advantage of having high throughput, sensitivity, and specificity. The development of proteomics has provided a means to study cellular processes, such as cell signaling, identifying protein modifications, and the characterization of specific biological markers[30].

For more than a decade, the study of proteomics has been sought to find new biomarkers determining sepsis diagnosis and prognosis. Su *et al*[31] selected 192 proteins in patients with sepsis and septic shock for investigation. Of these, vimentin (a molecule that modulates lymphocyte apoptosis and inflammatory response) increased significantly in patients with sepsis and septic shock compared to controls. The non-survivors had higher vimentin levels in serum, and its expression was increased in lymphocytes in particular. As such, this molecule could be a marker for prognosis prediction in patients with sepsis. In a previous study of 16 critically ill patients, Punyadeera *et al*[32] found that a combination of various proteins [*e.g.*, IL-1α, interferon gamma-induced protein 10 (IP-10), soluble tumor necrosis factor receptor (sTNF-R)2 and soluble cell death receptor (sFAS)] could induce the progression of sepsis to septic shock. Furthermore, a combined measurement of matrix metalloproteinase (MMP)-3, IL-1α, IP-10, soluble IL-2 receptor (sIL-2R), sFas, sTNF-R1, soluble receptor for advanced glycation end products (*i.e.*, sRAGE), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1β, and eotaxin could differentiate survivors from non-survivors. Latour-Pérez *et al*[33] observed that increased levels of activator receptor 1 expressed in myeloid cells (*i.e.*, sTREM-1) throughout the first 3 d of evolution were associated with high mortality in critically ill patients with sepsis. The high initial severity of illness explained this finding. Gibot *et al*[34] found that the progressive decrease in plasma concentrations of sTREM-1 indicated a favorable clinical course during the recovery phase of sepsis and discriminated between survivors and non-survivors. Decoux *et al*[35] analyzed the serum proteome in a group of patients with early sepsis. To cope with the large dynamic range of serum protein samples, the authors performed N-glycosylation, a chemical enrichment of glycopeptides and subsequent differences were found in the serum proteome between survivors and non-survivors. For instance, some modified proteins and glycopeptides belong to common pathways, such as the coagulation cascade and the complement system. The authors also found decreased total neutrophil gelatinase-associated lipocalin (NGAL) and vascular cell adhesion molecule 1 (VCAM-1) levels in non-survivors, two molecules believed to be part of the inflammatory response. Thus, even though VCAM and NGAL increase in sepsis, their study suggested that these increases may be part of a beneficial response necessary for survival, and pointed to the complexity of the regulatory network that is already activated in these patients at an early stage.

Proteomics has also helped to understand the role of proteolysis in sepsis by studying circulating peptides. Bauzá-Martinez *et al*[36] described a higher number of circulating peptides in patients with septic shock than in sepsis patients or non-hospitalized healthy subjects. The peptide count and abundance in septic shock patients were higher in non-survivors than in survivors, suggesting an association between the magnitude of proteolysis and the outcome. The predominant role of serine proteases,

such as chymotrypsin and MMPs, in causing the observed proteolytic degradation was demonstrated.

Ultimately, proteomics helps increase our understanding of the pathophysiology of sepsis and identify new molecules that can predict patients' evolution. This technology also aids in the identification of significant prognostic factors in sepsis patients. Therefore, proteomic approaches are promising for clinical applications and biomarker studies of sepsis.

Bioinformatics

A major trend today in research is improving the accuracy of the diagnosis of sepsis. The definition of sepsis was updated in 2016 and advocated using the quick Sequential Organ Failure Assessment (qSOFA), which assesses blood pressure, respiratory rate, and mental status for sepsis diagnosis[8]. A major criticism by the medical community of this score lies in its low specificity[37]. For this reason, different research teams are trying to enhance this scale through the addition of bedside parameters (*e.g.*, biomarker data), which could improve these diagnostic criteria. Another critical aspect in clinical research is obtaining a set of baseline phenotypes and patient trajectories in the ICU through multivariate analysis techniques, such as principal component analysis, factor analysis, and probabilistic clustering. For instance, a previous study[38] defined the following four different phenotypes for sepsis through consensus k-means clustering: (1) Patients with low vasopressor titration; (2) Patients with chronic conditions and renal dysfunction; (3) Patients with high inflammation and pulmonary dysfunction; and (4) Patients with liver dysfunction and septic shock. Another study [39] defined the following phenotypes predicting ICU outcomes: (1) Patients requiring mechanical ventilation support; (2) Patients with severe organ dysfunction; (3) Patients with high severity scores; and (4) Patients with hepatic dysfunction.

Therefore, improved versions of the qSOFA scale are evaluated in the context of all available data at hospital admission through standard machine learning techniques, such as multivariate logistic regression, relevance vector machines, support vector machines, shallow neural networks or random forests, taking the diagnosis of sepsis confirmed through hemocultures as the main outcome. To predict organ dysfunction before its onset, phenotypes are now being improved by adding different clinical traits and biomarkers that become altered before organ dysfunction is detected at a systemic level. Current initiatives are intended to enhance these phenotypes by applying a generalization of the factor analysis method with Deep Autoencoders to assess the strength of associations between variables and their importance within each patient phenotype.

Deep Reinforcement Learning has also become an important research line for assessing the continuum of organ dysfunction in sepsis. For instance, Raghu *et al*[40] proposed a continuous state-space model for sepsis management in a twist beyond the more traditional development and use of discriminative classifiers.

Other studies have used Bayesian Networks and Random Forests[41] for assessing patient trajectories of septic and septic shock patients in the acute phase. A common trend between these initiatives is that they all pave the way to study patient trajectories in the ICU. Patient trajectory assessment includes studying the prevalence of each phenotype and their impact on other clinical outcomes, such as long-term survival (*e.g.*, 100-d survival rate), vasopressor resistance, and days on organ support [38,39,42].

An accurate assessment of the organ dysfunction continuum is possible with the inclusion of biomarker data (*e.g.*, complement cascade, platelet degranulation, acute inflammation response, negative regulation of endopeptidase activity, and blood coagulation), through the development of comprehensive, interpretable and mathematically rigorous models of knowledge representation through Deep Learning techniques such as Deep Reinforcement Learning and standard machine learning techniques based on graphical models[42]. These techniques will improve diagnosis, trajectory, and long-term survival prediction in sepsis and septic shock. Also, they could set the basis for the personalized treatment of organ dysfunction.

Available biomarkers at clinics

The reliability of clinical assessments in patients with sepsis is often limited, and there is a need to individualize decision-making processes based on objective data. The heterogeneity of patients with sepsis has led to the use of biomarkers for patient stratification according to prognosis and severity of illness, improving phenotyping, intensifying medical therapy in high-risk patients, guiding antimicrobial stewardship, and allocating hospital resources.

Procalcitonin (PCT) is the most widely studied biomarker and is helpful as an adjunctive clinical tool for predicting prognosis and supporting clinical decisions in sepsis[43]. In a previous study of patients with septic shock and high vasopressor requirements, patients who had PCT levels of > 2 ng/mL benefited from receiving adjuvant therapy with hydrocortisone, vitamin C, and thiamine to reduce the progression of organ dysfunction[44]. High initial levels of PCT (> 6 ng/mL) are helpful to predict progressive organ dysfunction and an increased risk of mortality [45]. Thus, this subgroup of patients may be considered for receiving personalized rescue therapies, as conventional treatment may be insufficient to improve prognosis. Interestingly, PCT non-clearance is a predictor of adverse outcomes and treatment failure[46-48]. In a large observational study, the inability to decrease PCT by more than 80% was a significant independent predictor of mortality[49]. This finding may aid in sepsis care, potential suitability of adjuvant treatments, and allocation of resources. Well-designed randomized controlled trials (RCTs) and meta-analyses have shown a mortality benefit when using PCT-guided algorithms for antimicrobial stewardship in sepsis[50-52].

Mid-region fragment of pro-adrenomedullin (MR-proADM) is a biomarker mainly produced by vascular endothelial cells. MR-pro-ADM directly reflects plasma levels of adrenomedullin, a potent vasodilator agent with metabolic and immune-modulating properties. MR-proADM levels increase in sepsis, and high plasma clearance at day 5 has been associated with better outcomes[53]. Furthermore, the role of this biomarker for the early identification of patients at higher risk of organ dysfunction has been recognized. In a recent study, the use of MR-proADM performed better in the prediction of mortality compared to lactate, PCT, C-reactive protein, and SOFA score [54]. Former studies have evaluated MR-proADM to predict ICU admission and the need for urgent treatment[55]. Thus, MR-pro-ADM is found beneficial to guide clinical decisions regarding the use of ICU and hospital resources.

The use of sepsis biomarkers is evolving as one of the most promising developments in precision medicine. Identifying additional reliable biomarkers in sepsis will significantly improve our understanding of this heterogeneous disease and help the medical community refine clinical assessments. Likewise, comprehensive clinical assessments should be the starting point for developing and studying clinically accurate biomarkers in sepsis[56,57].

Recent progress in several biomarker research areas, including the development of point-of-care testing technologies[58], will extend their application for diagnosis, risk stratification, molecular phenotyping, and monitoring therapeutic responses, leading to more personalized medicine at the bedside. Further clinical validation of current biomarkers should be sought in certain patients [*e.g.*, renal dysfunction, receiving continuous renal replacement therapy (*i.e.* CRRT), trauma]. Point-of-care sepsis biomarkers have the potential to be a game-changer as their implementation becomes widely available.

ENDOTYPES AND SPECIFIC POTENTIAL TREATMENTS

Immunoglobulins

The pathogenesis of sepsis is associated with dysregulation of the innate and adaptive immune systems. The adaptive immune system's underlying altered mechanism is the function of antibodies and immunoglobulins (Igs)[59]. Still, the SSC guidelines[4] make a weak recommendation for using Igs as a potential treatment in sepsis patients, given the low certainty of evidence derived from the main studies and a meta-analysis [60,61]. Although the previous studies have not assessed Igs' baseline status as an inclusion criterion, it is reasonable to think that patients with hypogammaglobulinemia could benefit from Ig treatment.

The underlying mechanisms causing decreased levels of Igs in sepsis are not entirely clear. Still, impaired Ig production, vascular leakage secondary to endothelial dysfunction, an imbalance between IgG production and its utilization by the complement system, excessive catabolism, or reduced plasma cell Ig secretion may be involved. Also, patients with sepsis frequently have lymphopenia and quantitative or functional abnormalities within T cell and B cell populations[62].

Several studies have shown higher mortality in sepsis patients with hypogammaglobulinemia. Although the definition of hypogammaglobulinemia is variable, low levels of gammaglobulins can be defined as IgG below 500 mg/dL in individuals older than 5 years or 2 standard deviations below reference values for age[63-67]. Low plasma levels of IgG (hypo-IgG) is the most common deficiency, with a prevalence as

high as 70%[68]. Hypo-IgG is associated with an increased risk of severe illness [higher acute physiology and chronic health evaluation II (*i.e.* APACHE II) score], a greater incidence of acute respiratory distress syndrome, and a longer duration of shock[69], especially on the day of diagnosis and the following 48 h[70]. Also, a synergistic role of IgG, IgM, and IgA in sepsis and septic shock has been described[66,71]. The combined presence of low levels of endogenous IgG, IgM, and IgA in plasma is associated with reduced survival in patients with sepsis or septic shock[72].

Some studies have reported that immunoglobulin formulations containing IgG did not improve mortality rates in patients with sepsis[60]. Conversely, Welte *et al*[73] demonstrated a clinically significant reduction of mortality risk in patients with pneumonia treated with intravenous Ig (IVIg). That study identified a population with a very high risk of mortality, namely patients with high levels of C-reactive protein and PCT, and hypo-IgM.

Polyvalent intravenous Igs represent a promising approach to modulate both the pro-and anti-inflammatory responses[74]. In adults, the use of IgM-enriched IVIg has shown favorable results[60,61,73-79]. IgM-IgA-enriched IVIg preparations are associated with a reduction in mortality[61,73,75,76]. A recent meta-analysis of 19 trials and > 1500 patients showed a significant reduction in mortality when using IgM- and IgA-enriched IVIg compared to human albumin solution or no treatment[80,81]. However, the eligibility criteria for receiving polyvalent IVIg and the best treatment strategy should be well defined[77]. The administration of a single dose of polyclonal gammaglobulin of 1 or 2 g/kg is widely accepted (level of evidence 2C)[82]. Other strategies propose IgM and IgA-enriched polyclonal IVIg dose of 250 mg/kg/d by a 10-h infusion, for 3 consecutive days[83], or an infusion of 42 mg/kg body weight of IgM-enriched polyclonal IVIg once daily for 5 consecutive days[73]. In a retrospective study, 129 adult patients benefited from receiving IgM-IgA enriched IVIg, when the administration was performed within the first 23 h from admission[78].

The routine administration of IVIg in sepsis patients is not recommended, as stated in the 2016 SSC. However, patients with hypogammaglobulinemia could benefit from this treatment. Further studies are needed to clinically validate the most appropriate dose and administration regimen of IVIg in sepsis patients with hypogammaglobulinemia.

Endotoxin hemoadsorption

Endotoxin is a lipopolysaccharide (LPS) present in the outer membrane of Gram-negative bacteria and is one of the best examples of pathogen-associated molecular patterns (*i.e.* PAMPs). Its presence, together with that damage-associated molecular patterns (*i.e.* DAMPs) released by host injured cells, results in the elevation of pro-inflammatory and anti-inflammatory cytokines[84], activating the anti-infectious innate immune response and mediating the clinical syndrome of sepsis. LPS elicits its actions through a transmembrane protein, the TLR4, a type of pattern recognizing receptor expressed on innate immune system cells, in a process in which many important molecules are involved. In this process, the LPS-binding protein (*i.e.* LBP) transports circulating endotoxin and facilitates its recognition by the cell through receptor CD14. CD14 directs the LPS-LBP complex to TLR4, and the accessory protein myeloid differentiation 2 (MD2) associated with TLR4 on the cell surface is involved in the LPS-TLR4 union. Recognition of the LPS-LBP complex by these receptors transduces the endotoxin signal to the cell nucleus, leading to the expression of a complex network of inflammatory mediators. The presence of endotoxin activates changes in the expression of more than 300 genes, leading to the activation of macrophages, endothelial cells, neutrophils, and the coagulation cascade. It also triggers the release of a complex cascade of host-derived inflammatory mediators[85,86].

Endotoxin activity has emerged as a valuable marker of disease severity. The lipid-A domain of endotoxin induces most of the toxicity associated with LPS, characterized by fever, diarrhea, hemodynamic instability, multiple organ failure, and, ultimately, death[87]. A previous study highlighted the clinical relevance of circulating levels of LPS, showing a significant correlation between endotoxin levels and severity of septic shock, organ dysfunction, and mortality[86]. The prevalence of endotoxemia in patients with septic shock was high, and up to 82% of patients showing intermediate or high endotoxin activity[88]. Patients with endotoxemia also presented significantly higher lactate concentration and inotropic score.

In human illness, the measurement of endotoxin is notoriously difficult. The chromogenic limulus amebocyte lysate assay was the first diagnostic test developed. It was based on endotoxin's ability to induce coagulation of proteins in the hemolymph of the horseshoe crab, *Limulus polyphemus*[89]. Since other microbial products,

especially from fungi, can activate the limulus reaction, the assay is not specific for endotoxin. Since 2004, the endotoxemia measurement in humans has been made through the Endotoxin Activity Assay (EAA), a chemiluminescent rapid (30-min) assay described by Romaschin in 1998[90]. That test is based on the ability of an antibody to form an antibody-antigen complex in whole blood. This antibody targets the highly conserved lipid A epitope of endotoxin. It has a very high binding affinity, leading to very high sensitivity. In addition, the antibody does not cross-react with Gram-positive or fungal components, allowing for very high specificity. The results are expressed in EAA units, where < 0.39 is considered low, 0.40-0.59 intermediate, and ≥ 0.60 high. As this assay uses patient's neutrophils as a readout system, it is impossible to store specimens for later assaying, and measurements must be performed within 3 h of obtaining the sample. The EAA is the only assay that is approved by the United States' Food and Drug Administration for measuring endotoxin activity in whole blood.

Endotoxin has been considered as one of the therapeutic targets for the treatment of sepsis and septic shock. The possibility of eliminating endotoxin through blood purification techniques and, specifically, by hemoadsorption has been raised. Adsorption with a fiber column immobilized with polymyxin B (PMX) (Toraymyxin®; Toray, Tokyo, Japan), is one of the best-known endotoxin elimination therapies. Another possibility is the oXiris® hemofilter (Baxter, Meyzieu, France).

Four clinical trials have evaluated the efficacy of endotoxin hemoadsorption in septic shock. In a multicenter, open-label, pilot, randomized, controlled study conducted in Europe, 36 postsurgical patients with severe sepsis or septic shock secondary to intraabdominal infection were randomized to receive PMX treatment over 2 h (n = 17) or standard therapy (n = 19)[91]. There were no statistically significant differences in endotoxin levels from baseline to 6, 8 or 24 h after treatment between the two groups. Five of the eighteen (28%) patients in the control group and five of the seventeen (29%) patients in the PMX group died during the study period. The survival analysis showed no statistical significance between the two groups. There was also no statistically significant difference in the mean duration of ICU stay nor the number of ICU-free days between the two groups. However, patients treated with PMX demonstrated substantial increases in cardiac index and oxygen delivery index, and the need for CRRT after study entry was reduced. PMX was well tolerated and showed no significant side effects. Thus, that study showed the PMX cartridge to be safe and to have the potential to improve cardiac and renal dysfunction due to sepsis or septic shock. The early use of polymyxin B hemoperfusion in abdominal septic shock (*i.e.* EUPHAS) trial[92] evaluated hemoperfusion with PMX in a small sample of 64 patients with intraabdominal infection-related severe sepsis and septic shock. The design was oriented to assess hemodynamic improvement. The recovery of mean arterial pressure allowed for the reduction of vasoactive drugs in the PMX group. SOFA scores improved in the PMX group. Furthermore, a significant reduction in 28-d mortality was observed in the intervention group (32%) compared to the conventional treatment group (53%). The ABDOMIX trial[93] studied 243 patients with septic shock within 12 h after emergency surgery for secondary peritonitis due to organ perforation. The PMX hemoperfusion (*i.e.* PMX-HP) group (n = 119) received conventional therapy plus two sessions of PMX-HP. There were no significant differences in the SOFA score nor the 28-d mortality rate between PMX-HP and control groups (27.7% *vs* 19.5%). The severity of the disease and mortality were moderate. Among the 220 sessions performed, a premature interruption was observed in 25 cases (11%), mainly during the first session and primarily due to circuit clotting. A total of two PMX-HP sessions were completed in only 81 of 119 patients (69.8%). Of note, plasma EAA levels were not measured in any RCTs previously discussed.

The Euphrates trial[94] is one of the RCTs with the largest sample of patients and features the highest scientific rigor. Among its main characteristics is the use of EAA as a predictive biomarker. This trial studied 450 critically ill patients with septic shock and an EAA level of 0.6 or higher. The intervention consisted of two PMX-HP treatments (90-120 min) plus standard therapy, completed within 24 h of enrollment (n = 224) or sham hemoperfusion plus standard therapy (n = 226). PMX-HP was not associated with a significant difference in 28-d mortality. However, Klein *et al*[95] performed a post-hoc analysis of 194 patients with EAA between 0.6-0.89. A survival benefit was observed in patients who received therapy with PMX hemofilters. Monti *et al*[96] published the first study describing the use of PMX-HP as rescue therapy, involving 52 patients with refractory septic shock unresponsive to conventional therapy. The SOFA score was 10 (8-14) points and serum lactate level was 5.89 ± 4.04 mmol/L. All patients were on mechanical ventilation, and 90% were treated with corticosteroids. Rapid and early reversal of circulatory dysfunction and other organ

failures were obtained. The overall 30-d mortality was lower (29%) than expected by the SAPS II score (47%).

Consequently, it seems reasonable that patients with refractory septic shock and severe multiorgan dysfunction, with adequate control of the focus and EAA 0.6-0.9 could be candidates for endotoxin hemoadsorption. The TIGRIS study[97] is ongoing, recruiting patients with SOFA score > 9 and EAA levels between 0.60 and 0.89. The results of that study will provide more information on the possible benefits of endotoxin hemoadsorption in patients with septic shock, high requirement for vasopressor support, and severe multiorgan dysfunction.

Cytokine hemoadsorption

Sepsis appears when the initially appropriate host response to infection becomes amplified and subsequently dysregulated, leading to an imbalance between pro-inflammatory and anti-inflammatory responses[98]. An excess of pro-inflammatory cytokines can lead to endothelial injury and SIRS. Severe cases can progress to disseminated intravascular coagulation and multiple organ failure that eventually leads to death[99].

A tightly regulated balance in the cytokine network is crucial for eliminating invading pathogens on the one hand and restricting excessive, tissue-damaging inflammation on the other. This network comprises pro-inflammatory cytokines [tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-12, interferon-gamma (IFN-γ) and macrophage migration inhibitory factor (MIF)], anti-inflammatory cytokines [IL-10, transforming growth factor-beta (TGF-β), and IL-4], and soluble inhibitors of pro-inflammatory cytokines[100], such as soluble TNF receptor (TNFR), IL-1 receptor antagonist (IL-1Ra), and IL-2 receptor antagonist (IL-1R2)[101,102]. In endothelial cells, TNF-α enhances the expression of adhesion molecules and increases integrin adhesiveness in neutrophils, promoting their extravasation into tissues[103,104]. TNF-α and IL-1 are the main mediators of inflammation-induced activation of coagulation [105]. In addition, TNF-α and IL-1 amplify inflammatory cascades in an autocrine and paracrine manner by activating macrophages to secrete other pro-inflammatory cytokines, lipid mediators, and reactive oxygen and nitrogen species, leading to sepsis-induced organ dysfunction[98,106]. A key function of IL-6 is the induction of fever [107] and the mediation of the acute phase response[108,109]. The high concentration of IL-6 binds to the soluble form of the IL-6 receptor. This complex combines with the signal-transducing component glycoprotein 130 on the cells, including endothelial cells, to elicit IL-6 signal activation. Despite its pro-inflammatory properties, IL-6 also has been shown to promote anti-inflammatory responses. IL-6 inhibits the release of TNF-α and IL-1[110] and enhances the circulation levels of anti-inflammatory mediators[111-113]. IL-10 and TGF-β suppress the production of pro-inflammatory mediators in immune cells and stimulate the production of IL-1Ra and sTNFRs[114, 115].

Several studies have suggested an association of IL-6 hypercytokinemia with organ dysfunction, response to treatment, and prognosis in sepsis. Kellum *et al*[116] found that 82% of patients with community-acquired pneumonia had a systemic elevation of cytokine levels. Furthermore, patients with higher levels of IL-6 and IL-10 had associated severe organ dysfunction[117,118] and higher mortality[116,118]. The association between high levels of IL-6 and IL-10 with organ dysfunction and mortality has been confirmed in other studies[117-120]. Patients who survive sepsis show a rapid decrease in IL-6 Levels, in contrast to the non-decreasing values or a slowly progressive decrease in non-survivors[119,120]. Thus, the reduction of IL-6 Levels is associated with a better prognosis[121], and IL-10 overproduction is the main predictor of severity and mortality[122,123].

Given the central role of increased systemic inflammation in the pathophysiology of sepsis-induced organ dysfunction, the development of therapies aimed at dampening the cytokine storm could help improve immune homeostasis. Extracorporeal blood purification therapies have been proposed as a strategy to improve the outcome of septic patients, attenuating the systemic expression of pro-inflammatory and anti-inflammatory mediators and restoring immune homeostasis[116]. These include different cytokine hemoadsorption techniques. Currently, we have several devices for assessing cytokine adsorption; these include Cytosorb® (CytoSorbents Corporation, Monmouth Junction, NJ, United States), oXyris (Baxter, Meyzieu, France), Alteco LPS Adsorber (Alteco Medical AB, Lund, Sweden), HA 330 and 380 (Jafron Biomedical Co., Zhuhai, GuangDong, China).

CytoSorb® is the most widely used cartridge, and our experience is greatest with it. It has been evaluated for various clinical conditions, such as SIRS after cardiopulmonary bypass, liver failure, and rhabdomyolysis-associated myoglobinemia[118-

120]. In it, cytokines are adsorbed by polymer beads within a perfused cartridge, through extracorporeal circulation[117]. Cytosorb® can attenuate both the pro-inflammatory and anti-inflammatory responses, achieving a recovery of balance much earlier.

Several observational studies have suggested the clinical benefits of using Cytosorb® in septic shock to reduce vasopressor support and even achieve a mortality reduction. Friesecke *et al*[124] studied 20 consecutive patients with refractory septic shock after 6 h of standard treatment and hypercytokinemia. Refractory septic shock was defined as a progressive shock despite full-standard therapy and lactate ≥ 2.9 mmol/L (or increased compared to baseline), and high noradrenaline requirements (> 0.3 mcg/kg/min). The mean IL-6 Levels were 25.523 ng/mL (range: 1052-491260 ng/mL). In that study, Cytosorb® application was found to be associated with a significant decrease in noradrenaline requirements and an increase in lactate clearance, which resulted in shock resolution in 13 patients. In another case series of 45 patients with septic shock treated with hemoadsorption, Paul *et al*[125] described a significant vasopressor dose reduction (*i.e.*, norepinephrine by 51.4%, epinephrine by 69.4%, and vasopressin by 13.9%). Besides, a reduction in IL-6 Levels (by 52.3%) and lactate levels (by 39.4%) was observed in the survivors. A survival rate of 75% was reported in patients who received treatment within 24 h of admission to the ICU. Patients who received treatment within 24-48 h after admission to the ICU had a survival rate of 68%. In a retrospective study conducted by Brouwer *et al*[126], Cytosorb® was associated with decreased 28-d all-cause mortality in patients with septic shock.

The scientific evidence on the clinical benefits of cytokine elimination derived from RCTs is scarce. Hawchar *et al*[127] performed a proof of concept, prospective, randomized pilot trial on the application of Cytosorb® in 20 patients with early-onset septic shock. A significant reduction in the need for vasopressor support was observed. In the control group, this change was not achieved with therapy. Rugg *et al*[128] compared patients with septic shock who received CytoSorb® in addition to CRRT (n = 42) *vs* matched controls (n = 42). Median catecholamine requirements approximately halved within 24 h after the initiation of Cytosorb®. In-hospital mortality was significantly lower in the CytoSorb® group (35.7% *vs* 61.9%; P = 0.015). Derived from our current knowledge, we can attribute the benefits of cytokine hemoadsorption only to the elimination of cytokines in the subgroup of patients with very high hypercytokinemia and associated refractory septic shock. Further studies are needed to define the influence of hemadsorption in the elimination of other substances.

Cytokine hemoadsorption may have a role as rescue therapy in a particular subgroup of patients with refractory septic shock, hyperlactatemia, multiorgan failure, and very high hypercytokinemia. As such, appropriate and well-designed RCTs should be performed in patients with this clinical profile, to validate its benefits.

Immunoparalysis

More than 20 years ago, it was hypothesized that the early hyperinflammatory phase in sepsis was followed by a compensatory anti-inflammatory response to limit tissue damage[129]. In recent years, the therapeutic advances incorporated in sepsis treatment have facilitated a reduction in sepsis mortality, especially in early mortality derived from septic shock and severe multiorgan dysfunction. Some of the patients surviving the first few days evolve to a situation of chronic multiorgan dysfunction, dependent on mechanical ventilation and vasopressor therapy. This stage, known as sepsis-associated immunoparalysis, resembles the normal aging process of the immune system (immunosenescence), characterized by a general dysregulation of innate and adaptive immune responses. Monocytes and macrophages play a critical role in critically ill patients with severe infections. These cells are the front-line of the innate cellular response that initiates and promotes the adaptive immune response.

The human leukocyte antigen (HLA)-DR isotype is a major histocompatibility complex class II cell surface receptor encoded by the HLA complex and constitutively expressed on antigen-presenting cells (*e.g.*, monocytes/macrophages, dendritic cells, and B lymphocytes). It is also inducible on T lymphocytes[130]. Decreased HLA-DR expression has been demonstrated in septic patients, at both the protein- and RNA-levels. There is also a relationship between circulating HLA-DR mRNA and HLA-DR expression *in vivo*[131]. Various studies *in vitro* have shown that constitutive and IFN-γ inducible HLA-DR expression is predominantly regulated at the transcriptional level. The observed loss of HLA-DR expression in monocytes of septic patients implies a transcriptional regulation *via* a decrease of its transactivator, specifically the class II transactivator (*i.e.*, CIITA)[130].

Although no association has been found between the kinetics of monocytic (m)HLA-DR expression and primary infection sites or causative pathogens, it has been associated with severity. Patients with high SOFA scores have an associated low expression of mHLA-DR. The prognosis of patients with low mHLA-DR expression is poor compared to patients with a rapid increase in mHLA-DR expression, primarily because of the higher incidence of secondary infections and mortality rate[132]. The most reliable marker for monitoring the immune alterations in critically ill patients is the decreased mHLA-DR expression, measured by flow cytometry[133].

Immunoparalysis can be identified by studying the expression of HLA-DR in monocytes. Multiple studies have linked the low expression of mHLA-DR with the presence of more significant adverse effects and higher short and long-term mortality rates (at 7 d and 28 d) in sepsis and septic shock[134,135]. Measures of mHLA-DR levels can not only be used as a marker of monocyte functionality and severity of the disease but also to guide innovative clinical therapies based on restoring the immune system[135,136].

In patients with immunoparalysis, several immuno-adjuvant agents are under investigation. GM-CSF, IFN-g, anti-programmed death-ligand 1 (*i.e.*, anti PDL-1), or IL-7 could have a role in treating sepsis-associated immunoparalysis. For instance, decreased mHLA-DR has been used to stratify patients for GM-CSF administration in a clinical trial, including a small sample of sepsis patients. This biomarker-guided GM-CSF therapy was found to be safe and effective in restoring monocyte immunocompetence, shortening mechanical ventilation duration, and reducing ICU/hospital stay [135]. Another clinical trial tested the hypothesis that GM-CSF improves neutrophil phagocytosis in critically ill patients. They previously measured the neutrophil phagocytic capacity and included the subgroup of patients in whom phagocytosis was known to be impaired (to < 50%). The study showed that GM-CSF did not improve mean neutrophil phagocytosis but was safe and appeared to increase the proportion of patients with adequate phagocytosis[137]. Novel therapies targeting the restoration of monocyte immunocompetence are promising for improving outcomes in later stages of sepsis.

CONCLUSION

The heterogeneity of sepsis is a complex and engaging feature of the disease that elicits novel strategies for improved patient classification. Thus, precision medicine creates an individualized approach on a case-by-case basis by identifying subgroups of sepsis patients with a high risk of adverse outcomes who may benefit from specific treatments or rescue therapies according to their particular characteristics (*e.g.*, genotypes or phenotypes). Of note, we urge the implementation of predictive-enrichment strategies for the design and development of future clinical trials to improve the certainty of scientific assessments.

Although some clinical tools are still being evaluated in the early stages of research, such as the omics technologies, precision medicine is becoming a reality that improves our clinical approaches when currently available tools are implemented in patients with sepsis, septic shock, and organic dysfunction. Further scientific contributions in this field will be essential to identify specific endotypes responding to targeted therapies and translate individualized treatments to the bedside.

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MINIREVIEWS

Acute exacerbation of interstitial lung disease in the intensive care unit

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Abstract

Acute exacerbations of interstitial lung disease (AE-ILD) represent an acute, frequent and often highly morbid event in the disease course of ILD patients. Admission in the intensive care unit (ICU) is very common and the need for mechanical ventilation arises early. While non-invasive ventilation has shown promise in staving off intubation in selected patients, it is unclear whether mechanical ventilation can alter the exacerbation course unless it is a bridge to lung transplantation. Risk stratification using clinical and radiographic findings, and early palliative care involvement, are important in ICU care. In this review, we discuss many of the pathophysiological aspects of AE-ILD and raise the hypothesis that ventilation strategies used in acute respiratory distress syndrome might be implemented in AE-ILD. We present possible decision-making and management algorithms that can be used by the intensivist when caring for these patients.

Key Words: Interstitial lung diseases; Disease exacerbation; Mechanical ventilation; Intensive care unit; Pathophysiological aspect

Core Tip: During the acute and morbid event of acute exacerbation of interstitial lung disease, an intensivist needs to understand the pathophysiology and reversible causes of acute exacerbations, the diagnostics and treatments that are usually recommended, and the experimental therapies on the horizon. More importantly, the intensivist needs to be able to risk stratify the patients, selectively pursue mechanical ventilation,

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minimize ventilator induced lung injury, and involve palliative care early in non-lung transplant candidates.

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INTRODUCTION

Definitions and epidemiology

Acute exacerbations in interstitial lung diseases (AE-ILD) represent an acute, and frequently morbid, deterioration of the patients' respiratory function, often leading to hospital admission. Intensivists are at the forefront of care for these patients, and often need to make critical decisions about treatment and whether mechanical ventilation will be beneficial. While originally and most thoroughly described in idiopathic pulmonary fibrosis (IPF), acute exacerbations are increasingly recognized in other types of fibrotic interstitial lung disease (ILD) such as fibrotic (chronic) hypersensitivity pneumonitis[1,2] and connective-tissue disease related ILD[3-5]. To distinguish between the two entities, we will refer to i) acute exacerbations of IPF (AE-IPF) and ii) acute exacerbations of non-IPF interstitial lung disease (AE-nonIPF), grouped together as AE-ILD.

The definition of AE-IPF has shifted between 2007 (Idiopathic Pulmonary Fibrosis network, IPFnet)[6] and 2016 (revised criteria by international working group)[7]. The definition currently includes: (1) Known diagnosis of IPF; (2) Worsening dyspnea within the last 30 d; and (3) New bilateral ground glass opacities and/or consolidation upon a background of usual interstitial pneumonia (UIP); the previous requirement for exclusion of concurrent pulmonary embolism (PE) and identifiable infection has been eliminated[7].

The incidence rate of AE-IPF has been estimated to be 41 cases per 1000 person-years[8] with approximately 10% of IPF patients experiencing an acute exacerbation in the two years following their diagnosis[9]. AE-IPF tends to be more prevalent in those with more advanced disease, as measured by worse pulmonary function (especially forced vital capacity, and diffusing capacity for carbon monoxide), shorter 6 min walking distance, and lower baseline oxygenation[10-14].

Pathophysiology and triggers of acute exacerbations of ILD

An acute exacerbation occurring in patients with IPF and other fibrotic ILDs is often unpredictable, but specific intrinsic and extrinsic factors have been hypothesized to trigger the event. Intrinsic factors, such as epithelial homeostatic imbalance affecting fibrocyte differentiation, macrophage immune polarization, and possibly autoimmunity emergence against heat-shock proteins and phospholipid-binding proteins[15-18], have been identified in patients with AE-IPF. Several other factors, such as air pollution[19] and micro-aspiration[20,21], have also been identified. Interestingly, in a retrospective analysis of three well-known IPF placebo controlled clinical trials, none of the patients who developed AE-IPF were on anti-acid treatment[22,23]. A higher eosinophil percentage in bronchoalveolar lavage (BAL) has been associated with the onset of AE-IPF[24].

When an identifiable extrinsic trigger for AE-ILD is lacking, then the AE-ILD is considered idiopathic. On the contrary, infection, aspiration and drug toxicity are common extrinsic triggers of AE-ILD. Infection has been identified in 10% to 30% of patients with AE-ILD[25-27]. Furthermore, post-procedural AE-ILD has also been reported, including video-assisted thoracoscopic procedures and bronchoscopy with lavage[28-30]. The underlying mechanism is thought to be due to possible ventilator-induced injury (including hyperoxia or barotrauma), perioperative mechanical stretch, or fluid balance[7,31]. In a large study of acute exacerbations in all types of ILD, 52% of admissions for acute respiratory worsening were considered idiopathic, 20% due to infection, 15% due to subacute progression or end-stage disease, 6% due to heart failure or severe pulmonary hypertension, 4% due to venous thromboembolic disease, and 2% from diffuse alveolar hemorrhage or peri-procedural exacerbation[25].

Both AE-ILD and acute respiratory distress syndrome (ARDS) have bilateral ground glass opacities and/or consolidations on imaging and often refractory hypoxemia. Similar to ARDS, the most frequent histopathologic finding on lung biopsy seen in AE-ILD is diffuse alveolar damage[3,32], which involves an acute exudative phase followed by an organizing-proliferative phase[33]. It is likely that both patients with AE-ILD and ARDS have an aberrant and defective healing response to lung injury, that involves a pro-fibrotic positive-feedback loop[34-36].

Diagnostic evaluation indicated on hospital or intensive care unit admission

When a patient with ILD, or specifically IPF, is admitted for acute respiratory worsening, it is up to the inpatient physician, or more often the intensivist, to distinguish between idiopathic acute exacerbation *vs* acute exacerbation secondary to a specific "treatable" trigger such as infection. In-hospital survival is worse in those with idiopathic AE-ILD compared to those stemming from a known-trigger[25], possibly due to lack of targeted treatment.

Interestingly, acute exacerbation may be the first presentation of previously undiagnosed ILD, with such patients comprising 29% of one large academic cohort [25]. Radiologic findings of fibrotic disease including reticulation and traction bronchiectasis, in a patient without known pulmonary disease suggests undiagnosed ILD. Surgical lung biopsy is often avoided during AE-IPF as its results often do not alter the course of acute exacerbation[32], and have increased peri/post-operative morbidity[37].

If the patient has previously undiagnosed ILD as noted above, then autoimmune serologies, including evaluation for pulmonary vasculitis with antineutrophil cytoplasmic antibodies, would be indicated to further clarify any potential autoimmunity that would suggest a related connective-tissue disease or interstitial pneumonia with autoimmune features (IPAF). This may potentially affect management, as patients with autoimmune disease-related ILDs are more likely to be treated with immunosuppression, unlike in IPF patients[38].

Infection can be evaluated by various sources, including laboratory findings (white cell count, urine *Legionella* or *Streptococcus pneumoniae* antigens, procalcitonin[39], nasal or sputum viral polymerase chain reaction [PCR] tests), vital signs, and of course blood or respiratory cultures[40]. The yield of bronchoscopy has been found to be relatively low; only 13% of bronchoscopies in AE-ILD yielded abnormal results according to a major study[27], with 25% of patients having bronchoscopy on the general floor necessitating post-procedural ICU transfer. When bronchoscopy is performed, BAL specimens should be sent for bacterial, fungal and mycobacterial cultures, including viral PCR tests. Since AE-non-IPF patients are often immunocompromised, an intensivist should consider pneumocystis jirovecii and herpesvirus infections, which represented 25% and 18% of positive bronchoscopies in one study, respectively[27].

High-resolution computed tomography (CT) is critical in clarifying the extent of underlying fibrotic interstitial disease and suspected new or superimposed ground glass or consolidative abnormalities. The extent and pattern of superimposed infiltrates on high-resolution CT have been found to be predictive of survival in AE-IPF[41,42]. The separation of the Kaplan-Meier survival curves depending on 3 different types of CT findings (peripheral, multifocal, or diffuse pattern) was found to be quite striking[41]. A protocol assessing for pulmonary embolism - or a ventilation-perfusion and lower extremity doppler scan in patients with renal impairment - may be reasonable to exclude thromboembolic disease. However, a PE protocol study was performed in only 43% of admissions for acute respiratory worsening in ILD patients [25]. Interestingly, a link between a profibrotic and a prothrombotic state has been found[43], with studies reporting higher risk of venous thromboembolism (VTE) in IPF patients[44,45]. Physical examination, serum brain natriuretic peptide concentrations, and echocardiography are used to evaluate for any component of heart failure and pulmonary hypertension[7].

TO INTUBATE OR NOT TO INTUBATE?

When an intensivist encounters a deteriorating patient with AE-ILD, the decision for invasive mechanical ventilation (IMV) must be balanced with the prognosis and reversibility of the patient's condition. Multiple studies have shown poor outcomes in this population, including studies that analyzed admissions before[46-48] and after[25, 49] changes in lung protective ventilation following the publication of the ARDSnet

trial in 2000. In-hospital mortality may reach 50% with 1-year mortality at 70%. In the years before lung protective ventilation strategies, studies identified that 85% mechanically ventilated patients with AE-IPF died while ventilated, and proposed that ICU admission and intubation may be futile[46]. Nevertheless, both due to: (1) the acceptance of lower tidal volumes in ICUs; and (2) Changes in the definition of AE-IPF to include potentially reversible causes, the outcomes of ventilated patients with AE-IPF have improved, but still remain poor. In a nationwide cohort from 2006-2012, in-hospital mortality of AE-IPF patients who received mechanical ventilation was 51.6% (although improved from 58.4% in 2006 to 49.3% in 2012) and of patients who received non-invasive ventilation (NIV) was 30.9%[49]. In another study of patients in French ICUs from 2002 to 2009, only 30% of those mechanically ventilated were successfully weaned[50]. As expected, in-hospital mortality varies according to ventilation type, being higher in patients requiring IMV compared to patients requiring NIV or no ventilation support in a large multicenter ICU database study[51]. NIV is a reasonable therapeutic option which may allow certain patients to avoid the morbidity of IMV[51, 52].

In general, mortality is affected by disease type, with IPF for example having worse outcomes compared to other fibrotic ILD associated with autoimmune disorders or hypersensitivity pneumonitis. In a landmark study that explored admissions for acute respiratory worsening in patients with chronic fibrotic lung disease, in-hospital mortality was the same between IPF and patients without IPF (55% *vs* 45%, $P > 0.05$) [25], although other studies found nonspecific interstitial pneumonia to be associated with a relatively good discharge rate and long-term prognosis[4]. In a different study, 90-day mortality was found to be significantly higher in AE-IPF than AE-non-IPF (69% *vs* 34%)[53]. One-year mortality after hospitalization for acute exacerbation was worse in IPF than non-IPF (87% *vs* 71%), yet still very high in both groups[25]. Furthermore, while infection accounted for a third of AE-ILD cases in another United States cohort, outcomes did not differ between those with infection and those without[26]. However, post-operative exacerbation and respiratory failure in ILD patients is associated with a better prognosis[54]. Specific findings on high-resolution CT at admission in AE-IPF patients have been correlated with prognosis[41,42]. Artificial intelligence software is increasingly showing application and promise in the analysis of CT scans in ILD patients, and may potentially be used for prognostication[55].

In the authors' opinion, risk stratification and goals of care discussion need to take place early on when a patient with AE-ILD is admitted to the ICU. Studies have shown that a subset of patients can be weaned from mechanical ventilation and discharged, suggesting that IMV should not be systematically denied to these patients but considered individually[50]. Risk stratification certainly depends on clinical judgement, but can also be assisted by other published insights, including the aforementioned CT characteristics[41,42]. On admission to the hospital for respiratory worsening, only 20% of patients with fibrotic lung disease have a "do not resuscitate, do not intubate" code status[25]. Palliative care should be consulted early in the patients' admission, and eligibility (or pre-existing enrollment with previous work-up completion) of patients for lung transplant should play important roles in the management decision tree (Figure 1). While the poor outcomes of mechanical ventilation place it in the role of "bridge therapy", lung transplant is a potential "destination therapy" even for patients with severe acute exacerbations and deteriorating oxygenation. In non-transplant candidates who are deemed high risk for poor outcome, hospice should be brought up early in family discussions and goals of patient comfort and wishes for end-of-life strongly taken into consideration.

USUAL TREATMENTS IN ACUTE EXCERBATIONS

While the outcomes of AE-ILD patients have been well described, well-designed prospective clinical research in the management of these patients is lacking. It is unclear if the high morbidity and mortality of acute exacerbations creates a fertile environment for research as accepted by distressed patients and their families. International guidelines for AE-IPF make a weak recommendation for the use of corticosteroids, namely that corticosteroids should be used in the majority of patients with acute exacerbation of IPF, but not using may be reasonable in a minority[56]. This weak recommendation is based on expert opinion and retrospective reports[41,46,53]. No particular corticosteroid formulation has been found preferrable over another in AE-ILD, despite good outcomes with dexamethasone in ARDS and Coronavirus disease 2019 (Covid-19) associated lung injury[57,58]. Doses ranging from 1mg/kg of

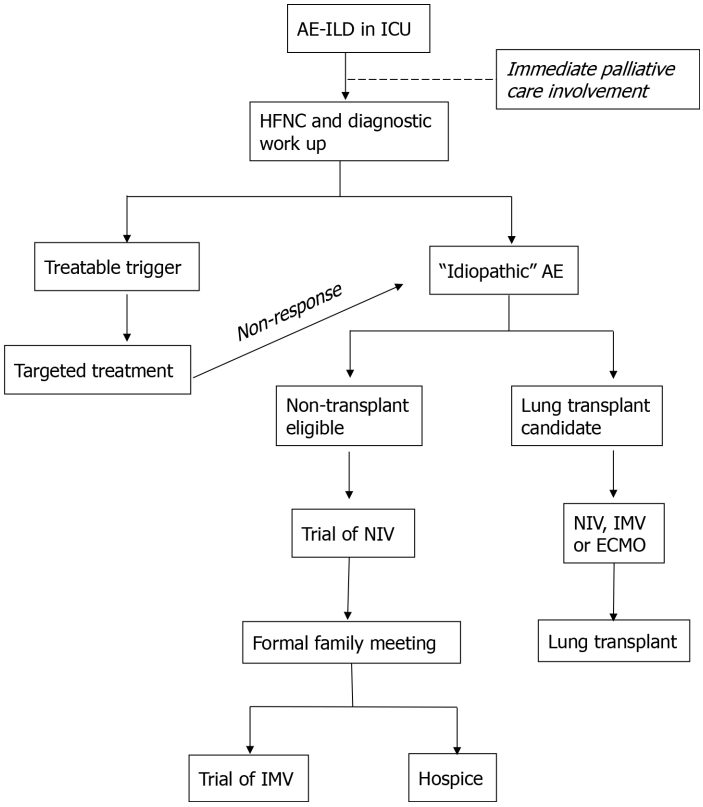

Figure 1 Suggested decision-making tree and management approach of patients admitted to the intensive care unit with acute exacerbation of interstitial lung disease. AE-ILD: Acute exacerbation of interstitial lung disease; ICU: Intensive care unit; HFNC: High flow nasal cannula; AE: Acute exacerbation; NIV: Non-invasive ventilation; IMV: Invasive mechanical ventilation; ECMO: Extracorporeal membrane oxygenation.

prednisone to pulse steroids (methylprednisolone 1 g daily for 3 d) have been used, depending on institutional preference and severity of presentation. In studies comparing corticosteroid treatment in acute exacerbations in idiopathic interstitial pneumonias *vs* connective tissue disease-associated ILD, both groups were observed to be treated with corticosteroids[53]. While others have argued for a steroid-free approach in AE-IPF[59,60], the frequent misdiagnosis of fibrotic hypersensitivity pneumonitis as IPF may be confounding[61]. The uncertainty but routine use of corticosteroids in AE-ILD supports a need for a prospective clinical trial.

Antibiotics are routinely used in AE-ILD, accompanied by appropriate work up to evaluate underlying infection. Both broad spectrum and coverage for atypical pathogens should be considered. Azithromycin, which has been reported to improve outcomes in acute lung injury[62], has also shown particular promise in AE-ILD[63]. This is thought to a result of azithromycin's anti-inflammatory and immune-modulating effects rather than antimicrobial activity, as it has been compared to fluoroquinolones which also cover atypical bacteria[63]. If no underlying infection is found, a routine 7 to 10 day course is reasonable. In a randomized trial, use of procalcitonin to guide antibiotic therapy in patients with AE-IPF resulted in reduced exposure to antibiotics without adversely affecting patient outcomes[39]. Since AE-non-IPF patients are often immunocompromised prior to admission, search for opportunistic pathogens and targeted treatment is prudent (Figure 2).

Key treatments that have been shown to partially prevent AE-IPF or AE-ILD in the outpatient setting - such as antacid therapy[22] and nintentanib[64] - have not been evaluated clinically during acute exacerbation. From the authors' point of view, it is reasonable to continue inpatient use of both antacids and antifibrotics in patients previously treated with them. While there is no peer-reviewed evidence for benefit in initiating antifibrotics in the acute setting except rare case reports[65], antacid therapy should be easily and already instituted in AE-ILD patients treated with corticosteroids and/or mechanical ventilation.

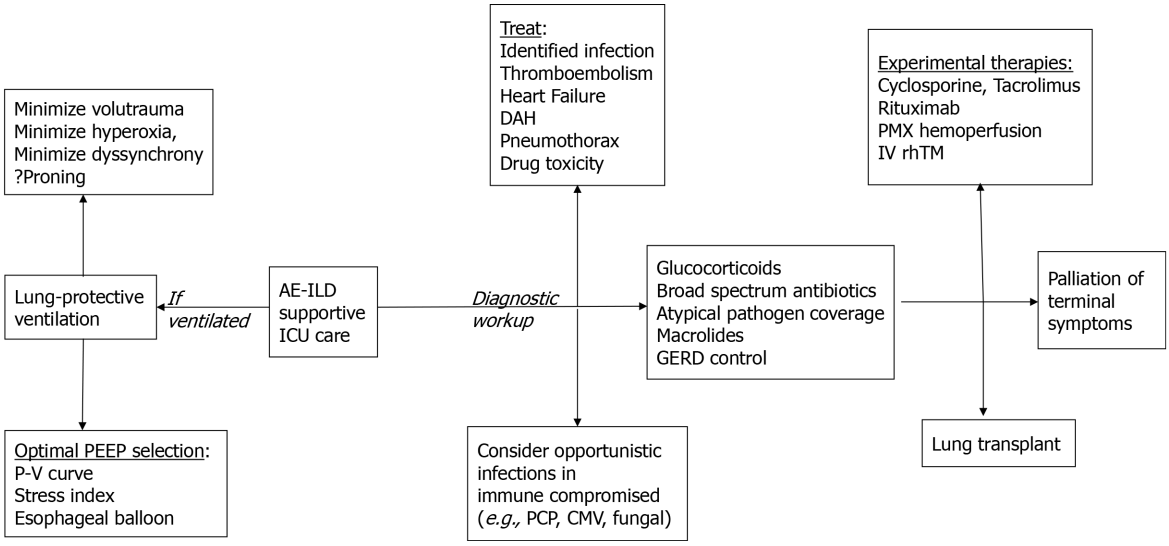

Figure 2 Treatment approaches for acute exacerbation interstitial lung disease. AE-ILD: Acute exacerbation interstitial lung disease; ICU: Intensive care unit; PEEP: Positive end-expiratory pressure; P-V curve: Pressure-volume curve; PCP: Pneumocystis jirovecii pneumonia; CMV: Cytomegalovirus; DAH: Diffuse alveolar hemorrhage; GERD: Gastro-esophageal reflux disease; PMX: Polymyxin-B immobilized fiber column hemoperfusion; IV rhTM: Intravenous recombinant human thrombomodulin.

OPTIMIZATION OF MECHANICAL VENTILATION

AE-ILD has some parallels with ARDS both from a clinical (ground glass infiltrates and severe hypoxemia) and histological (diffuse alveolar damage on pathology) perspective. Similar to ARDS, patients with AE-ILD are prone to ventilator induced injury. Thus, mechanical ventilation strategies used in ARDS should be reasonably utilized in patients with AE-ILD[66]. Avoidance of ventilator-patient dyssynchrony (causing stacked inspired tidal volumes) and prevention of ventilator induced lung injury are of particular importance. Notably 42% of AE-ILD patients required paralytics in a large cohort, although paralytic use was associated with higher mortality in unadjusted analysis and possibly reflective of underlying disease severity [67]. Optimization of positive end-expiratory pressure (PEEP) and lung recruitment using pressure-volume hysteresis curves, stress index, or calculation of transpulmonary pressure with esophageal balloons present an opportunity to at least prevent iatrogenic contribution to a patient's already difficult prognosis. While prone positioning of ventilated patients is strongly supported in ARDS[68], patients with pulmonary fibrosis may be less responsive to proning[69] in the presence of end-stage fibrosis and absence of significant non-hydrostatic pulmonary edema.

Only two studies have examined the effect of ventilator parameters on mortality in patients with AE-ILD[54,67]. The largest study examined 114 admissions for AE-ILD, of which 34% were AE-IPF and 66% were AE-nonIPF[67]. Only 50% of patients in this study achieved a low tidal volume strategy (plateau pressure ≤ 30 cm H_2O) within 3 h of intubation. A variety of modifiable and nonmodifiable parameters - including increased time to intubation, higher initial fraction of inspired oxygen or PEEP, higher mean airway pressures, vasopressor use and right ventricular systolic pressure - were associated with in-hospital mortality. In the second retrospective study, step changes in positive end-expiratory pressure > 10 cm of water were found to have been attempted in 20 patients and resulted in increased airway pressures and decrease in respiratory system compliance suggestive of overdistension[54].

The importance of fluid management - with a goal of net-neutral or net-negative fluid balance - has been increasingly recognized[70], similarly to the management of ARDS. A retrospective study of postoperative AE-IPF patients surgically treated for lung cancer, a common finding in the IPF population[71], showed that more intraoperative fluid administration was associated with higher probability of AE-IPF[31]. Total net fluid status was also an important adjusted risk predictor for mortality in a large study of mechanical ventilation in AE-ILD[67].

EXPERIMENTAL TREATMENTS

In light of currently limited therapeutic options and the high mortality of patients with AE-ILD, experimental therapies have been tested in only a few small studies. Based on the premise of immune dysregulation being a primary driver of AE-IPF and/or AE-nonIPF[72], studies have focused on alternative immunosuppressants or cytokine filtration removal, often in conjunction with corticosteroids (Figure 2). Cyclophosphamide has not been studied using matched controls, but in one single-institution study administration of 1 g daily of methylprednisolone for 3 d followed by monthly cyclophosphamide administration for up to 6 doses showed a favorable overall survival at 3 mo (73%), 6 mo (63%) and 12 mo (55%) compared to the general literature [73]. Calcineurin inhibitors, such as tacrolimus and cyclosporine, have shown some benefit but have only been evaluated in small retrospective studies of 15-45 patients [74-76]. Due to possible autoantibodies in AE-IPF[18], rituximab and plasma exchange were studied in 11 patients with AE-IPF and compared to 20 controls, showing 82% of treated patients improved in terms of oxygenation with some sustaining a relapse-free response[77]. Polymyxin-B immobilized fiber (PMX) hemoperfusion is an alternative approach mostly studied in removing bacterial toxins, but has also been postulated for removing proinflammatory cytokines[78,79] and promoting antifibrotic cytokines[80]. Retrospective studies have shown notable survival benefit from PMX treatment in AE-IPF (12-month survival 41.7% in the PMX group *vs* 9.8% in the non-PMX group)[81, 82], although this has not been confirmed in randomized trials. Disordered hypercoagulation has also been implicated in AE-IPF pathophysiology. Recombinant human thrombomodulin (rhTM), a cofactor for thrombin and anti-coagulant molecule, was recently evaluated as add-on therapy to routine corticosteroid-treated AE-IPF patients decreasing 3 mo mortality to 30%-40 from control levels of 65%-70%[83-85].

CONCLUSION

Despite the relatively common occurrence of AE-IPF and AE-ILD in general[8,9], randomized clinical trials of interventions in acute exacerbations are lacking. As noted in a recent International Working Group report, the optimal management of AE-IPF represents an area of major unmet medical need[7]. Robust prospective clinical studies and randomized trials of therapeutics and maybe ventilation strategies are critical to advance the field and improve the grim prognosis of these patients.

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MINIREVIEWS

Endotracheal intubation sedation in the intensive care unit

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Abstract

Endotracheal intubation is one of the most common, yet most dangerous procedure performed in the intensive care unit (ICU). Complications of ICU intubations include severe hypotension, hypoxemia, and cardiac arrest. Multiple observational studies have evaluated risk factors associated with these complications. Among the risk factors identified, the choice of sedative agents administered, a modifiable risk factor, has been reported to affect these complications (hypotension). Propofol, etomidate, and ketamine or in combination with benzodiazepines and opioids are commonly used sedative agents administered for endotracheal intubation. Propofol demonstrates rapid onset and offset, however, has drawbacks of profound vasodilation and associated cardiac depression. Etomidate is commonly used in the critically ill population. However, it is known to cause reversible inhibition of 11 β-hydroxylase which suppresses the adrenal production of cortisol for at least 24 h. This added organ impairment with the use of etomidate has been a potential contributing factor for the associated increased morbidity and mortality observed with its use. Ketamine is known to provide analgesia with sedation and has minimal respiratory and cardiovascular effects. However, its use can lead to tachycardia and hypertension which may be deleterious in a patient with heart disease or cause unpleasant hallucinations. Moreover, unlike propofol or etomidate, ketamine requires organ dependent elimination by the liver and kidney which may be problematic in the critically ill. Lately, a combination of ketamine and propofol, "Ketofol", has been increasingly used as it provides a balancing effect on hemodynamics without any of the side effects known to be associated with the parent drugs. Furthermore, the doses of both drugs are reduced. In situations where a difficult airway is anticipated, awake intubation with the help of a fiberoptic scope or video laryngoscope is considered. Dexmedetomidine is a commonly used sedative agent for these procedures.

Key Words: Critically ill; Endotracheal intubation; Etomidate; Hypotension; Intensive care

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Core Tip: Intensive care unit endotracheal intubations are associated with a higher risk of complications such as hypotension, hypoxemia, and cardiac arrest when compared to non-intensive care unit endotracheal intubations. A necessity of endotracheal intubations, sedation, is a modifiable risk factor in the pathway to cardiovascular instability. The goal of this review is to present the pros and cons of each sedative agent used for endotracheal intubation while comparing the outcomes. This will help the reader to make an informed decision when choosing a sedative agent for endotracheal intubation in the intensive care unit.

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INTRODUCTION

Endotracheal intubations are one of the most common, yet most dangerous procedures performed in the intensive care unit (ICU). Complications from ICU endotracheal intubations are seen in approximately 40%-45% of patients and include severe hypotension (10%-43%), severe hypoxemia (9%-25%), and cardiac arrest(2%-3%)[1]. Severe cardiovascular collapse is one of the most common complications after ICU endotracheal intubation[2]. Understandably, identification of risk factors for cardiovascular collapse surrounding endotracheal intubation becomes extremely imperative to mitigate or avoid this devastating complication. In a multicenter observational study, Perbet *et al*[2] identified patient risk factors for cardiovascular collapse which included advanced patient age, higher sequential organ failure assessment score, acute respiratory failure, brain injury, trauma, and chronic obstructive pulmonary disease. Procedural risk factors included multiple intubations, use of propofol for induction, and desaturation during intubation[2]. Recently, a multicenter observational prospective study derived and validated a hypotension prediction score for patients undergoing endotracheal intubation in the ICU. The investigators identified 11 variables (increasing illness severity; increasing age; sepsis diagnosis; endotracheal intubation in the setting of cardiac arrest, mean arterial pressure < 65 mmHg, and acute respiratory failure; diuretic use 24 h preceding endotracheal intubation; decreasing systolic blood pressure from 130 mmHg; catecholamine or phenylephrine use immediately prior to endotracheal intubation; and use of etomidate during endotracheal intubation) that were independently associated with peri-intubation hypotension with a C-statistic of 0.75 [95% confidence interval (CI): 0.72-0.78]. Of the 11 variables, the use of etomidate was found to protect against peri-intubation hypotension[3].

Incidence of adverse events like death or hypoxic brain damage are higher with intubations done in ICUs compared to those performed in the operating rooms[4]. In contrast to the ICU, endotracheal intubations in the operating room are frequently performed in a controlled fashion under non-emergent conditions. Although patients may have numerous comorbidities, personnel are specifically trained in airway management, and due to the elective nature of surgical procedures, preparations can be made for difficulties encountered[5,6].

Thus, based on the above evidence, preparation and planning for endotracheal intubations is paramount in critically ill patients to avoid life-threatening complications. An element of endotracheal intubation that is modifiable is the choice of sedative agents administered, which as the evidence suggests, may alter ICU complications, in particular, severe hypotension.

ICU SEDATION AGENTS

Propofol

Propofol is currently the most common anesthetic induction agent used worldwide. Its rapid onset and short duration of action is ideally suited to settings such as the ICU. Propofol's sedative effects are mediated through gamma aminobutyric acid receptors with some activity on N-methyl-D-aspartate receptors. Termination of action of propofol is by redistribution and is independent of organ elimination, thereby making it very useful in ICU patients who may have organ impairment. Standard induction doses of propofol in a healthy adult are 2-2.5mg/kg[7]. However, dosing in the ICU is dramatically different due to the nature of the patent population with patients usually requiring endotracheal intubation for acute respiratory failure or cardiovascular collapse as illustrated recently[1]. In fact, propofol has been shown to have increased potency in shock states indicating less is more[8]. This finding demonstrates the profound vasodilatory effects and associated cardiac depression of propofol[7]. For the healthy patient, this is well tolerated but in patients who are in septic or cardiogenic shock, this attribute can have a detrimental effect on patient hemodynamics. Hence, caution is warranted when using propofol in the critically ill population. A recent study evaluating intubation practices in critically ill patients from 29 countries showed that propofol is the most used sedative and was significantly associated with hemodynamic instability in 63.7% of patients who exhibited precarious hemodynamics, as compared to etomidate with only 49.5% of patients developing hemodynamic instability[1]. Another study performed at the Long Island Jewish Medical center looked at safety of propofol in urgent endotracheal intubations in the medical ICU[9]. Propofol was the sole sedative agent used in 87% of the patients, in 4% it was combined with other agents like benzodiazepines and in the remaining 9%, other sedative agents were used. Interestingly, only 4% of the patients in which propofol was used developed hypotension. This may be explained by the observation that patients were pre-emptively administered vasoactive agents along with propofol to maintain a targeted perfusion pressure. Despite the hemodynamic decompensation known to be associated with propofol, it remains an ideal induction agent in the ICU because of its rapid onset, short duration of action, minimal drug interactions, and organ independent elimination likely explaining its frequent use in the critically ill.

Ketamine

Ketamine is an anesthetic agent which causes complete anesthesia while providing analgesia at the same time. In addition, its causes less respiratory depression and has hemodynamic effects that are opposite that of propofol[7]. This property makes it a desired drug in multiple settings. It is a phencyclidine derivative which acts on the N-methyl-D-aspartate receptor[10,11]. The standard induction dose of ketamine is 1-2 mg/kg. Ketamine's hemodynamic effects are mediated through central nervous system stimulation and inhibition of catecholamine reuptake. However, it is also a known direct myocardial depressant. Thus, in severely ill patients such as the patient in septic shock who is depleted of catecholamines, the direct myocardial depressant effects can be unmasked[7,12]. In addition, ketamine may cause increased intracranial pressure through increased cerebral perfusion thereby limiting its use in trauma patients[13]. Lastly, ketamine is known to induce salivation which can be problematic in airway management in the setting of difficult airways where visualization of the airway is paramount[7]. Although medications such as atropine or glycopyrrolate can be administered to help reduce this effect, these medications may alter the patient's hemodynamics which may not be desirable. When compared to etomidate in the setting of rapid sequence intubation for trauma patients, no significant difference was observed for peri-intubation outcomes such as first pass intubation success, need for rescue surgical airway, and peri-intubation cardiac arrest. However, ketamine was associated with lower odds of hospital acquired sepsis [adjusted odds ratio [OR] 0.72, 95%CI: 0.52-0.99] but higher number of days on vasopressor therapy (adjusted OR 0.74 95%CI: 0.58-0.95)[14]. Another trial which compared these two agents was the Ketased trial which failed to show any difference in immediate post-intubation complications, catecholamine free days at day 28, or 28-d mortality[15].

Etomidate

Etomidate is an anesthetic induction agent commonly used because of its ability to maintain stable hemodynamics. Etomidate causes sedation by its agonistic action on gamma aminobutyric acid receptors and it is thought to maintain hemodynamics through simultaneous stimulation of α-2b adrenoreceptors[16]. In addition to this,

etomidate also reversibly inhibits 11β-hydroxylase and therefore suppresses the adrenal production of cortisol for at least 24 h after a single induction dose[17]. This specific adverse effect is a major reason that causes many intensivists to shy away from using etomidate in the critically ill. Furthermore, the use of etomidate for endotracheal intubation in septic patients has been associated with increased mortality and poor outcomes[18-20]. Moreover, this trend has been seen in surgical patients[21]. For example, a study at Cleveland Clinic in non-cardiac surgery patients showed that patients who received etomidate had a 2.5 (98%CI: 1.9–3.4) higher odds of dying than those who received propofol anesthesia. In addition, patients who received etomidate had a prolonged hospital stay without a significant difference in intraoperative vasopressor requirements[21]. A recent metanalysis that included 29 trials totaling 8584 patients comparing etomidate with other induction agents demonstrated that etomidate was associated with adrenal insufficiency [risk ratio (RR) = 1.54, 95%CI: 1.42, 1.67, $P < 0.001$] and increased overall relative mortality rates (RR = 1.09, 95%CI: 1.04, 1.16, $P = 0.001$). However, on meta-regression, the increased mortality was associated with increasing severity of disease[22]. Hence, the association between etomidate and increased mortality should be interpreted with caution. It is likely that etomidate does lead to additional organ dysfunction, through adrenal suppression, in the critically ill resulting in possibly increased morbidity and mortality.

In the past, high doses of benzodiazepines and opioids were used for sedation during endotracheal intubation. However, with the association of benzodiazepines and increased delirium combined with the awareness to maintain lighter sedation levels, these practices have decreased[23,24].

Ketamine-Propofol Admixture ("Ketofol")

Lately, a combination of two sedatives, namely ketamine and propofol ("Ketofol"), has demonstrated efficacy in terms of hemodynamic preservation when sedating for airway management. This is supported by two randomized controlled trials in which "Ketofol" was compared to propofol only and to half-dose etomidate. In addition to the hemodynamic stability offered by "Ketofol", both trials also suggested that "Ketofol" reduced opioid requirements as compared to the competitor[25,26]. In one trial, "Ketofol" was associated with reduced transfusion requirements as compared to etomidate due to cortisol's role in maintaining vascular homoeostasis (inhibited by etomidate)[26]. Other systemic reviews and meta-analyses have suggested that "Ketofol" is associated with less respiratory events than propofol alone[27,28]. Thus, this unique drug combination has the ability to cause less hemodynamic alterations than either parent compound while providing non-opioid pain control, which may translate into improved metrics such as reduction in post-intubation hypotension and therefore, morbidity and mortality.

Clinical implications of "Ketofol"

An ideal anesthetic is one that has a balanced effect on the cardiopulmonary system while providing hypnosis and analgesia[7]. The "Ketofol" admixture possesses these qualities and as such, its use is applicable to a variety of patient care settings. The rationale behind the drug combination is to provide an admixture that when used together, attenuates blood pressure swings and provides a smooth blood pressure profile during endotracheal intubation and beyond (Figure 1). Although this depends on dosing used for both individual medications, most of the evidence points to a stabilizing effect on blood pressure. This stabilization has the potential to translate into direct and indirect benefits to patients across multiple hospital settings (*e.g.*, emergency room, ICU, operating room, procedural suites) throughout the world. For example, the admixture may offer neuroprotection *via* maintenance of cerebral perfusion through mean arterial pressure, which may reduce post-ICU psychological phenomena (*e.g.*, cognitive dysfunction, depression, *etc.*) in long-term critical care survivors as well as delirium in surgical patients through reduction of benzodiazepines. Moreover, maintenance of hemodynamics in these settings has the potential to translate into reduced rates of adverse cardiac events, acute kidney injury, and mortality. This is of major significance as propofol is the most common anesthetic in use today[29]. Equally important is the ability to limit opioid medications with this admixture due to the properties of ketamine[7]. Every day, more than 130 people in the United States die after overdosing on opioids resulting in an economic burden of 78.5 billion dollar/year[30]. Thus, the admixture may result in reduced exposure to opioid medications by providing a non-opioid alternative to patients needing sedation in multiple locations (e.g., pre-hospital, emergency room, ICU, operating room). This initiative aligns with the United States Health Human Services' opioid crisis strategy [30]. Thus, the "Ketofol" admixture offers the advantage of stable hemodynamics that

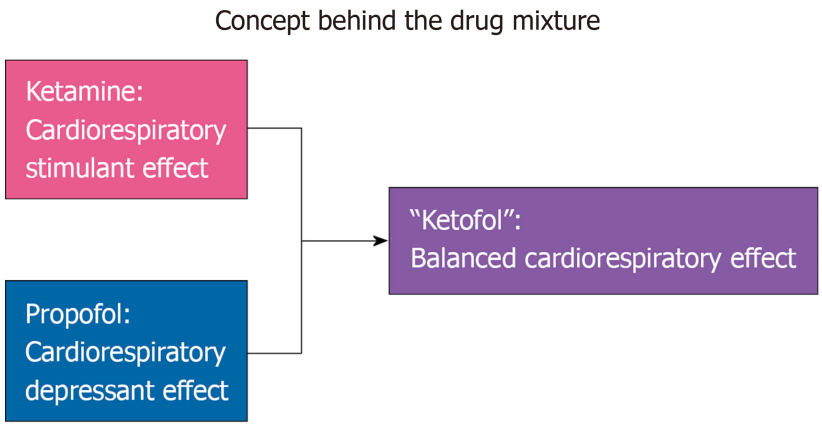

Figure 1 Ketofol concept. In addition, this drug mixture provides hypnosis and analgesia (closest to an ideal anesthetic agent).

is similar to etomidate with non-opioid pain control and minimal, if any, ill effects on patients over ketamine, propofol, or etomidate.

Muscle relaxants

Use of muscle relaxants also varies for endotracheal intubations in the ICU. An observational study comparing outcomes of intubation with or without the use of muscle relaxants failed to show any significant difference in post intubation complications, however, it did show that excellent intubation conditions were achieved in patients in which muscle relaxants were used[31]. Another observational study showed higher first attempt success rate when neuromuscular blockers were used (80.9% *vs* 69.6%, $P = 0.003$)[32].

Special occasions

There are many unique occasions which affect the choice of sedatives in the ICU other than those mentioned above. Cardiac arrest is one such occasion. Typically, no drugs are administered during the intubation. For difficult airways, sedatives may be chosen that provide quick onset and offset or have specific reversal agents associated with their use. Burns, angioedema, and superior vena cava syndrome are some examples when awake fiberoptic intubation might be preferred over routine intubation. In addition, another setting in which sedatives are altered from the usual intubation practice include awake video laryngoscopy, which has been increasingly used to avoid a lost airway or spontaneous respirations[33]. Dexmedetomidine has been used during these situations, along with topical anesthesia, due to its anxiolytic effect with minimal adverse effects on spontaneous respirations[34].

CONCLUSION

Endotracheal intubation is a common procedure, yet can be associated with devastating complications, namely hypoxemia and cardiovascular collapse, that increase when conducted outside a controlled setting such as the operating room. Sedation is frequently administered to facilitate this procedure. However, sedation can sometimes exacerbate these complications, especially relevant when endotracheal intubation is carried out in an urgent/emergent context (*e.g.*, ICU, emergency department, *etc.*). Several sedatives are available to facilitate airway management. Each has its own drawbacks as discussed above which the clinician needs to take into consideration when performing this procedure. As an alternative to the individual sedatives, a combination of sedatives may be needed to achieve the desired outcome such as "Ketofol" in which available evidence suggests a hemodynamic sparring effect with reduced opioid requirements.

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ORIGINAL ARTICLE

Retrospective Study

Medico-legal risks associated to hand and wrist trauma

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Abstract

BACKGROUND

Acute hand and wrist injuries are common and may lead to long-term disability if not managed adequately. Claims for negligence have been increasing in medical practice over the past few decades, with hand and wrist injuries and their treatment representing a significant percentage of orthopedic surgery lawsuits. There is no available literature regarding medical malpractice claims in hand and wrist injuries and surgery in Greece.

AIM

To identify claims related to hand and wrist trauma and surgery and to define the reasons of successful litigations.

METHODS

We performed a retrospective study of all legal claims of negligence for hand and upper extremity surgery that went to a trial, attributed to all surgical specialties, in Greece for a 20-year period. Data was further analyzed to identify claims related to hand and wrist trauma and surgery.

RESULTS

There were six malpractice claims related to hand and wrist trauma that ended in a trial. A missed diagnosis, which resulted in failure of initial management of the injury, was the main reason for a claim. Three of the six cases resulted in complete or partial loss of a finger. Two cases are still open, requiring an expert witness's report, two cases were closed in favor of the defendant, and two cases were closed

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in favor of the plaintiff with a mean compensation of €2000 (€1000-€3000).

CONCLUSION
Missed diagnosis was the main reason for a malpractice claim. Better understanding of factors leading to successful claims will help surgeons improve their practice to minimize legal implications and litigation.

Key Words: Hand trauma; Wrist trauma; Litigation; Claim; Negligence

Core Tip: This is the first report related to hand and wrist trauma malpractice claims in Greece. Hand and wrist injuries, although non-fatal, can lead to long-term disability if a delay in diagnosis or treatment occurs. Additionally, missed diagnosis and inadequate management of these injuries can be the leading cause for medical malpractice claims, which appear to have an upward trend over the last decades. We present six malpractice claims related to hand and wrist trauma that resulted in a trial over a 20-year period in Greece and their outcomes, aiming to determine the reasons that lead to successful litigations.

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INTRODUCTION

Hand and wrist injuries are common and account for approximately 10%-30% of all presentations to emergency departments (EDs), affecting mainly young and economically productive people[1,2]. Although not commonly life threatening, delayed diagnosis or mismanagement of these injuries can result in prolonged recovery and likely long-term disability, having a negative impact on patient's quality of life, income, social activities and occasionally mental health[3,4].

Claims for negligence have been increasing in medical practice over the past few decades, with hand and wrist injuries and their treatment representing a significant percentage of orthopedic surgery lawsuits[5,6]. There are a few articles addressing the issue of malpractice in hand and wrist surgery, with most studies being performed in Europe[6]. However, there are no reports related to medical malpractice claims in hand and wrist injuries and surgery in Greece.

The purpose of this study was to seek the available data about medical malpractice in hand and wrist trauma and surgery in Greece, to define the reasons and to evaluate the burden of successful litigations in Greece and to compare this data with the international malpractice data.

MATERIALS AND METHODS

Data on all legal claims of negligence for hand and upper extremity surgery attributed to all surgical specialties that ended in a trial during the period of 2000-2019 was obtained after permission from the archives of the Council of State in Greece. We further analyzed the data to determine the number of claims related to hand and wrist trauma, the reasons that a claim was filed, the outcome of each claim and the financial size of the plaintiff's compensation in the case of a successful claim.

Our study was approved by our institutional research ethics board. All data was anonymized as indicated by the General Data Protection Regulation.

RESULTS

Among the malpractice claims related to hand and upper extremity surgery that went to a trial in the period between 2000 and 2019, six cases were correlated to hand and wrist trauma. Missed diagnosis, which resulted in failure of management and in one case in delayed referral to a specialized unit, was the main reason for a claim. Substandard surgery was an additional reason for claim in one case.

The mean time between injury and definite treatment was 9.1 (1-25) d. In all but one case adult patients were involved. The majority of cases (5) concerned the soft tissues, while one case was related to a wrist bone (scaphoid fracture). Three of six cases resulted in complete or partial loss of a finger.

Two of six cases are still open, requiring an expert witness's report, two cases were closed in favor of the defendant, and the remaining two cases were closed in favor of the plaintiff, with a mean compensation of €2000 (€1000-€3000). A brief summary of each case follows.

Case 1

A 51-year-old man presented to the ED of a district hospital on a Greek island, reporting high pressure injury of the proximal phalanx of his left index finger while cleaning a painting machinery. He was initially reviewed by a general surgery resident who under the guidance of a general surgeon cleaned the wound. On a follow-up visit 3 d after the injury, the wound was found to be necrotic. Due to lack of an orthopedic surgeon in the hospital, he was advised to visit the hospital of a nearby island, where this specialty was available. Following assessment by an orthopedic surgeon there, the patient was finally referred to a plastic surgery unit in Athens. Six days after the injury, the patient underwent an amputation of his left index finger at the level of the metacarpophalangeal joint.

A claim was filed by the patient stating that the amputation was the result of missed diagnosis and delayed referral to a specialized hand trauma unit. The case is still open, and an expert witness's report is required before a final decision is made.

Case 2

A fireman presented to the ED of a general hospital with a deep laceration of his left thumb following an injury by a satellite dish. The patient was reviewed by an orthopedic surgeon, and the wound was closed. On follow-up visit 15 d later, the patient complained of persistent pain and inability to move his thumb. Despite his complaints, no further action was taken. Due to persistence of symptoms 25 d after his injury, the patient was examined by a hand surgeon, and laceration of the flexor pollicis longus and the digital nerve was diagnosed. Reconstruction of the structures followed.

The patient filed a claim for initial missed diagnosis of his injury with subsequent late reconstruction and delay in his recovery. Compensation of €1000 was set for the patient. The case closed 8 years after the claim was filed.

Case 3

A 40-year-old woman presented to the ED of a general hospital with pain and swelling of her index finger and her thumb following an injury with a knife 4 d before. She was examined by a plastic surgery resident, who prescribed oral antibiotics and suggested reassessment in 2 d. The following day the patient was examined in a different hospital, where infection of her right hand and ischemic changes of the index finger were reported, necessitating surgical debridement. Four days later, in a specialized hand and microsurgery unit of a private hospital, the patient underwent amputation of the distal phalanx, further debridement of the index finger and reconstruction with a cross-finger flap. The patient filed a claim reporting missed diagnosis and improper management of her injury. The case was closed in favor of the defendant 10 years after the claim was filed.

Case 4

A woman presented to the ED of a general hospital following an injury to her left wrist with a glass. She was reviewed by both an orthopedic and a general surgeon. The wound was closed, and oral antibiotics were prescribed. On reassessment 12 d later, laceration of her ulnar nerve was diagnosed. Therefore, she was referred to a specialized unit and had her ulnar nerve repaired. Despite management in a specialized center, the patient was not able to fully use her left hand postoperatively. The patient filed a claim reporting missed diagnosis of her injury. The case was closed

in favor of the plaintiff and compensation of €3000 was set. The case closed 7 years after the claim was filed.

Case 5

A man presented to the ED of a general hospital following a fall from 2.5 m height and injury of his left wrist. He was assessed by an Orthopedic Surgery resident, and a radiograph was performed the same day. His wrist was splinted, and a follow-up visit was scheduled in 8 d. The follow-up radiograph depicted a fracture of the scaphoid bone, and 2 d later the patient was treated surgically. The fracture was fixed with Kirschner wires. Intraoperatively, one of the wires broke, and the remnant of the wire was left in the bone. The patient complained of reduced range of motion of his left wrist postoperatively. The patient filed a claim reporting missed diagnosis and substandard surgery. The case is still open, and an expert witness's report is required before a final decision is made.

Case 6

A 9-year-old boy was brought to the ED of an urban general hospital by his parents following a crush injury to his left index, middle and ring fingers. He was there assessed by a general surgery resident who sutured the lacerations. Three days later the boy was brought back to the ED due to ischemic changes to his middle finger. Despite admission in the hospital, the parents' wish was to visit a pediatric surgeon in another hospital. A degloving injury of the boy's middle finger was diagnosed, and amputation of the finger was performed (the level of the amputation was not mentioned in the claim). The family filed a claim reporting missed diagnosis of the boy's injury and subsequent mismanagement. The case was finally closed in favor of the defendant 7 years later.

Verdicts

In our study two cases were closed in favor of the plaintiff and two cases were closed in favor of the defendant. The reasonings behind the court's final decisions varied. Documentation, rarity of injury, functional outcome and delay in recovery have been the main reasons for the verdicts.

The two cases which were closed in favor of the plaintiff involved delay in the diagnosis of ulnar nerve laceration and of flexor pollicis longus and digital nerve laceration. In the first case, compensation was set because there was no full recovery of the nerve, even though the reconstruction was performed within the allowed time-period for nerve reconstruction. According to the decision, nerve reconstruction within the first days of the injury would have higher chances for full recovery. In the second case there was full recovery of both the nerve and the tendon despite the delay in diagnosis. However, due to the delay in diagnosis the plaintiff experienced pain and inability to use his hand for 25 d until the reconstruction of the structures and that was the reasoning for a verdict in favor of the plaintiff.

The two cases that were closed in favor of the defendant involved a degloving injury of a finger and an infection of a finger. The first case concerned a rare injury of the finger, the degloving injury, which a junior resident of an allied specialty (general surgery) was unlikely to know and have experience on its management. The degloving injury of the finger would be approached by every non-experienced doctor in the way the involved doctor did. The verdict of the second case was based on the clear documentation the involved doctor presented regarding the findings on the day of examination. The different and contradictory clinical presentation that the plaintiff contended could not be supported by any documentation or image to prove any inaccuracy in the doctor's documentation.

DISCUSSION

Acute hand and wrist injuries represent a common cause of visit to the ED. Hand injuries occur with a significant rate, constituting a considerable proportion of non-fatal injuries requiring medical attention[3]. Missed diagnosis and subsequent inadequate initial management of these injuries may lead to a prolonged period of disability and absence from work and social activities, further procedures and potentially a suboptimal outcome. The hand has complex anatomical and functional features and may be affected by a wide range of trauma, ranging from simple lacerations to injuries that require multiple reconstructive procedures. Adequate knowledge of the different mechanisms of injury and their association with certain

patterns of injury is essential to help the surgeon decide on the diagnostic and therapeutic process[4].

In Greece, hand and wrist injuries that present to the ED are initially assessed by orthopedic, plastic or general surgery residents, who usually review the cases with a consultant. The residents examine the patient, request laboratory and imaging evaluations and decide treatment in "simple" cases, while complex cases that cannot be managed in the hospital are referred to specialized hand surgery units. In district hospitals, initial assessment and management is performed by an orthopedic or a general surgeon. However, management of hand injuries by non-specialists (residents or consultants) carries the risk of poor outcome with subsequent increase in the cost for the patient, employer and society as stated by Kenesi and Masmejean in 2004[7].

Claims for negligence is a global problem with an upward trend[5]. According to the Greek Penal Code (article 28) "whoever due to lack of attention - that he should and could have paid according to the circumstances - didn't foresee the punishable result which his action caused or had foreseen it as possible but didn't believe it would actually happen, is acting in the content of negligence". Gidwani *et al*[8] reported substandard surgery and delay in diagnosis or treatment having been the most frequent reasons for litigation[8-10]. Similarly, in a study of all claims related to hand injuries against EDs in England during the period 2004-2014, failure or delay in the diagnosis and in the treatment of the injury were the two most common reasons for litigation[10].

Despite best efforts, hand and wrist injuries may be missed, and therefore proper management can be delayed. Morrison *et al*[11] studied 500 acute hand injuries that were referred to the Regional Plastic Surgery Unit in Northern Ireland. There were 16 (3.2%) missed injuries, and these were more common in patients examined by junior medical staff and in patients with trauma caused by glass. In minor lacerations the extent of the underlying injury can sometimes be underestimated. Previous studies reported that perioperative clinical findings of upper limb injuries may have an 8%-14% error rate when compared to intraoperative findings. Miranda *et al*[12] compared the clinical and intraoperative findings of 1526 hand injuries that were referred to a Hand Trauma Unit. Flexor tendon injuries were associated with a poor diagnostic concordance, while lacerative injuries were most likely to be associated with additional injuries. Mahdavian Delavary *et al*[7] studied all the claims related to hand and wrist injury for a period of 15 years in the Netherlands. A significant number of claims were related to the management of wrist fractures, while the commonest cause for a claim was inadequate management (34.8%), followed by missed diagnosis (33.8%). In the same study, 102 cases involved a missed nerve or tendon injury after a cut, and in 74.5% of these misdiagnosed cases, initial diagnosis was made by a resident. Finally, it was concluded that general surgeons, who occasionally treat hand conditions, were more likely to be involved in litigation[7].

In an ED setting the assessment of hand injuries can be challenging. Distracting injuries may also be present, patient's compliance may be poor due to alcohol or substance use, complexity of hand anatomy and the involvement of junior doctors or general surgeons, with limited experience in hand surgery can all contribute to errors [10].

In general, management of fractures has been associated with a high risk of claims. It has been reported that approximately 49% of the upper extremity claims are related to fracture management. The higher risk is associated with the patient's expectation to return to their pre-injury condition and with treatment by the on-call doctor, who may have a different area of expertise[14].

Scaphoid fractures are common wrist injuries, accounting for 82%-89% of carpal injuries. However, radiographs are often false-negative, and thus their contribution in diagnosing this injury is poor[13]. Litigation in wrist trauma is common with 48% of the claims related to hand and wrist surgery being for wrist fractures according to a study of Khan and Giddins[9]. Ring *et al*[13] studied all orthopedic claims registered in the National Health Service Litigation Authority between 1995 and 2012. Of all registered orthopedic claims, 36.3% were related to wrist and scaphoid fractures, with an average settlement per case of £45500 for wrist fractures and £51500 for scaphoid fractures[13]. The main reasons for successful claims was delayed, incorrect or missed diagnosis (43.5%), followed by alleged mismanagement (29.5%), poor patient care (10.1%) and alleged incompetent surgery[13].

Soft tissue injuries of the hand represent up to 82% of all hand injuries assessed in EDs. They can range from simple lacerations to more complex injuries requiring structural repair, with the high-pressure injection injuries being the "most urgent of all emergencies of the hand". High-pressure injection injuries, although not very frequent with an estimated incidence of 1 in 600 injuries, can be catastrophic for the patient if

Table 1 Learning points from the present study

First report of medical negligence claims related to hand and wrist trauma and surgery in Greece
Missed diagnosis was the main reason for filling a claim in hand and wrist trauma surgery
Missed diagnosis and subsequent inadequate management resulted in partial or complete loss of a finger in half of the cases
Junior doctors and doctors from allied specialties (other than orthopedic or plastic surgery) were involved in most of the claims
The main reasoning of the verdicts included accurate documentation, rarity of injury, functional outcome and delay in recovery

not referred to a hand unit promptly and not managed adequately. They have been associated with a high risk of amputation of the affected finger, ranging from 16% to 48% as well with the risk of systemic intoxication, if missed and not treated appropriately[15]. On the contrary, tendon injuries are common with an incidence of approximately 33.2 injuries per 100000 person-years and accompany most penetrating injuries of the hand. A concomitant tendon injury may be present in 54.8% of small lacerations and 92.5% of deep injuries through a small laceration[16].

Claims for negligence have been increasing in medical practice over the past few decades. In a retrospective study by Ajwani *et al*[5] of 325 successful claims related to hand and wrist injuries and surgery in England from the period 2002-2012, payouts for hand injuries were reported to range from £1000 to £374077 while for wrist injuries from £200 to £669471. In the same study, poor outcome, nerve damage, unnecessary pain due to delayed diagnosis or management, additional procedures and fracture were identified as the commonest reasons for successful litigation[5].

In our study, all claims were for missed diagnosis that resulted in delay of proper treatment. The amounts of plaintiff's compensation (€1000, €3000) were lower compared to the ones described in the literature. The limited case law regarding compensation for hand and wrist injuries in Greece may explain the low compensation payments. Additionally, more than half of the cases were initially examined and treated by residents in plastic, orthopedic or general surgery, and failure in diagnosis was attributed to them by the plaintiff. In one case a high-pressure injury was assessed and managed by a general surgeon, who did not have experience in the management of this pattern of injury.

In the present study we reviewed only the claims related to hand and wrist trauma that went to a trial. It cannot be interpreted as representative of all malpractice claims in hand and wrist trauma. At present, there is no official authority in Greece where all negligence claims can be registered. Therefore, we cannot estimate the total amount of negligence claims for hand and wrist trauma that were filed between 2000 and 2019 and the number of claims that were settled outside court (Table 1).

CONCLUSION

This is the first report of medical negligence claims related to hand and wrist injuries that went to a trial in Greece. We presented six cases of hand and wrist trauma that reached the court room and their decisions. The main cause for filing a claim was missed diagnosis, which resulted in delayed management and in loss of a finger in 50% of cases. Hand and wrist injuries are common with possible long-term disability if treated inadequately. Therefore, a better understanding of the factors that lead to successful claims will help surgeons improve their practice to minimize legal implications and litigation.

ARTICLE HIGHLIGHTS

Research background

Medical negligence claims have presented an upward trend over the last decades worldwide, with hand and wrist liability representing a significant burden of orthopedic surgery lawsuits. Hand and wrist injuries are common, affecting mainly young and economically productive people. However, even small injuries may lead to long-term disability if treated inadequately, with affected people becoming unable to work, socialize and perform routine daily activities.

Research motivation

Literature addressing the issue of malpractice in hand and wrist surgery has been scarce, with most studies being performed in Europe and the United States. However, there are no studies related to liability in hand and wrist trauma and surgery in Greece.

Research objectives

The purpose of this study was to identify medical malpractice claims in hand and wrist surgery in Greece, to define the reasons for filing a claim and to define the reasons of successful litigations. Additionally, the results of the study were compared with the international malpractice data.

Research methods

This is a retrospective study of all medical malpractice claims for hand and upper extremity surgery that went to a trial attributed to all surgical specialties in Greece over a 20-year period. Claims were further analyzed to identify claims related to hand and wrist trauma and surgery.

Research results

We presented six medical malpractice cases related to hand and wrist trauma that ended in a trial. Missed diagnosis and subsequent failure of initial management of the injury was the main reason for filing a claim. In half of the cases mismanagement resulted in complete or partial loss of a finger. Two cases are still open, two cases were closed in favor of the defendant, and two cases were closed in favor of the plaintiff with a mean compensation of €2000.

Research conclusions

This is the first report of medical negligence claims related to hand and wrist trauma in Greece. A missed diagnosis of hand and wrist injury can result in long-term disability for a patient and has been the main reason for a malpractice claim. In the present study, missed diagnosis resulted in partial or complete loss of a finger in half of the cases.

Research perspectives

Better understanding of the factors that lead to successful claims can result in the improvement of services to hand trauma patients and will help surgeons improve their practice to minimize legal implications and litigation.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of remdesivir for hospitalized COVID-19 patients with end stage renal disease

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Author contributions: Selvaraj V, Finn A and Lal A were responsible for the conception and design of the work, screening of papers and drafting the manuscript; Jindal A was responsible for the literature review and contributed to manuscript writing; Tanzer JR and Baig M performed analysis and final approval; Jindal A, Dapaah-Afriyie K and Bayliss G contributed to research oversight, data review and manuscript revision.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were

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Abstract

BACKGROUND

Since the beginning of corona virus disease 2019 (COVID-19) pandemic, there has been a widespread use of remdesivir in adults and children. There is little known information about its outcomes in patients with end stage renal disease who are on dialysis.

AIM

To assess the clinical outcomes with use of remdesivir in adult patients with end stage kidney failure on hemodialysis.

METHODS

A retrospective, multicenter study was conducted on patients with end stage renal disease on hemodialysis that were discharged after treatment for COVID-19 between April 1, 2020 and December 31, 2020. Primary endpoints were oxygen requirements, time to mortality and escalation of care needing mechanical ventilation.

RESULTS

obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors declare no conflict of interest.

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Grade B (Very good): 0
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Grade D (Fair): 0
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A total of 45 patients were included in the study. Twenty patients received remdesivir, and 25 patients did not receive remdesivir. Most patients were caucasian, females with diabetes mellitus and hypertension being the commonest comorbidities. There was a trend towards reduced oxygen requirement (beta = -25.93, X^2 (1) = 6.65, P = 0.0099, probability of requiring mechanical ventilation (beta = -28.52, X^2 (1) = 22.98, P < 0.0001) and mortality (beta = -5.03, X^2 (1) = 7.41, P = 0.0065) in patients that received remdesivir compared to the control group.

CONCLUSION
Larger studies are justified to study the effects of remdesivir in this high-risk population with end stage kidney disease on dialysis.

Key Words: COVID-19; Remdesivir; End stage renal disease; Dialysis; Hemodialysis; Kidney disease

Core Tip: Little known information exists regarding the efficacy of remdesivir in corona virus disease 2019 patients with end stage renal disease on dialysis. Use of remdesivir was associated with a trend towards reduced oxygen requirement, reduced probability of progression to mechanical ventilation and better prognosis. Larger studies are justified in this high risk, vulnerable population.

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INTRODUCTION

Corona virus disease 2019 (COVID-19) is a clinical syndrome arising from infection with severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) coronavirus that has led to several hospitalizations and intensive care unit admissions. Remdesivir, a viral RNA polymerase inhibitor, has demonstrated in vitro activity against viruses such as Middle East Respiratory Syndrome - CoV (MERS-CoV), Ebola, and SARS-CoV1.

In the Adaptive COVID-19 Treatment Trial-1 (ACTT-1), remdesivir was noted to reduce the median time to recovery when compared to the placebo group (10 *vs* 15 d) [1]. The Infectious Diseases Society of America (IDSA) recommended the use of remdesivir in hospitalized patients with severe COVID-19 with SpO2 < 94%, including patients on supplemental oxygen or mechanical ventilation[2]. The World Health Organization (WHO) issued a 'weak or conditional' recommendation against the use of remdesivir in hospitalized COVID-19 patients[3]. Despite this, the use of remdesivir is widespread in hospitalized COVID-19 patients. Many of the clinical trials on remdesivir excluded COVID-19 patients with severe renal dysfunction (CrCl < 30 mL/min/1.73m^2). Little is known about clinical outcomes with use of remdesivir in COVID-19 patients with severe renal dysfunction or end-stage renal disease (ESRD) who are on hemodialysis (HD).

As remdesivir has poor water solubility, Sulfobutylether-β-Cyclodextrin (SBECD) is added to the intravenous preparation as a vehicle. Dialysis and renal replacement therapy readily remove SBECD, and significant accumulation of SBECD only occurs when dialysis is held for prolonged periods in ESRD patients. Voriconazole is another medication that has been safely used in patients with kidney failure using the same carrier (SBECD)[4].

Our hypothesis is that the addition of remdesivir to dexamethasone as part of the treatment regimen in COVID-19 patients with ESRD may have impact on the overall length of stay, need for supplemental oxygen, mortality, and mechanical ventilation. The aim of this study was to evaluate the feasibility and efficacy of using remdesivir in

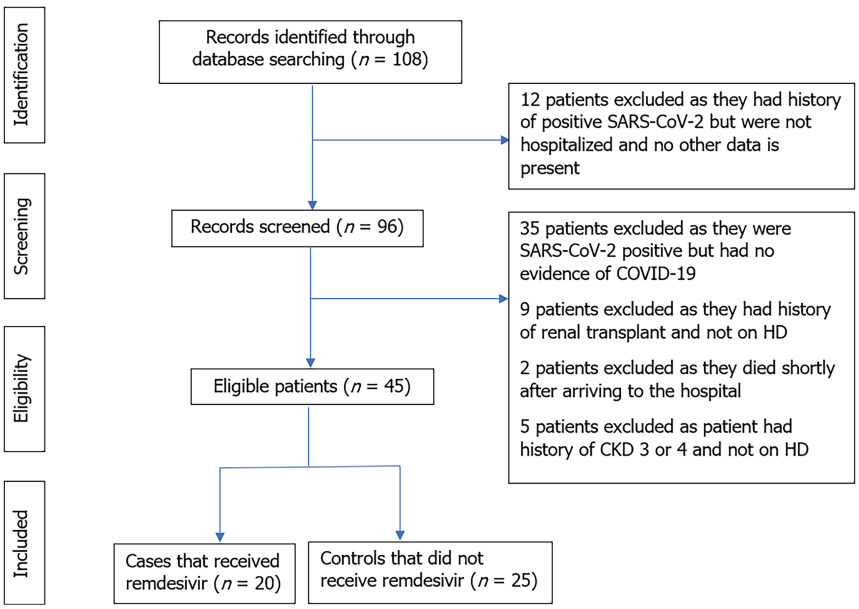

Figure 1 Flow chart outlining patient selection. SARS-CoV-2: Severe acute respiratory syndrome-coronavirus 1; COVID-19: Corona virus disease 2019; CKD: Chronic kidney disease; HD: Hemodialysis.

patients with COVID-19 and ESRD on HD.

MATERIALS AND METHODS

We collected data from two quaternary, acute care hospitals, Rhode Island Hospital (RIH) and The Miriam Hospital (TMH), located in Providence, Rhode Island. All hospitalized patients above the age of 18 years with ESRD on HD from April 1 to December 31, 2020, with a positive polymerase chain reaction (PCR) nasopharyngeal or oropharyngeal SARS-CoV-2 swab were screened for potential study inclusion (Figure 1). ESRD was defined as a GFR of less than 15 mL/min/1.73m^2 according to the chronic kidney disease epidemiology collaboration (CKD-EPI) formula. The study was reviewed and approved by the Institutional Review Board of TMH. Data was collected by physicians in the Division of Hospital Medicine at Miriam Hospital (an affiliate of Warren Alpert Medical School of Brown University).

Patients with moderate disease included patients with CRP levels between 50-200 mg/L (normal 0-10 mg/L) and 2-6L/min of oxygen requirement. Patients with severe disease included patients with CRP levels greater than 200 mg/L and oxygen requirements greater than 6 L/min. Prone positioning was instituted in all patients with moderate to severe disease if they could tolerate it.

Remdesivir group selection

All patients with ESRD on HD hospitalized with PCR-confirmed COVID-19 in both hospitals were screened for inclusion. To be considered eligible for study inclusion, patients had to meet the following criteria: (1) Hospitalized for at least 48 h, aged ≥18 years; (2) SARS-CoV-2 infection confirmed by RNA PCR test; (3) SpO2 ≤ 94% on room air or requiring supplemental oxygen; and (4) Presence of radiographic evidence of pulmonary infiltrates. These patients were given 200mg of intravenous (iv) remdesivir on day one, followed by 100 mg once daily for 2-10 d or until discharge, death or if there was elevated AST/ALT, with levels greater than ten times the upper limit of normal.

Control group selection

For the purposes of this study, we created a control group consisting of hospitalized ESRD patients on HD with PCR-confirmed COVID-19 who did not receive remdesivir (during the same study period). To identify controls, we screened all patients with ESRD on HD who were admitted to both hospitals from April 1 to December 31, 2020 and did not receive remdesivir. After identifying those patients and to minimize selection bias, we used the following inclusion criteria: (1) Hospitalized for at least 48

Table 1 Baseline characteristics of study population

	Remdesivir (*n* = 20)	Control (*n* = 25)
Mean age (yr)	64.20 (± 15.16)	68.32 (± 12.67)
Age groups in years (*n*, %)		
18-40	2 (10)	1 (4)
41-64	5 (25)	7 (28)
Above 65	13 (65)	17 (68)
Females (*n*, %)	11 (55)	12 (48)
Race or ethnic group (*n*, %)		
White or Caucasian	9 (45)	12 (48)
Hispanic	5 (25)	9 (36)
Black or African American	2 (10)	2 (8)
Other	4 (20)	2 (8)
Tobacco use (*n*, %)	11 (55)	14 (56)
Diabetes mellitus (*n*, %)	13 (65)	20 (80)
Hypertension (*n*, %)	19 (95)	24 (96)
Coronary artery disease/peripheral vascular disease (*n*, %)	8 (40)	9 (36)
Congestive heart failure (*n*, %)	10 (50)	12 (48)
History of lung disease- no. (%)	6 (30)	9 (36)
Obesity (BMI>30 kg/m^2) (*n*, %)	8 (40)	12 (48)
Arrhythmia (*n*, %)	6 (30)	9 (36)
Length of stay - d (± SD)	13.00 (± 7.35)	12.16 (± 8.38)
Treatment (*n*, %)		
Corticosteroids	20 (100)	17 (68)
Antibiotics	13 (65)	13 (52)
Therapeutic anticoagulation	9 (45)	11 (44)

h, aged ≥18 years; (2) SARS-CoV-2 infection confirmed by PCR test; (3) SpO2 ≤ 94% on room air or requiring supplemental oxygen; and (4) Presence of radiographic evidence of pulmonary infiltrates.

Patients who met the following criteria were excluded: (1) Patients < 18 years of age; (2) Patients with ESRD who received renal transplant and are not on dialysis; and (3) Patients with AST, ALT > 10 times the upper limit of normal. The Nephrology service at Miriam Hospital (an affiliate of Alpert Medical School of Brown University) followed these patients while they were admitted. Patients also received antibiotics if there was a concern for superimposed bacterial infection in addition to the other interventions keeping in line with the institutional standard of care.

Endpoints

Our primary endpoint was comparing the oxygen requirements, time to mortality and escalation of care needing mechanical ventilation in patients that received remdesivir *vs* control group.

Data collection

Data were obtained from the Epic Electronic Medical Record system and recorded in a standardized form. Demographic data, laboratory findings, maximum oxygen requirements in Liters Per Minute (LPM), length of stay (LOS), and comorbid conditions were ascertained. Outcome measures were assessed through the date of study completion, hospital discharge or death; whichever came first.

Statistical analysis

To compare rates of oxygen and ventilator use, generalized linear modeling was used. Estimation was by maximum likelihood using SAS proc genmod software[5]. Mean oxygen use was modeled first as a normal distribution with an identity link, and the progression to mechanical ventilation was modeled as a binomial distribution with a logit link. For the length of stay and patient disposition, survival analysis was used, estimation by SAS proc phreg[6]. Here the length of stay is modeled as a ratio for patients who discharge *vs* patients who do not survive. The complete outcome data was available for both the cases and controls until death or discharge from the hospital. The risk of patient health deterioration as a function of time is modeled given covariates. Model selection was based on expert medical knowledge as well as the visual examination of residual plots.

Patient experience of COVID-19 pneumonia is highly variable, differences between patients were modeled as conditional on patient health status. Comparisons were made between patients with diabetes because this is a known risk population that would be highly susceptible to disease. Additionally, to identify the specific patients with severe condition, comparisons were also made based on d dimers. Grouping patients by rate of d dimers was selected because there were clear groupings among respondents. The histogram demonstrated a bimodal distribution, with some patients having very few d dimers, and some having many (skew = 2.64, kurtosis = 7.30). To account for this, patients above the mean were classified as "high d dimer" and patients below the mean classified as "low d dimer." The three-way interaction could then be modeled as a 2 (remdesivir or control) × 2 (diabetic or not diabetic) × 2 (high or low d dimer) ANOVA style design with interactions. While there were data available on corticosteroids, the observational nature of the study raised concerns that this may be a biased estimate because treatments were not given at random. As the research question mainly focused on the clinical outcomes with use of remdesivir, only patients' health characteristics were used as control variables, rather than introducing the complexity of various drug interactions within a small study sample.

Before analyzing the data, a brief power analysis was done to calibrate the limitations of the sample size. This was accomplished using G × Power software and the equations provided by Schoenfeld[7]. For the general regression models (oxygen, ventilator use), it was estimated that the effect of remdesivir needed to be large to be significant, accounting for 28% of the variance (2% is considered small, 13% medium, and 26% large). The effects of the additional covariates would also need to be large, accounting for an additional 25% of the variance. The survival analysis had better power, sensitive to a small to moderate effect size, risk ratio 2.32 (convention is 1.68 small, 3.47 medium, 6.71 Large)[8]. While the sample is smaller than would be preferred, the urgency of this research question outweighs the risk of statistical power.

RESULTS

A total of 108 charts were reviewed, of which only 45 met the inclusion criteria. A total of 20 patients received remdesivir while 25 patients were in the control group. Baseline statistics are reported in Table 1. There was no significant difference in length of stay in patients that received remdesivir (M = 13.00 ± 7.35 d) compared to patients that did not receive remdesivir (M = 12.16 ± 8.38 d). Table 2 has the main effect parameter estimates for the primary research questions and covariates, and Table 3 provides the estimated means by risk group for all three endpoints. Oxygen usage was considered first. The main effect of remdesivir was significant and the parameter was negative, indicating that across patients, those who were on remdesivir tended to use less oxygen (beta = -25.93, X^2 (1) = 6.65, P = 0.0099). That said, the three-way interaction term was significant (X^2 (1) = 6.37, P = 0.0116), indicating that the means varied based on patient risk conditions. Comparing remdesivir and control groups within risk groups, differences were only significant among patients who did not have diabetes (see Table 3).

Examining the covariates, the only significant finding at alpha = 0.05 was for sex, such that women tended to have lower oxygen need on average (beta = -9.49, X^2 (1) = 4.43, P = 0.0198). In addition, there was a trend for older patients and patients who used tobacco toward higher oxygen use (age: beta = 0.32, X^2 (1) = 3.25, P = 0.0712; tobacco use: beta = 8.49, X^2 (1) = 3.82, P = 0.0507). We anticipate that with larger sample size these results would reach the threshold of statistical significance.

Table 2 Main effect parameter estimates for the primary outcomes and covariates

	Outcome: Max O2			Outcome: Ventilation			Outcome: Time to Mortality		
Variable	**PE**	**X^2 (1)**	***p***	**PE**	**X^2 (1)**	***P* value**	**PE**	**X^2 (1)**	***P* value**
Age	0.32	3.25	0.0712	0.04	0.56	0.4562	0.05	1.75	0.1860
Tobacco use	8.59	3.82	0.0507	1.29	0.91	0.3399	-0.89	0.91	0.3398
Female Sex	-9.49	5.43	0.0198	-2.94	3.80	0.0511	0.05	< 0.01	0.9529
Black, Hispanic, and Other races	7.02	2.69	0.1011	2.14	1.96	0.1614	1.18	1.91	0.1672
Obesity	5.35	1.36	0.2444	1.46	0.74	0.3904	0.32	0.16	0.6932
Diabetes	-20.59	5.21	0.0224	-4.06	3.61	0.0575	-4.17	9.25	0.0024
High d dimers	-21.50	2.22	0.1358	-0.01	< 0.01	0.9971	-5.86	7.41	0.0065
Remdesivir	-25.93	6.65	0.0099	-28.52	22.98	< 0.0001	-5.03	7.42	0.0065

PE stands for parameter estimate. For Max O2, this is the average difference between the specified group and the overall mean. For ventilation, this represents the log odds difference between the specified group and the overall odds of being on a ventilator. For time to mortality, this represents the difference in risk of mortality as a function of time for the specified group relative to the overall risk of mortality for corona virus disease 2019 patients. Because age was specified as a continuous value, the values in PE represent the change in mean, odds, or risk for a one-year increase or decrease in age.

Next the progression to mechanical ventilation was considered. As before, remdesivir use was associated with much better outcome (beta = -28.52, X^2 (1) = 22.98, P < 0.0001). The three-way interaction term was not significant, reducing the model fit overall, however the interactions between remdesivir and each of diabetes and high d dimer status was significant (P < 0.0001), indicating dependencies between patient characteristics and health outcomes. Examining the conditional probabilities of mechanical ventilation need, remdesivir was found to be helpful for patients who were not diabetic and had low d dimer values (P < 0.0001). No covariates showed statistically significant association with the risk of needing a ventilator; female sex reached very close to statistical significance (X^2 (1) = 3.80, P = 0.0511), indicating less risk of ventilator use on average (beta = 2.94).

Finally, the time to mortality was examined, providing similar results to the previous analyses. The main effect of remdesivir was significant (X^2 (1) = 7.41, P = 0.0065) indicating on average patients on remdesivir had a better prognosis (beta = -5.03). The three-way interaction was not significant (X^2 (1) = 0.63, P = 0.4262), however all two-way interactions were significant or close to significant (remdesivir-high d dimers: X^2 (1) = 3.56, P = 0.0591; remdesivir-diabetes: X^2 (1) = 4.59, P = 0.0322; high d dimers-diabetes: X^2 (1) = 4.58, P = 0.0324) indicating dependent risks given patient characteristics. Again, it was specifically patients who did not have diabetes and had low d dimers for whom remdesivir demonstrated to significantly reduced risk (P = 0.0032, risk ratio < 0.01). No covariates demonstrated significant association with COVID-19 pneumonia prognosis.

DISCUSSION

Our study demonstrated a trend towards lesser oxygen requirement in the group of ESRD patients on HD who received remdesivir for the treatment of COVID-19 pneumonia. There was also a trend towards lower progression to mechanical ventilation in patients with COVID-19 that received remdesivir as compared to the control group. There was a trend towards better prognosis in terms of mortality in patients that received remdesivir compared to patients in the control group. However, due to the smaller number this trend did not reach statistical significance. None of the patients' treatment was interrupted due to hepatotoxicity. To our knowledge, only case series have been previously published on the safety of remdesivir in COVID-19 patients with ESRD.

Remdesivir is a monophosphoramidate prodrug of a nucleoside analogue and an inhibitor of the viral RNA-dependent RNA polymerase (RDRP). Intracellularly, the prodrug is rapidly converted into GS-704277 and subsequently into a monophosphate form that is finally converted into the active triphosphate form. Dephosphorylation of

Table 3 Group mean comparisons

D dimers	Diabetes	Condition	Mean	Z	*P* value	Cohen's d
Outcome: Max O2						
High	Yes	Remdesivir	28.80	-0.75	0.2260	0.43
		Control	36.81			
	No	Remdesivir	46.23	2.38	0.0087	1.76
		Control	13.22			
Low	Yes	Remdesivir	13.99	-0.33	0.3712	0.09
		Control	15.72			
	No	Remdesivir	8.79	-2.06	0.0199	1.38
		Control	34.72			
Outcome: Probability of being on a ventilator						
D dimers	Diabetes	Condition	% on ventilator	Z	*p*	Risk ratio
High	Yes	Remdesivir	6.16	-1.21	0.1125	0.11
		Control	55.34			
	No	Remdesivir	67.92	-0.07	0.4708	0.90
		Control	75.47			
Low	Yes	Remdesivir	8.22	0.27	0.3955	1.62
		Control	5.07			
	No	Remdesivir	0.00	-4.45	< 0.0001	0.00
		Control	75.66			
Outcome: Time to mortality						
D dimers	Diabetes	Condition	Hazard ratio	Z	*p*	Risk ratio
High	Yes	Remdesivir	-3.13	0.11	0.4570	5.78
		Control	-4.92			
	No	Remdesivir	-5.98	-0.02	0.4930	0.89
		Control	-5.86			
Low	Yes	Remdesivir	-4.84	-0.12	0.4512	0.52
		Control	-4.17			
	No	Remdesivir	-5.03	-2.72	0.0032	0.01
		Control	0.00			

Cohen's d effect size is conventionally defined as small = 0.2, medium = 0.5, and large = 0.8. Effect sizes for risk ratios are conventionally defined as small = 0.60 or 1.68, medium = 0.29 or 3.47, and large = 0.15 or 6.71.

the monophosphate form produces the nucleoside core (GS-441524), which becomes the predominant circulating plasma metabolite. The triphosphate form acts as an analog of adenosine triphosphate (ATP) and competes for incorporation by RDRP, causing premature chain termination and inhibition of viral replication. Originally developed as an investigational drug for Ebola virus, remdesivir has potent in vitro inhibitory activity against SARS-CoV1, MERS coronavirus, and SARS-CoV2. Remdesivir is usually intravenously administered at a dose of 200 mg once followed by 100 mg daily for a total of 5-10 d in adults and children ≥ 40 kg. The plasma $t_{1/2}$ of parent remdesivir is 1-2 hours, however the $t_{1/2}$ of GS-441524 is approximately 20-25 hours[9,10].

The intravenous preparation of remdesivir also contains a solubilizing agent, SBECD. Every 100 mg of remdesivir contains 3-6 g of SBECD (maximum recom-

mended threshold dose 250 mg/kg per day)[11]. Animal studies have shown that SBECD accumulation may only cause hepatic and renal toxicity at doses 50 to 100 times higher than the present patients' exposure during a 5-to-10-day course of remdesivir[12,13]. SBECD does not undergo significant tubular reabsorption and remains in an ionized state after glomerular filtration. Only less than 10% of remdesivir is renally excreted while 49% is recovered in the urine as GS-441524. In a case series by Davis *et al*, remdesivir's half-life in 66% of the COVID-19 patients with ESRD was twice as long as in healthy volunteers. While there was a decline in remdesivir concentrations by the end of the dosing interval, GS-441524 levels were also considerably higher than reference values. Despite this, post-HD concentrations of GS-441524 were 45%-49% lower than pre-HD measurements[14].

The results from our feasibility study are hypothesis generating. We see interesting trends towards lower oxygen requirements, and reduced progression to mechanical ventilation in the ESRD patients that received remdesivir as a part of the treatment for COVID-19. If remdesivir is an efficacious treatment as hypothesized, it would be expected that patients receiving this treatment would have better outcomes. This was observed in the data, at least for patients who were lower risk (i.e., not diabetic, low d dimer rates). This provides early support for remdesivir, though larger studies could show the effect of remdesivir on these patient centric outcomes.

Our study has many limitations. Firstly, only 68% of the patients in the control group received dexamethasone. However, all the patients in the remdesivir group received dexamethasone. This is mainly because some patients in the control group presented before July 2020 when dexamethasone use was not considered standard of care. In place of dexamethasone, alternative treatments such as hydroxychloroquine and convalescent plasma were used. Steroids were only used in these patients if they were in septic shock requiring vasopressors. Secondly, the sample size was relatively small. The study may not have been adequately powered to detect a significant difference. However, being a feasibility study, we did not expect the results to be statistically significant. Lastly, being a retrospective study, the study design has inherent biases such as selection and confounding biases.

CONCLUSION

The use of remdesivir in COVID-19 patients with ESRD showed a trend towards lesser oxygen requirements, lower progression to mechanical ventilation and survived longer. Our feasibility study is hypothesis generating and these patterns need further exploration with larger studies. Further research is also needed to study the clinical effects of remdesivir in COVID-19 patients with CKD stage 4 or 5 that are not on hemodialysis.

ARTICLE HIGHLIGHTS

Research background

Little known information exists regarding the efficacy of remdesivir in COVID-19 patients with end stage renal disease on dialysis.

Research motivation

With increasing use of remdesivir in COVID-19 patients we need more information about specific group of patients who could potentially benefit from the use of this medication and its safety profile.

Research objectives

To assess the clinical outcomes with use of remdesivir in adult patients with end stage kidney failure on hemodialysis.

Research methods

A multicenter, retrospective study was conducted on COVID-19 patients with end stage renal disease on hemodialysis that were discharged from the hospital between April 1st and December 31st, 2020. The primary outcomes were oxygen requirements, time to mortality and escalation of care needing mechanical ventilation.

Research results

A total of 45 patients were included in the study. Twenty patients received remdesivir, while 25 patients did not receive remdesivir. Most of the patients were females, Caucasians, and had diabetes mellitus and hypertension as the commonest comorbidities. There was a trend towards reduced oxygen requirement (beta = -25.93, X^2 (1) = 6.65, P = 0.0099, probability of requiring mechanical ventilation (beta = -28.52, X^2 (1) = 22.98, P < 0.0001) and mortality (beta = -5.03, X^2 (1) = 7.41, P = 0.0065) in patients that received remdesivir compared to the control group.

Research conclusions

Larger studies are justified to study the effects of remdesivir in this high-risk population with end stage kidney disease on dialysis.

Research perspectives

We believe that larger studies (both observational and randomized clinical trials) are warranted to further confirm the findings of this study.

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ORIGINAL ARTICLE

Prospective Study

Epidemiology of electrical burns and its impact on quality of life - the developing world scenario

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Abstract

BACKGROUND

Electrical burns are devastating injuries and can cause deep burns with significant morbidity and delayed sequelae. Epidemiological data regarding the etiology, socioeconomic differences and geographic variation are necessary to assess the disease burden and plan an effective preventive strategy. These severe injuries often lead to amputations and thus hamper quality of life in the long term

AIM

To identify the population at maximum risk of sustaining electrical burns. We also studied the impact of electrical burns on these patients in terms of quality of life as well as return to work.

METHODS

The study was conducted at a tertiary referral teaching hospital over a period of eighteen months. All patients with a history of sustaining electrical burns and satisfying the inclusion criteria were included in the study. All relevant epidemiological parameters and treatment details were recorded. The patients were subsequently followed up at 3 mo, 6 mo and 9 mo. The standardized Brief Version of the Burn Specific Health Scale (BSHS-B) was adopted to assess quality of life. Statistical analysis was conducted using IBM SPSS statistics (version 22.0). A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 103 patients were included in the study. The mean age of the patients was 31.83 years (range 18-75 years). A significant majority (91.3%) of patients were male. The mean total body surface area (TBSA) in these patients was 21.1%. In most of the patients (67%), the injury was occupation-related. High voltage injuries were implicated in 72.8% of patients. Among the 75 high voltage burn patients, 31 (41%) required amputation. The mean number of surgeries the patients underwent in hospital was 2.03 (range 1 to 4). The quality of life

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parameters amongst the patients sustaining high voltage electrical burns were poorer when compared to low voltage injuries at all follow-up intervals across nine domains. In eight of these domains, the difference was statistically significant. Similarly, the scores among the amputees were poorer when compared to non-amputees. The difference was statistically significant in six domains.

CONCLUSION
Electrical burns remain a problem in the developing world. Most injuries are occupation-related. The quality of life in patients with high voltage burns and amputees remains poor. Work resumption was almost impossible for amputees. These patients could not regain pre-injury status. Steps should be taken to create awareness and to implement an effective preventive strategy to safeguard against electrical injuries.

Key Words: Electrical burns; Quality of life; Amputation; Return to work; Occupational therapy; High voltage injuries

Core Tip: Electrical burns remain a problem in the developing world. Most injuries are occupation-related. The quality of life in patients with high voltage burns and amputees remains poor. Work resumption was almost impossible for amputees. These patients could not regain pre-injury status. Steps should be taken to create awareness and implement an effective preventive strategy to safeguard against electrical injuries.

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INTRODUCTION

Electrical appliances are used in domestic as well as industrial settings on a daily basis, and it is difficult to imagine normal life without electricity. Electrical injuries are probably as old as the discovery of electricity itself. The first recorded case of electrical injury was in 1879 in France when a carpenter suffered a low voltage injury (250 V) when operating a generator[1], and today electrical injury is considered the most common cause of occupation-related injury in developing as well as developed nations [2,3].

An electrical injury does not only involve the superficial layers of the skin but can injure the deeper tissue and can cause multiorgan damage and even death[4,5]. Electrical injuries occur due to passage of the electric current through the body and can be challenging to manage due to progressive necrosis as a result of injury to the microvasculature. The injury may lead to limb loss and disfigurement of the victim which will have a lasting impact on the ability of the individual to resume work (Figure 1). Most electrical injuries are preventable provided there are appropriate safety precautions. Epidemiological data regarding the etiology, socioeconomic differences and geographic variation are necessary before an effective prevention strategy can be planned[6,7]. Patients with electrical burns can suffer cognitive disturbances including slower thinking, impaired concentration, language and memory problems, as well as emotional distress[8,9]. Therefore, patients can have long-term residual effects affecting their quality of life. Knowledge of the characteristics of the injury and mechanism by which the injuries are sustained in our area we can help formulate specific preventive strategies. Those people who are at maximum risk of sustaining these injuries can be educated in terms of preventive measures. This will help reduce the morbidity and mortality associated with this injury.

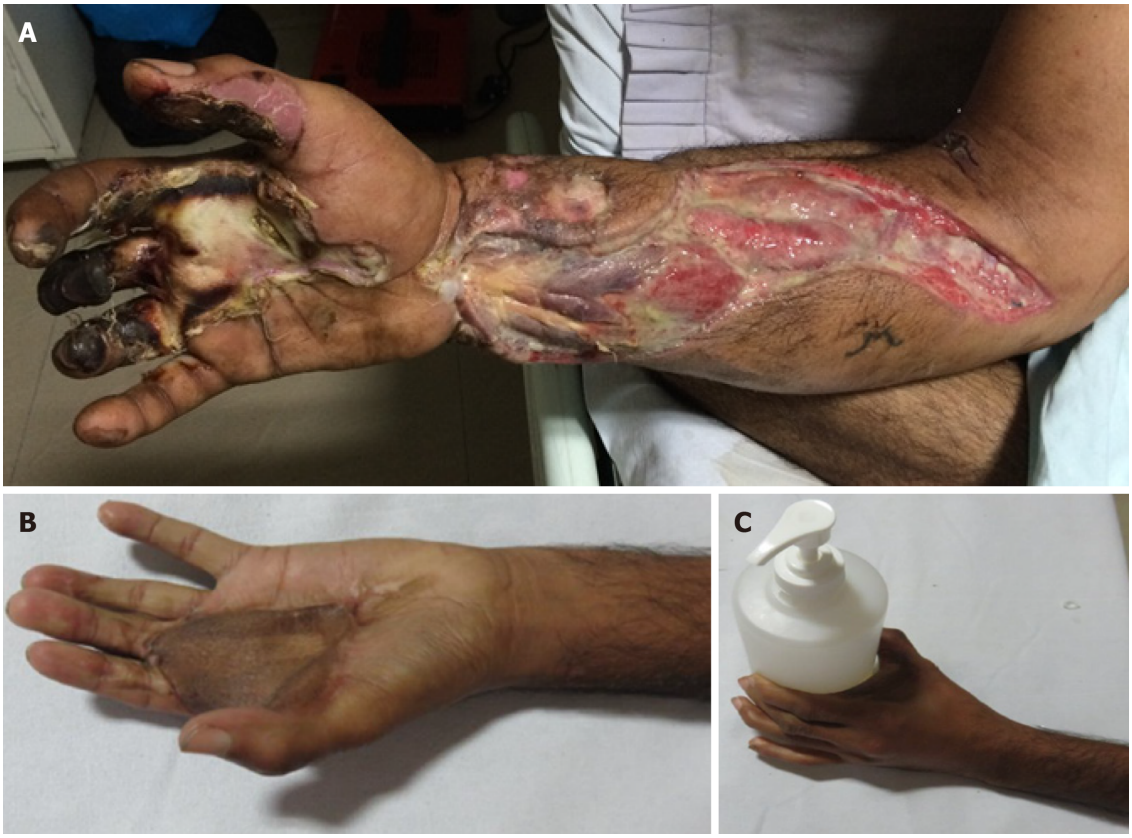

Figure 1 The injury may lead to limb loss and disfigurement of the victim which will have a lasting impact on the ability of the individual to return to work. A: Appearance on day 5 following fasciotomy in a high voltage electrical burns patient showing a gangrenous middle finger and ring finger along with nonviable tendons; B: Following skin necrosis due to electrical burns, debridement and a groin flap were performed; C: Same patient shown in Figure 1A and B using his injured hand to hold a bottle.

MATERIALS AND METHODS

Patient selection

The study was conducted in the Department of Plastic Surgery, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, over a period of eighteen months. This prospective case series consisted of all patients presenting to the Advanced Trauma Centre, PGIMER with electrical burns. Patients who had pre-existing comorbidities, or who were incoherent/intubated were excluded from the study. Patients less than 18 years of age were also excluded as they would not be able to complete the quality of life questionnaire satisfactorily.

Patient evaluation and follow-up

A thorough history and physical examination was undertaken to determine the mechanism of injury, and an evaluation of possible associated life-threatening injuries was carried out. The wounds were evaluated and the need for emergency procedures such as fasciotomy for compartment syndrome were carried out when required.

Immediate complications were ruled out or addressed and resuscitation of the patient was started after determining the percentage of total body surface area (TBSA) involved (calculated using the Lund and Browder chart). Fluid resuscitation was guided by the Parkland formula. Adequate resuscitation was confirmed by maintaining adequate urine output.

An electrocardiogram was performed to rule out arrhythmia and necessary treatment was given if required. Urine myoglobin was determined in all patients with electrical burns. Routine blood investigations including serum electrolytes were evaluated to rule out any anomalies and if necessary corrective treatment was given.

The patient's course was followed in the ward and epidemiological data were collected using a burn proforma and surgical procedures undertaken were recorded. Follow-up was carried out at 3 mo, 6 mo and 9 mo. The standardized and valid Brief Version of the Burn Specific Health Scale (BSHS-B) was adopted to assess health-related quality of life (HRQOL) in patients with extensive severe burns in 40 items

among nine domains: heat sensitivity, affect, hand function, treatment regimens, work, sexuality, interpersonal relationships, simple abilities, and body image[10]. The items were scored using a five point Likert scale with 0, extremely; 1, quite a bit; 2, moderately; 3, a little bit; and 4, none (not at all). Higher scores indicated greater HRQOL. Among the specific instruments available for measuring burn patients' quality of life, BSHS-B is the most widely used[11].

Statistical analysis

Discrete categorical data are represented either as a number or a percentage (%); Continuous data are represented as either the mean and standard deviation or the median and interquartile range. The normality of quantitative data was checked using the Kolmogorov-Smirnov tests of normality. For normally distributed data the means of BSHS in 3 types of electrical burns were compared using One-Way ANOVA followed by the post hoc Multiple Comparisons test. For normally distributed data, the Student t-test was applied to compare 2 groups. For comparison of 2 groups of skewed data the Mann-Whitney U-test was used. Proportions were compared using the Chi square or Fisher's exact test, depending on their applicability. For time related variables of skewed data the Wilcoxon Signed rank test was applied; for normally distributed data ANOVA was carried out. Analysis was conducted using IBM SPSS statistics (version 22.0). A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 103 patients who satisfied the inclusion criteria were enrolled in our study.

Patients were aged 18 years to 75 years with a mean age of 31.83 years. 65% of patients were less than 30 years of age with the majority (46.6%) between 21 and 30 years, 91.3% were male and 8.7% were female. Sixty-nine patients (67%) had occupation-related injuries. Seventy-five patients (72.8%) had high voltage electrical burns and only 28 patients (27.2%) had low voltage electrical burns (Table 1). Data regarding the exact mechanism of the burns were collected (Table 2). Thirty-three patients were injured due to contact with a live wire either in the field, roof or the factory. A total of 22 patients had burns related to working with a transformer. Fifteen patients were injured by a home appliance, 8 by farming machinery and 7 youngsters while playing came into contact with a live wire. Six patients were injured at a construction site. Two patients were injured when flying a kite.

Fifty-eight patients (56.3%) had pure contact burns and 30 patients (29.1%) had pure electrical flash burns. Fifteen patients (14.6%) had a mixed injury with a flash as well as a contact burn. The TBSA of the burns ranged from 1% to 90%. The mean area was 22% with a standard deviation of 18.3%. The 25th percentile was 10%, 50th percentile was 18%, and the 75th percentile was 18%.

Of the 103 patients, 40 patients underwent an amputation. A total of 32 patients who suffered a high voltage electrical burn underwent upper limb amputation at different levels. Eight patients with low voltage electrical burns also underwent amputation but this was limited to finger amputation only. Of the 32 patients with high voltage electrical burns who had upper limb amputation, 8 patients had bilateral upper limb amputation at various levels. Seventeen patients also underwent lower limb amputation of which 7 had bilateral lower limb amputation.

Patients with electrical burns are likely to have "progressive necrosis" and hence may need multiple surgeries. The patients usually required two debridements with a debridement in the first 24 h after resuscitation and a relook debridement after another 48 h. In most cases definitive cover was feasible during the second intervention (Figure 2). However, some patients required multiple debridements before the wound was ready for definitive cover. The maximum number of surgeries in a single patient was 4 (Table 3).

Of the total number of patients, 13 (12.6%) succumbed to the injury. The cause of death included acute renal failure, cardiac arrhythmia, and sepsis due to extensive exposed areas.

Of 103 patients, there were 13 deaths and 17 patients were lost to follow-up during the study period. We followed up the remaining 73 patients at 3 mo, 6 mo and 9 mo.

The 40 questions in the BSHS were divided in 9 domains. The quality of life in patients with low voltage electrical burns *vs* those with high voltage electrical burns were recorded.

The mean of scores for all the questions and the standard deviation in the 9 domains at 3 mo, 6 mo and 9 mo are shown in Table 4.

Table 1 Characteristics of electrical burn injuries

Age distribution	Minimum age 18 yr, %	Maximum age 75 yr, %
Sex distribution	Male 94 (91.3)	Female 9 (8.7)
Occupation-related injury	Yes 69 (67)	No 34 (33)
High voltage *vs* low voltage burns	High voltage 75 (72.8)	Low voltage 28 (27.2)

Table 2 Mechanism of sustained injury

Mechanism of injury	Frequency (*n*)	Percent (%)
Construction site	6	5.8
Domestic line repair	2	1.9
Farming machinery	8	7.8
Flying kite	2	1.9
Home appliance	15	14.6
Live wire in field	15	14.6
Live wire in factory	7	6.8
Live wire on roof	11	10.7
Loading in truck	3	2.9
Playing	7	6.8
Transformer	22	21.4
Welding	5	4.9
Total	103	100.0

Table 3 Mean number of surgeries performed with standard deviation and percentiles

Number of surgeries		
Mean number of surgeries (*n*)		2.03
SD		0.842
Minimum number of surgeries (*n*)		1
Maximum number of surgeries (*n*)		4
Percentiles	25	1.00
	50	2.00
	75	3.00

When the *t* test was applied to the data in Table 4, differences in the domains when compared were significant in all except hand function at 3 and 6 mo, treatment regimen at 3 mo, 6 mo and 9 mo, and return to work at 3 mo, 6 mo and 9 mo (Table 5).

We also compared the quality of life amongst the patients who underwent amputation (Figure 3) *vs* those who did not undergo amputation. The mean total scores at 3 mo, 6 mo and 9 mo and the standard deviation are represented in Table 6.

We applied the *t* test to determine if the differences in the scores were significant. Comparisons between amputees and non-amputees showed that the differences in heat sensitivity, treatment regimens and body image were non-significant. All the other parameters were significant at 3 mo, 6 mo and 9 mo (Table 7).

Table 4 Mean scores in patients with high voltage and low voltage burns as per various domains at 3 mo, 6 mo and 9 mo

Domain	Voltage (*n*)	3 mo, mean ± SD	6 mo, mean ± SD	9 mo, mean ± SD
Heat sensitivity	High voltage (49)	12.55 (4.92)	15.14 (4.03)	16.73 (3.41)
	Low voltage (24)	15.71 (4.57)	17.46 (3.01)	18.21 (2.13)
Affect	High voltage (49)	16.12 (7.14)	19.00 (6.59)	20.82 (6.77)
	Low voltage (24)	23.33 (4.07)	25.46 (3.34)	26.5 (2.72)
Hand function	High voltage (49)	11.29 (6.29)	13.88 (6.25)	15.04 (6.09)
	Low voltage (24)	12.08 (5.93)	15.63 (3.94)	17.50 (3.48)
Treatment regimens	High voltage (49)	13.31 (4.35)	14.61 (4.19)	15.9 (4.05)
	Low voltage (24)	14.96 (4.71)	16.38 (3.89)	17.29 (3.22)
Work	High voltage (49)	6.33 (5.83)	7.96 (6.11)	8.73 (6.26)
	Low voltage (24)	8.83 (5.29)	10.50 (5.32)	11.71 (5.47)
Sexuality	High voltage (49)	8.14 (2.89)	9.24 (2.90)	9.63 (2.95)
	Low voltage (24)	10.75 (1.89)	11.21 (1.53)	11.54 (1.10)
Interpersonal relations	High voltage (49)	8.82 (3.97)	10.39 (3.80)	11.69 (3.76)
	Low voltage (24)	13.08 (2.80)	14.58 (2.13)	15.08 (1.67)
Simple abilities	High voltage (49)	6.78 (3.08)	8.85 (2.74)	9.98 (2.68)
	Low voltage (24)	9.0 (2.6)	10.71 (1.4)	11.46 (1.06)
Body image	High voltage (49)	6.39 (3.19)	8.45 (2.93)	10.37 (2.95)
	Low voltage (24)	11.38 (3.28)	13.33 (2.44)	14.50 (1.84)

Table 5 *P* value of the various domains in patients sustaining high voltage *vs* low voltage electrical burns

Domains	3 mo, *t* value (*P* value)	6 mo, *t* value (*P* value)	9 mo, *t* value (*P* value)
Heat sensitivity	- 2.63 (0.010)	-2.49 (0.015)	- 1.93 (0.057)
Affect	- 4.59 (0.000)	- 4.52 (0.000)	-3.95 (0.000)
Hand function	-0.52 (0.606)	-1.25 (0.215)	-1.84 (0.071)
Treatment regimens	-1.48 (0.142)	-1.73 (0.088)	- 1.47 (0.146)
Work	-1.78 (0.080)	-1.74 (0.086)	-1.98 (0.051)
Sexuality	-4.02 (0.000)	-3.11 (0.003)	-3.06 (0.003)
Interpersonal relations	-4.71 (0.000)	-5.03 (0.000)	-4.21 (0.000)
Simple abilities	-3.04 (0.003)	-3.12 (0.003)	-2.60 (0.011)
Body image	-6.22 (0.000)	-7.05 (0.000)	-6.28 (0.000)

DISCUSSION

Electrical burns are devastating injuries and can cause deep burns with significant morbidity, leading to prolonged hospital admission and multiple surgeries to achieve complete wound healing. These injuries are also responsible for amputation of limbs making the patient dependent on caregivers even for basic activities of daily living if multiple limbs are involved. Even after limb salvage surgery, the patient may have to undergo multiple admissions for reconstruction of tendons and nerves in the affected limb before adequate functionality of the limb is achieved. In the present study we attempted to examine the epidemiology of this injury and identify individuals at maximum risk of this injury.

We enrolled patients from 18 years to 75 years of age with 65% of patients below 30 years of age and a mean age of 31.83 years. Buja *et al*[12] in their study included patients with an age distribution of 2 years to 67 years and a mean age of 33.6 years. Ambikavathy Mohan in his study of electrical burns in South India included almost

Table 6 Mean scores in patients undergoing amputation and those not undergoing amputation at 3 mo, 6 mo and 9 mo

Domain	Amputee *vs* non-amputee (*n*)	3 mo, mean ± SD	6 mo, mean ± SD	9 mo, mean ± SD
Heat sensitivity	Amputee (30)	13.64 (4.77)	16.17 (3.41)	17.47 (3.05)
	Non-amputee (43)	13.56 (5.22)	15.72 (4.18)	17.05 (3.18)
Affect	Amputee (30)	14.33 (6.82)	17.80 (6.86)	20.17 (6.91)
	Non-amputee (43)	21.40 (5.84)	23.44 (5.08)	24.44 (5.30)
Hand function	Amputee (30)	7.83 (5.77)	11.13 (6.17)	13.17 (6.62)
	Non-amputee (43)	14.14 (5.00)	16.77 (3.84)	17.72 (3.51)
Treatment regimens	Amputee (30)	14.13 (4.01)	15.43 (3.62)	16.97 (3.43)
	Non-amputee (43)	13.65 (4.86)	15.02 (4.52)	15.93 (4.08)
Work	Amputee (30)	4.47 (4.71)	6.03 (5.38)	7.10 (6.20)
	Non-amputee (43)	9.02 (5.70)	10.72 (5.60)	11.53 (5.46)
Sexuality	Amputee (30)	7.93 (3.40)	9.10 (3.33)	9.53 (3.25)
	Non-amputee (43)	9.74 (2.16)	10.44 (1.99)	10.77 (2.02)
Interpersonal relations	Amputee (30)	8.17 (3.87)	10.43 (4.01)	11.67 (3.73)
	Non-amputee (43)	11.65 (3.72)	12.70 (3.54)	13.60 (3.30)
Simple abilities	Amputee (30)	5.40 (2.88)	7.87 (2.86)	9.27 (3.01)
	Non-amputee (43)	8.98 (2.31)	10.62 (1.41)	11.3 (1.30)
Body image	Amputee (30)	7.03 (3.80)	9.10 (3.52)	11.23 (3.21)
	Non-amputee (43)	8.72 (3.99)	10.72 (3.55)	12.07 (3.31)

Table 7 *P* value of the various domains among amputees and non-amputees

Domains	3 mo, *t* value (*P* value)	6 mo, *t* value (*P* value)	9 mo, *t* value (*P* value)
Heat sensitivity	-0.063 (0.950)	-0.482 (0.631)	-0.564 (0.574)
Affect	4.743 (0.000)	4.040 (0.000)	2.989 (0.004)
Hand function	4.973 (0.000)	4.810 (0.000)	3.814 (0.000)
Treatment regimens	-0.447 (0.656)	-0.413 (0.681)	-1.139 (0.259)
Work	3.601 (0.001)	3.575 (0.001)	3.230 (0.002)
Sexuality	2.781 (0.007)	2.153 (0.035)	2.001 (0.049)
Interpersonal relations	3.872 (0.000)	2.549 (0.013)	2.340 (0.022)
Simple abilities	5.868 (0.000)	5.390 (0.000)	3.952 (0.000)
Body image	1.814 (0.074)	1.927 (0.058)	1.076 (0.286)

50% of patients aged less than 30 years. These were young adults and most of them the sole earners in the family. Sustaining an electrical burn and losing the ability to work is a great loss to the family as well as society in general which has huge economic consequences[13]. In the present study, 91.3% of patients were male and only 8.7% were female. These results may be due to occupational predisposition among the male population. This is consistent with previous data regarding the sex distribution of electrical burns[14,15]. The electrical burns in 67% patients were occupation-related and 33% were due to unrelated causes. Electrical burns are considered the most common job related-injury in both developing as well as developed countries[2,3]. Our findings are consistent with the available literature.

Amongst the 103 patients, 72.8% were injured by a high voltage electric current, whereas 27.2% sustained burns by a low voltage source. High voltage injuries are more distressing causing larger body mass necrosis and have a higher chance of amputation and requiring extensive reconstruction[16]. 41% of patients with high voltage burns underwent amputation. On the other hand, only 8 patients with low

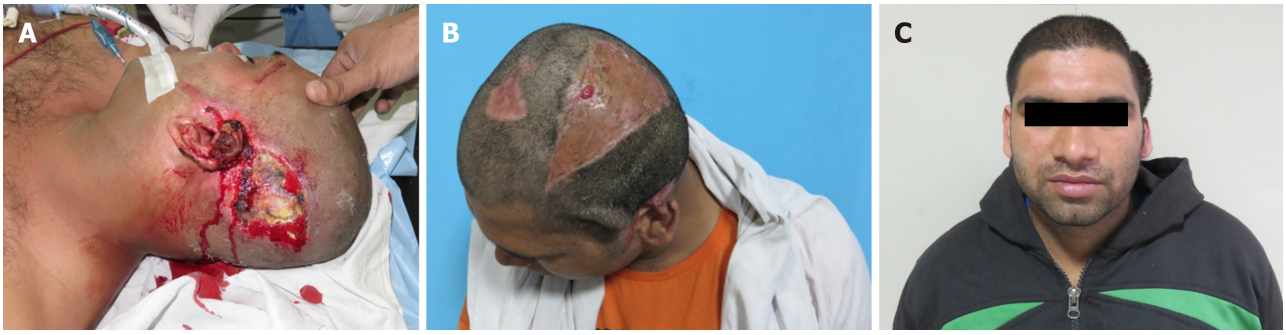

Figure 2 In most cases definitive cover was feasible during the second intervention. A: Electrical contact burns with the entry point at the left parietal region; B: Transposition flap cover after second debridement; C: Same patient shown in Figure 2A and B at 3 mo follow-up.

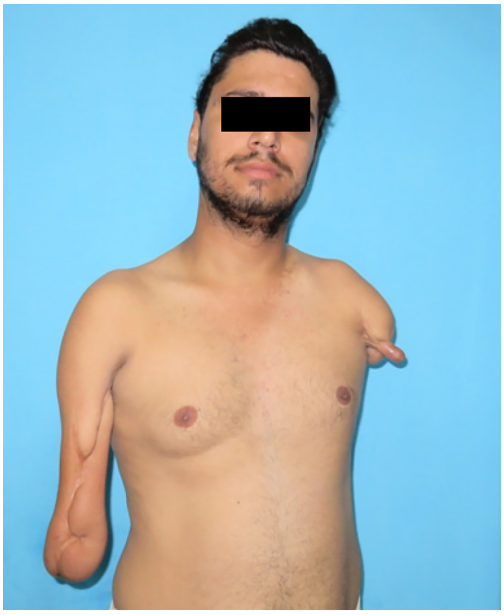

Figure 3 Bilateral amputee following electrical burns.

voltage burns underwent minor amputation of fingers. Also all 13 deaths during the study period occurred in patients with high voltage electrical burns.

71% of patients had a contact burn component, and 43.7% of patients had a flash burn component. 29.1% of patients had pure flash burns. The contact burn injuries were deeper and required multiple surgeries and flap cover. Flash burns which were limited to the superficial layer of the dermis healed with regular dressings within 2 weeks of the injury. In general, flash burns are superficial and usually do not damage deeper tissues. Surgery is required in these patients and sometimes multiple procedures may be required, but amputations are not usually required[17].

The mean TBSA in these patients was 21.1% with a standard deviation of 18.3%, and the range was from 1% to 90%. In the study by Kym *et al*[18] a mean TBSA of 14% was observed. Agakhani *et al*[19] found that the mean TBSA was 13.5%. The study by Hamid Karimi *et al*[20] in Iran found that the mean TBSA was 13.2%. The reason for the slightly higher mean TBSA in our study can be attributed to inter-observer variation in estimating the burns and to the large number of cases of electrical flash burns with larger TBSA burns.

Forty of the 103 patients (38.8%) underwent amputation. Of the 75 high voltage burn patients, 32 (42%) underwent amputation. Nine patients with low voltage electrical burns (32%) underwent amputation, but these were mainly minor amputations. Agakhani *et al*[19] reported similar results. The study by Kym *et al*[18] in South Korea demonstrated that 625 patients (74.7%) underwent amputation, but most of these were minor. They reported an amputation rate of 15.6% in the low tension group. This high rate of amputation following electrical burns indicates the morbidity associated with these burns and suggests that prevention is better than cure. It also

shows the importance of limb salvage by timely fasciotomy and early stable wound coverage after adequate debridement[21].

Thirty-two of our patients had upper limb amputation and 8 of these patients underwent bilateral amputation. Seventeen patients underwent lower limb amputation of which 7 had bilateral lower limb amputation. This is consistent with other studies[22]. In general, upper limbs are affected as they are frequently in contact with the electrical source.

The mean number of surgeries the patients underwent was 2.03 and ranged from 1 to 4. The 25th percentile was 1, 50th percentile was 2 and the 75th percentile was 3. Extensive raw areas following flash burns required 2 surgeries consisting of split thickness skin grafts.

Early adequate debridement is the key to successful reconstructive procedures. The injury is usually most severe in the small muscle branches, where blood flow is slower [22]. Sometimes complete damage is not initially evident. As the smaller vessels become thrombosed tissue damage then becomes evident. This creates the illusion of progressive tissue necrosis. Performing a flap and then having problems of pus discharge from below the flap is distressing both for the patient as well as the surgeon. We therefore found it prudent to occasionally have a second look when we had doubts about the viability of the tissue. This in our view prevented problems with both over debridement as well as under debridement. Frankly necrotic and devitalized tissue was removed in the first surgery and indeterminate tissue was left behind. Then further surgery was performed after 48 to 72 h to provide definitive cover. The only disadvantage of this technique is increasing management by one stage and the patient undergoing anesthesia an additional time and therefore increasing the cost of management. As our hospital is a government hospital the cost factor did not have much bearing, but this approach may increase the cost of management in a private setup. Hence this method was not followed in all patients.

During our study period, a total of 13 deaths (12.6%) were observed. The patients with a higher percentage of flash burns succumbed to sepsis, while acute renal failure and cardiac events were the cause of death amongst patients with contact burns. Mortality is reported to be between 3% and 15% in the U.S.[23]. A possible reason for the number of deaths being higher is that ours is a tertiary referral center with a lot of complex cases being referred to us on a regular basis.

The morbidity associated with burns is huge especially if the patient undergoes major amputation. It may be impossible for patients to return to work[24] and they may also become dependent on caregivers even for activities of daily living. This has an impact on the psychology of the patient.

The patients in our study were followed up at 3 mo, 6 mo and 9 mo to determine their quality of life. We compared quality of life based on the domains in patients with high voltage electrical burns *vs* low voltage electrical burns. In the total heat sensitivity domain the difference in the score was significant at all stages of follow-up. Patients with a flash component and large surface who underwent grafting had more problems regarding heat sensitivity. The difference in the score of the affect of high voltage electrical burns and low voltage electrical burns was significant at all stages. This may be due to the fact that usually high voltage burns are more devastating and have a poor affect as compared to patients with low voltage electrical burns. The hand function scores between the two groups showed that patients with low voltage burns fared better, but the difference was not statistically significant different between the groups at all stages of follow-up.

In general, patients with low voltage electrical burns had more trouble coping with the treatment regimen. This may be due to the fact that a lot of these patients required grafts and thorough post-graft skin care is required. The difference between the low voltage and high voltage groups was not significant, possibly because some patients in the high voltage group required grafts and they too needed to take care of the skin thus confounding the results.

With regard to work, the difference in scores between the low voltage and high voltage groups was significant, and patients sustaining low voltage electrical burns were significantly better at 3 mo, 6 mo and 9 mo. This is because high voltage electrical burns are usually more destructive[16].

Amongst the other domains, sexuality, interpersonal relationship, simple abilities and body image, patients with low voltage electrical burns were significantly better placed than those with high voltage electrical burns. We also compared the quality of life of amputees *vs* non-amputees. The domains of affect, hand function, sexuality, work, interpersonal relationship and simple abilities were significantly different and patients with amputation were significantly poorly placed as compared to non-amputees. The difference between the score for body image was non-significant. The

reason for this could be due to amputees not liking their "incomplete" body and non-amputees not being able to accept their bodies with extensive scars.

As 67% of electrical burns are related to occupation we strongly feel that a good education program for the at-risk population would be extremely beneficial.

From the available data it is clear that a prevention strategy should include the following 2 aspects: (1) Strict implementation of existing laws; and (2) An education program aimed at the at-risk population and the general public regarding the devastating outcome of electrical burn injuries and essential safety measures.

Strict implementation of existing laws can be ensured by heavy fines for the contractor or the builder responsible for breaking the law. Sign boards indicating danger depicted pictorially should be used. These sign boards will get the message across even to the uneducated population keeping them away from the areas where accidents are likely to happen. Various education programs regarding the effects of these devastating injuries and safety measures to be undertaken for prevention will go a long way to reduce the incidence of such injuries. Today we live in a world where communication is very easy and has become a powerful tool. There are countless means of mass communication including the internet, social media, television and radio. Only constant reminders will probably finally reduce accidental burn victims in our country[25] and we can use all these media to our advantage to spread the message.

CONCLUSION

In conclusion, electrical burns are still a major problem in India and most injuries are occupation-related. Furthermore, extensive injuries need to be managed in a tertiary care center using a multidisciplinary approach. Quality of life in patients with high voltage electrical burns and amputees is poor. Thus, steps should be taken to create awareness as well as plan and implement a good preventive strategy for electrical burns

ARTICLE HIGHLIGHTS

Research background

We have come a long way since the discovery of electricity and have become totally dependent on it. Yet there are numerous hazards associated with it. The accidental injuries sustained from electricity can potentially cripple individuals making them completely dependent on others for activities of daily living. There are a limited number of studies investigating the causes and characteristics of electrical injuries and the quality of life in these patients following treatment. In-depth evaluation of the circumstances of injuries and overall quality of life in this particular subset of patients has not been thoroughly evaluated.

Research motivation

Knowledge of the characteristics of electrical burn injuries and understanding the circumstances in which these injuries are sustained can help to formulate specific preventive strategies. The subjects who are at maximum risk of sustaining these injuries can be educated on these preventive measures. This will help reduce the morbidity and mortality associated with these devastating injuries.

Research objectives

To study the epidemiology of electrical burns and to define the population which is at maximum risk of sustaining such injuries. The impact of electric burns on these patients and their quality of life along with the potential of returning to previous work were also evaluated.

Research methods

This prospective study was conducted over a period of 18 mo at a tertiary care teaching hospital. All patients presenting to the Trauma Center with a history of sustaining electrical burns and satisfying the inclusion criteria were included in the study. The course of the patient in hospital was followed and epidemiological data were collected using a burn proforma. Follow up was carried out at 3 mo, 6 mo and 9

mo. The standardized and valid Brief Version of the Burn Specific Health Scale (BSHS-B) was adopted to assess health-related quality of life (HRQOL). The normality of quantitative data was assessed by the Kolmogorov-Smirnov test. Normally distributed data were compared using One-Way ANOVA followed by the post hoc Multiple Comparisons test. For time related variables of skewed data the Wilcoxon Signed rank test was applied; for normally distributed data ANOVA was carried out. Analysis was conducted using IBM SPSS statistics (version 22.0). A P value of < 0.05 was considered statistically significant.

Research results

These injuries were more common in males and in the younger population. The majority of injuries were occupation-related and mostly accidental in nature, mainly due to ignorance as well as carelessness on the part of the victims. Hence, many injuries and resultant morbidities could have been prevented by mass education and awareness. A significant number of patients were uneducated. Thus, they had to take menial jobs without being aware of the appropriate safety measures. There was also a lack of awareness amongst their supervisors. Patients had a combination of contact and flash burns. The variety of associated injuries in these patients made a multidisciplinary approach vital for effective management. The patients underwent a variety of surgeries depending on the extent of the initial injury, of which amputation was the most devastating. Limb salvage necessitated multiple complex procedures which required intricate planning and execution. The quality of life among patients sustaining high voltage electrical burns and amputees was poor.

Research conclusions

Electrical burns cause extensive damage requiring multiple surgeries and reconstructive techniques. This makes it a major economic burden for the patient as well as the government. In addition, there are various social and rehabilitative challenges for the patient as well as his or her family. The patients who underwent multiple limb amputations became dependent on caregivers even for basic activities of daily living for the rest of their lives. It is a major challenge for these patients to return to pre-injury status due to the significant stigma of initial injury and persistent tissue damage. This underscores the importance of effective preventive strategies to reduce these injuries.

Research perspectives

Future studies should be carried out to determine the efficacy of various preventive strategies to decrease the frequency of these injuries and to reduce the morbidity and mortality associated with electrical burns.

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