Uncommon Diseases in the ICU

Marc Leone
Claude Martin
Jean-Louis Vincent
Editors

Springer

Uncommon Diseases in the ICU

Marc Leone · Claude Martin
Jean-Louis Vincent
Editors

Uncommon Diseases in the ICU

Springer

Editors
Marc Leone
Claude Martin
Anesthésie et réanimation
CHU Nord
Marseille
France

Jean-Louis Vincent
Department of Intensive Care
Erasme Hospital
Brussels
Belgium

Translation from the French language edition 'Maladies rares en réanimation' by Marc Léone, © Springer-Verlag France, Paris, 2010; ISBN 978-2-287-99069-4.

ISBN 978-3-319-04575-7 ISBN 978-3-319-04576-4 (eBook)
DOI 10.1007/978-3-319-04576-4
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014934138

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Goals of the Book

This book aims to provide concise and pragmatic guidelines to clinicians managing patients with uncommon diseases at the bedside. After a brief introduction, the book is divided into nine chapters including several questions. Each chapter is related to either a specific organ (heart and vessels, lungs, nervous system, skin, kidneys, liver) or a type of affection (infections, internal medicine diseases). The authors received specific guidelines: short introduction focusing on epidemiology and pathophysiology, detailed description of the diagnostic approach, and practical management recommendations. Illustrations and algorithms are requested in order to facilitate the understanding of the disease. A minimal number of references are needed, including an exhaustive review published in a major journal, if available.

In the chapter related to the cardiovascular system, the readers will find articles related to the Tako-Tsubo cardiomyopathy, Brugada syndrome, calcium channel disorders, pulmonary hypertension, and pheochromocytoma. The chapter related to infectious diseases includes descriptions of the Lemierre's syndrome, rickettsiosis, Strongyloides hyperinfection syndrome, dengue virus infection, and Chikungunya virus infection. The chapters "respiratory diseases," "renal disease," and "liver system" detail the pulmonary fibrosis, Gitelman and Bartter syndromes, and uncommon liver diseases. In the chapter on the nervous system, the reader will find responses on myasthenia, amyotrophic lateral sclerosis, and Parkinson disease. Immunological diseases, metabolic disease, and mitochondrial affection are presented in a chapter entitled "internal medicine diseases." In a chapter related to the hematological system, the reader will find details about the hemolytic anemia, retinoic acid syndrome, and thrombotic thrombocytopenic purpura. The "skin diseases" chapter includes descriptions of the hereditary angioedema and toxic epidermal necrolysis.

Summary for Readers

Although uncommon diseases have a low prevalence in the general population, they can affect a large number of patients admitted to intensive care units. An uncommon disease can be diagnosed in the intensive care unit. Often, a complication of the disease by itself leads to the patient's admission to intensive care unit.

This book does not aim to provide an exhaustive description of those diseases. The goals were to focus on the major diseases that the intensivists can meet in their clinical practice. The most relevant features for the management in intensive care unit are reported.

The authors have promoted the practical characteristics of uncommon disease. After a brief introduction on the epidemiology and pathophysiology of each disease, the authors emphasize the aspects related to diagnosis and treatment. In this book, the residents and intensivists facing patients with uncommon diseases would appreciate to find concise and pragmatic responses.

Contents

Part I
Introduction

Genetic Aspects of Uncommon Diseases

Julien Textoris and Marc Leone

Key Points

- Hereditary diseases represent 80 % of the rare diseases
- Hereditary diseases are the consequence of the pathological modification of one or a few genes
- The diagnosis, which may be done before birth, is confirmed by the identification of one or more mutations
- The knowledgebase "Orphanet" (http://www.orpha.net/) is the reference website for updated informations on genetic and rare diseases.

Genetic diseases are those that are caused by the alteration of a gene. They represent 80 % of so-called "rare diseases" (whose prevalence is less than one case for 2,000 persons), or approximately 6,000 pathologies. Interestingly, the prevalence of adult respiratory distress syndrome is estimated at 30/100,000. It shows that the notion of disease rarity is relative when it comes to intensive care medicine! Genetic diseases affect 1–2 % of births in the world, or approximately 10 million people in Europe. People suffering from genetic diseases are therefore alone and isolated but, at the same time, they represent a large population. That explains why these diseases are a real public health priority. Fortunately, not all genetic diseases lead to intensive care unit. Aggressive medical management in the intensive care unit is not always the only available solution and should in most cases be considered in light of a multidisciplinary team and ethical approach.

Rare or orphan diseases have been acknowledged since the beginning of the 1980s. The United States provided a first definition in the Orphan Drug Act that

J. Textoris (✉) · M. Leone
Service d'anesthésie et de réanimation, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille, Université de la Méditerranée, Chemin des Bourrely 13915, Marseille Cedex 20, France
e-mail: julien.textoris@ap-hm.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_1,

passed in 1983: "Any disease affecting less than 200,000 people", which at the time was equivalent to a prevalence of 7.5/10,000 in the United States. The prevalence threshold is 4/10,000 in Japan. In France, it is 5/10,000. Various plans to provide medical care for rare diseases have emerged in France. In 1992, a fast-tracked procedure was implemented to allow orphan diseases drugs to be granted marketing authorisation. In 1995, a commission for orphan drugs was established and in 1997, *Orphanet*, a portal on rare diseases and orphan drugs, was set-up. More recently, the National Plan on Rare Diseases (2005–2008) was launched to "ensure equity in the access to diagnosis, treatment and provision of care". The plan led to the creation of centres of reference on rare diseases. To give a few examples, in France, about 15,000 people suffer from sickle cell disease, 8,000 from amyotrophic lateral sclerosis, 6,000 from cystic fibrosis, 5,000 from Duchenne muscular dystrophy, 500 from leukodystrophy, while only a few cases of progeria are reported. 65 % of rare diseases in France are serious and debilitating; they have an early onset (appearing before the age of 2 in two cases out of five); they cause chronic pain in one patient out of five; they lead to the occurrence of a motor, sensory or intellectual deficit in half of the cases, and to a disability or loss of autonomy in one case out of three. Overall, rare diseases are life-threatening in half of the cases.

Physiopathology of Genetic Diseases

Genetic diseases result from a pathological change in one or several gene(s). Among these are distinguished:

- Hereditary genetic diseases, transmitted to the offspring via the reproductive cells, namely gametes.
- Multifactorial diseases, the majority of which are caused by multiple factors: environment, lifestyle and type of food consumption, biological and genetic factors. This is the case for cancers, for some types of cardiovascular diseases, for neurodegenerative diseases, and for infectious diseases. The respective roles played by the various factors in these diseases is highly variable. And so is the degree of incidence of the mutated genes.

Among genetic diseases, a distinction can be made between those caused by the mutation of a single gene and those resulting from the "accumulation" of multiple genetic abnormalities. The first ones are called "monogenic" or "Mendelian" since their transmission pattern follows the laws discovered by Mendel. The genetic diseases whose transmission is not Mendelian involve several genes, as well as non-genetic factors. This is the case of mitochondrial diseases (mitochondria are elements present in the cells, intended to generate the necessary energy for the cells), where the mutation affects the mitochondrial genome. Their transmission is particular as only women can pass them on and because the

mutated-gene expression is often mosaic. It is also the case of chromosomal diseases linked to the absence of a chromosome or to its presence in excess (such as Trisomy 21), or to abnormalities of the chromosome structure itself. Genetic diseases are also classified according to the organs and physiological functions they affect.

Finally, the penetrance of the disease is extremely variable, even within a family, which often complicates diagnosis and prenatal counselling.

Diagnosis and Treatments

Today, a gene mutation associated with a multifactorial disease can be identified through genetic testing.

However, given the many genes involved in these diseases, these tests do not so much provide information to foresee the evolution of these pathologies, as they provide information on the existence of a risk factor in a family's genetic makeup. However, the main benefit of genetic testing is to help formulate a diagnosis for patients showing clinical signs. Erroneous clinical diagnoses can therefore be definitely ruled out and those at risk can be screened.

Prenatal diagnosis is a genetic test performed on a fetus. It is a rare procedure, only intended for parents who may transmit a severe, incurable hereditary disease to their child. A prenatal diagnosis is proposed to families at risk following a specialized consultation. In addition to providing information and assessing the risk of a genetic disease, this consultation also allows the parents to benefit from a suitable psychological support.

The acknowledgement of rare diseases being recent, the development of specific treatments has only been prioritised by public authorities in the last 20 years. For the majority of the diseases, there is still no hope for a cure. Gene therapy is a very promising perspective.

The principle of gene therapy is simple: the genome of a cell is corrected by replacing a defaulting gene with its functional copy into the cell. Through this technique, it is therefore possible to correct a defective function or to compensate for a missing function in the target cell. The first significant success of this method was obtained in 2000 by the team of Dr. Marina Cavazzana-Calvo and Pr Alain Fischer, who succeeded in curing young children suffering from rare severe combined immunodeficiency (SCID), through the introduction of a gene-drug in their bone marrow cells.

Cell therapies use specific cells, administered to prevent, cure or mitigate a disease. Some of them have already proven their worth: transfusion of red blood cells and platelets to treat some types of blood diseases; skin graft for victims of severe burns; transplantation of stem cells that can produce massive populations of different cells and regenerate a damaged tissue; transplantation of insulin-producing cells (the islets of Langherans) to treat insulin-dependent diabetes; transfer of dendritic cells which induce and regulate an immune response when the

Table 1 Genetic diseases that may be seen in ICU and whose prevalence is estimated between 5 and 50/100,000

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Tetralogy of fallot	45	Spo./ AD	Neo./Inf.	Survival >85 % after ttt	Heart (peri-operative, or initial heart failure)	Surgery
Arrhythmogenic right ventricular dysplasia	44	AD/AR	Ad.	Normal risk = sudden death	Heart (sudden death, or heart failure at advanced stages)	Drugs, implantable cardioverter-defibrillator++
Elliptocytosis	35	AD	Variable	Normal (only 5–20 % have a severe disease)	Severe anemia, POC	Folic acid, transfusion, splenectomy
Osteochondritis dissecans	35	AD	Ado./Ad.	Normal	POC	Physiotherapy, Surgery
Malignant hyperthermia	33	AD	Variable	Mortality <5 %	Rhabdomyolysis	Dantrolene
Marfan syndrome	30	AD	Childhood	Depends on cardiovascular complications	Cardio-vascular	Multidisciplinary
Congenital hypothyroidism	29	AR	Neo./Inf.	Normal if early detection	Coma, …	Substitutive opotherapy
Alpha-1-antitrypsin deficiency	25	AR	Variable	Linked to the pulmonary and hepatic dysfunction	Liver (cirrhosis) lung (emphysema)	Alpha-1 antitrypsin (IV) ongoing clinical trials, lung/liver transplant
Long QT syndrome	25	AD/AR	Childhood	Normal risk = sudden death	Heart (sudden death)	Beta-blockers, cardiac sympathic neurolysis Implantable cardioverter-defibrillator
Atresia of the small intestine	20	Spo./ AR	Neo./Inf.	Depends on the length of the small intestine	POC	Surgery
Isolated scaphocephaly	20	Spo./ AD	Neo./Inf.	Normal	POC	Surgery
Hereditary spherocytosis	20	AD/AR	Variable	Normal if newborn bilirubin-encephalopathy is avoided	Severe anemia in neonates	Transfusion ± EPO Splénectomie

(continued)

Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Agenesis of the corpus callosum—neuropathy	19	AR	Neo./Inf.	Depends on mental status	Epilepsy	Symptomatic/palliative
Dilated cardiomyopathy, familial	17.5	RX/AD/AR/MH	Variable	Slightly reduced (risk of sudden death)	Heart (sudden death, or heart failure at advanced stages)	Drugs, implantable cardioverter-defibrillator ++
Bilateral renal agenesis	17	AD	Neo./Inf.	Death in utero, or near birth	–	Symptomatic/palliative
MELAS syndrome	16	MH	Childhood	Variable but prognosis is severe	Cerebral (seizures), Lung (myopathy), heart (heart failure)	Ongoing clinical trials
Disease of the maple syrup	15.6	AR	Neo./Inf.	Acute form: death in the first weeks of life if undiagnosed	Cerebral (coma, encephalopathy)	Hemodiafiltration, some rare forms are cured by thiamine administration
Deficiency of acyl-CoA dehydrogenase medium chain fatty acids	15	AR	Neo./Inf.	Normal if diagnosed	Severe hypoglycemia	Glucose (massive amounts)
Von Willebrand disease	12.5	AD/AR	Variable	Normal	Cerebral (hemorragic stroke), hemorragic shock (perioperative, delivery, …)	Depends on subtypes, von Willebrand factor, desmopressine
Supravalvular aortic stenosis	12.5	AD	Variable	Variable but almost normal	Heart (Infarction, heart failure, sudden death), hypercalcemia, POC	Surgery
Cystic fibrosis	12	AR	Neo./Inf.	~35–40 years	Lung (failure), liver (cirrhosis)	Symptomatic/palliative

(continued)

Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Sickle cell disease	11	AR	Variable	Unpredictable	Lung (thoracic syndrome), cerebral (Stroke)	Transfusion, hydroxyurea in severe forms
Prader-Willi syndrome	10.7	Chr 15	Neo./Inf.	Reduced (30–40 years)	Lung (chronic failure), heart (heart failure)	Substitutive opotherapy GH), special diet
Nephroblastoma	10.1	AD	Childhood	Survival >90 % with treatment	POC	Chemotherapy + surgery
Congenital adrenal hyperplasia	10	AR	Neo./Inf.	Good	Acute metabolic events (hyopnatremia, hyperkaliemia, acidosis; severe hypoglycemia)	Substitutive opotherapy
Isolated plagiocephaly	10	Spo./AD	Neo./Inf.	Normal	Intra cranial hypertension, POC	Surgery
Catecholaminergic polymorphic ventricular tachycardia	10	AD/AR	Childhood	Without treatment, sudden death before 20. Risk is reduced by treatment	Heart (sudden death)	Beta-blockers
Abnormal mitochondrial oxidative phosphorylation (nuclear DNA)	9	AR/MH	Variable	Reduced, but depends on the age of onset	Lung (chronic failure), heart (heart failure)	Symptomatic/palliative
Tuberous sclerosis	8.8	AD	Childhood	Normal with the exception of uncontrolled seizures	Cerebral (seizures), lung (failure)	Depends on localisation of tumors
Pierre Robin syndrome isolated (isolated Pierre Robin sequence)	8.8	Spo./AR	Neo./Inf.	Normal if diagnosed early	Lung (obstructive disease)	Surgery
Duodenal atresia	8.6	Spo./AD	Neo./Inf.	Normal	Neonatal ICU and POC	Surgery

(continued)

Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Acute hepatic porphyria	8	AD/AR	Variable	May be normal. Depends on the frequency and severity of seizures	Neurological (Guillain-Barré), liver	Hemine (IV) carbone hydrates, liver transplant
Hemophilia	7.7	RX	Neo./Inf.	Normal	Hemorragic shock, POC	Transfusion of the missing factor
Beckwith-Wiedemann syndrome	7.3	AD/MF	Neo./Inf.	–	POC (omphalitis), Severe hypoglycemia	Surgery, glucose
Dystrophy Facioscapulohumeral	7	AD	Childhood	Normal	Lung failure	Physiotherapy, mechanical ventilation
Fryns syndrome	7	AR	Neo./Inf.	About 10–20 % in neonatal period	Lung (hypoplasia (diaphragmatic hernia), heart (malformations), Neuro	Surgery, but mainly palliative
Holoprosencephaly	7	AD	Neo./Inf.	High heterogeneity, so variable. Severe forms die in neonatal period	Lung (apnea), heart (rythmic disease), cerebral (seizures), metabolic (diabetes insipidus)	Symptomatic/palliative
Sotos	7	AD	Neo./Inf.	Normal	Heart (malformations), cerebral (seizures), hypoglycemia	Symptomatic/palliative
Galactosemia	6.6	AR	Neo./Inf.	Normal if diagnosed early	Liver failure, septic shock	Galactose-free diet
Autosomal recessive polycystic kidney disease	6.5	AR	Childhood	Normal	Kidney (chronic failure)	Dialysis, transplantation
Amyotrophic lateral sclerosis	6	Spo./AD/AR	Adult	60–65 years	Lung (failure)	Symptomatic/palliative

(continued)

Table 1 (continued)

Disease's name	Estimated prevalence (/100,000)	Type of heredity	Onset (year)	Lifespan	Reason for ICU admission	Treatment
Treacher-Collins syndrome	6	AD	Neo./Inf.	Variable: adults with few symptoms and severe forms with neonatal death	Lung failure	Surgery, symptomatique
Wilson disease	5.8	AR	Childhood	Normal	Liver (acute hepatitis, cirrhosis)	D-penicillamine, Triethylenetetramine
X-linked adrenoleukodystrophy	5	RX	Variable	Variable	Adrenal deficiency	Substitutive opotherapy, genetic therapy currently evaluated
Ciliary dyskinesia	5	AD/AR	Neo./Inf.	Slightly reduced is lung disease is well treated	Lung (obstructive disease), heart (malformations)	Symptomatique, Kine respiratoire, transplantation pulmonaire dans de rares cas
Duchenne muscular dystrophy and Becker	5	RX	Childhood	Duchenne : 30–40 years Beckert: sub-normal	Lung (restrictive disease), heart (chronic heart failure)	Symptomatic/palliative
Hereditary fructose intolerance	5	AR	Neo./Inf.	Normal if diagnosed early	Acute liver failure and hemorragic shock if masive amounts of fructose are ingested	Fructose, sorbitol and saccharose free diet

Heredity: *Spo.* sporadic, *AD* autosomic dominant, *AR* autosomic recessive, *X* recessive linked to X, *MH* mitochondrial heredity, *MF* multifactorial. Onset age: *Neo.* neonatal, *Inf.* infancy, *Ado.* adolescence, *Ad.* adult, *POC* post operative care

immune system no longer recognizes, and therefore no longer rejects, foreign tumor cells; transfer of a certain type of liver cells, hepatocytes, which present a selective advantage to repopulate and rebuild a damaged liver.

Protein replacement therapy consists in replacing a defective protein by a recombinant protein. For example, in the case of Gaucher's disease, characterized by a deficiency in glucocerebrosidase, an enzyme whose recombinant form has been developed and used to replace the missing enzyme.

Finally, one should also mention the classic approach based on drug administration, which for example has been explored in the treatment of hereditary tyrosinemia, a liver disease occurring in children under the age of one, which results from the accumulation of metabolites causing oxidative damages to the cell. The treatment of this disease is nowadays improved by the administration of an inhibitor of the tyrosine metabolism.

Genetic Disease and Intensive Care

Given the large number of genetic disorders which can lead to intensive care admission, we have opted to present in a table the Mendelian genetic diseases whose prevalence range from 5 to 50/100,000 (in comparison, the prevalence of pulmonary fibrosis is 7/100,000, that of familial forms of Parkinson's disease is 15/100,000 and that of lupus is 50/100,000). All the information presented in the table is drawn from the *Orphanet* website (http://www.orpha.net/), a world reference in the field of rare diseases. It has a good search engine, and for each pathology it provides links to additional articles in French or English. Because the diseases mentioned in this work are very rare, the information presented here is likely to be obsolete by the time you read it. Therefore, it is advised to check the *Orphanet* website, which is regularly updated. One can also find on that website a document listing the centres of reference that are approved to provide medical care for a specific rare disease or a group of rare diseases. (http://www.orpha.net/orphacom/cahiers/docs/FR/Liste_des_centres_de_reference_labellises.pdf) This information is essential in order to obtain expert advice and whenever possible, to transfer the patients to these centres of reference (Table 1).

Part II
Cardiovascular System

Takotsubo Syndrome

Aude Charvet

Key Points

Acute stress cardiomyopathy and differential diagnosis of acute coronary syndrome, Takotsubo syndrome is rare.

Nevertheless, this pathology may necessitate cardiovascular resuscitation.

Introduction

Takotsubo syndrome, also known as transient apical ballooning syndrome of the left ventricle, is a stress cardiomyopathy initially witnessed in Japan and increasingly frequent amongst the Caucasian population [1]. It affects predominantly female elderly patients and mirrors an acute coronary syndrome, most often stress induced. Clinically, it presents itself as an acute haemodynamic failure associated to thoracic pain, electrocardiogram anomalies, and a moderate increase of cardiac enzymes, without significant lesions of coronary arteries. Diagnosis is supported by the echocardiogram showing an apical systolic dilation of the left ventricle. The development of this pathology has spontaneously favourable outcomes, although resuscitation can be necessary. The pathophysiology of Takotsubo syndrome is still open for debate.

A. Charvet (✉)
Service d'anesthésie et de réanimation, Hôpital Nord Assistance Publique-Hôpitaux de Marseille, Université de la Méditerranée, Chemin des Bourrely 13915 Marseille Cedex 20, France
e-mail: Aude.CHARVET@ap-hm.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_2,

History

This pathology was first observed in Japan in 1990 by Sato et al. The name "Takotsubo cardiomyopathy" was given to this syndrome due to the ultrasound appearance of the left ventricle during the systolic phase: with a dilated background and a narrow neck, it resembles a ceramic amphora-shaped pot called a Takotsubo, used for octopus fishing in Japan. The majority of publications that followed were principally Japanese, so that it was initially thought of as a phenomenon limited to Asia up to the years 2000. Then, numerous incidences were reported throughout the world, especially in Europe, the United States and Australia. In 2006, Takotsubo syndrome is included within the acquired cardiomyopathies classification by the American Heart Foundation [2].

Epidemiology

The exact occurrence of Takotsubo syndrome is unknown, due to the novelty of this pathology, the varying of its symptomatology and its changing diagnostical criteria. Nonetheless, most studies find a similar incidence, around one to two percent of patients admitted for acute coronary syndrome [1]. Contributing factors are equally found in a unanimous fashion: this syndrome usually affects post-menopausal women and is the result of a stressor. Indeed, about 90 % of all reported cases are linked to the female gender, within an age range from 58 to 75 years [3]. It is unknown as to why there exists a strong predominance of female cases. Several hypotheses have been put forward, such as the pathophysiological role of estrogens, or the fact that the atheromatous illness being frequent among males could conceal this syndrome amongst them. Those female patients do not usually have any noteworthy antecedent or any coronary disease risk factor, except for an ongoing smoking habit found in around 50 % of them. At last, approximately two-thirds of female patients have previously suffered a significant stressor, whether it be physical (surgery, trauma, meningeal hemorrhage, sepsis, severe pain, local or general anesthesia, weaning from opiates, cocaine poisoning, endocrinopathies, electro convulsive treatment, chemotherapy, etc.…) and/or psychological (death or severe illness of a loved one, divorce, road traffic accident, etc.…) [3].

Clinical

The clinical presentation of Takotsubo syndrome is usually close to acute coronary syndrome, of which it constitutes the main differential diagnosis. Over half of female patients describe a brutal and sudden onset of an angina type chest pain.

Other possible manifestations can be dyspnea and much more rarely fainting, pulmonary œdema or cardiac arrest [3]. A haemodynamic failure is frequent, although cardiogenic shock has only been reported as a rare complication.

Paraclinical

The E.C.G. also suggests acute coronary syndrome, frequently accompanied by a convex elevation of the ST segment (from 34 to 100 % depending on studies), most of the time in the antero-septo-apical area (V1–V4), sometimes in the inferior or lateral areas. Other anomalies indicating myocardial ischemia, such as T-wave negativity in precordials, dielectric constant and AVL, along with occurrence of Q-wave in V3 and V4, are all frequent. Widespread micro-voltage, left branch blocking or QT-interval prolongation have been observed less frequently [4, 5]. The E.C.G can be normal. In each case, analyzing E.C.G. anomalies does not allow to differentiate Takotsubo syndrome from acute coronary syndrome [4], and does imply a link to the seriousness of ventricular dysfunction, or to its development [5].

Cardiac enzymes levels most of the time show a moderate increase, particularly troponin T peaking within 24 h. However, the increase in these markers is lower than during a genuine acute myocardial infarct, and especially disproportionate to the widespread reach as observed in imaging.

The coronarography is normal amongst most patients [3, 4], but assumes the appearance proper to the ventriculography in late systole: hypokinesia or antero-apical akinesia of the left ventricle, responsible for a ballooning, associated to a reverse basal hypercontractility. The coronarography can sometimes show non-significant coronary lesions, as well as vasospasms, which will fade following local administering of nitrated derivatives. In fact, diagnosing Takotsubo syndrome is most of the time possible during a left ventriculography done on female patients with suspected acute coronary syndrome.

Transthoracic echocardiography is a key examination enabling the diagnosis of Takotsubo syndrome. It mimics anomalies specific to apical or septal segmental kinetics, responsible for a distortion of the left ventricular functioning (left ventricular function of emission of 15–40 % in the acute phase) [6] and for a distal ballooning. Usually there are no right-hearted anomalies, nor a pericardial outpouring. However, an associated right ventricular dysfunction is possible (Fig. 1).

A cardiac M.R.I. can also confirm left ventricular kinetics anomalies, without ischemic attack or necrosis, shown by an absence of contrast after a gadolinium injection. Equally, it allows forecasting the reversibility of noted disorders [6]. When undertaken early, kine-M.R.I. recognizes kinetics-associated disorders, characteristic to this pathology (Fig. 2).

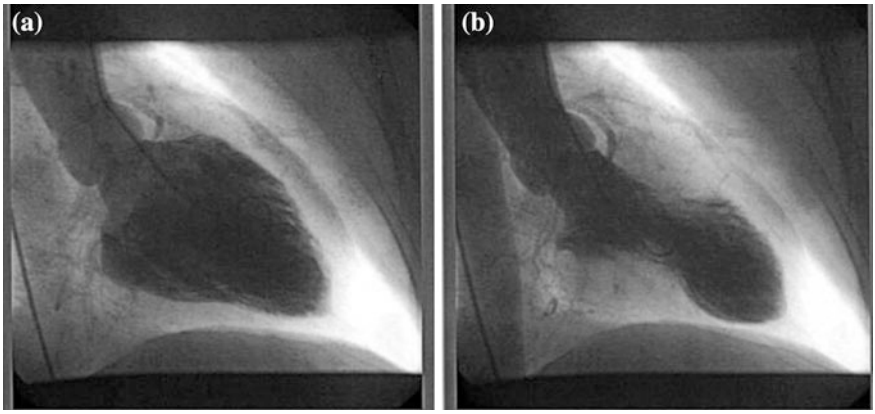

Fig. 1 *Left* ventriculogram during Takotsubo syndrome, **a** diastole; **b** systole; apical dyskinesia (ballooning) and basal hyperkinesia

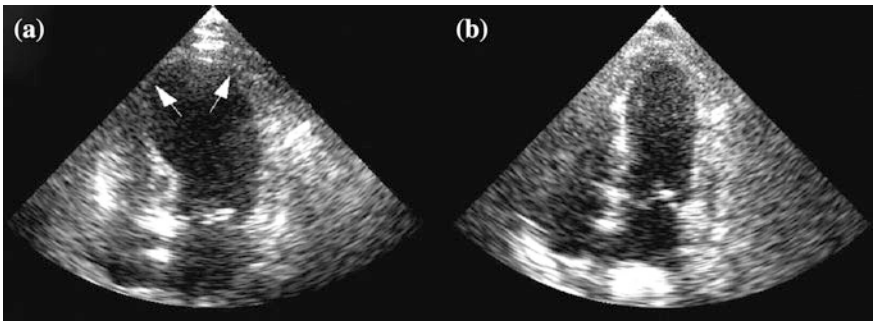

Fig. 2 Echographic image of Takotsubo syndrome, **a** dilation of the *left* ventricle in acute phase; **b** spontaneous recovery at day 6

Treatment

The optimal treatment for Takotsubo syndrome has not been defined. Most of the time, patients are already being treated for acute coronary syndrome at the time of diagnosis by the use of antiplatelets, nitrated derivatives, heparin and beta-blockers. Once the illness has been diagnosed and in the absence of ventricular dysfunction, the initial medical treatment may consist of administering renin-angiotensin system inhibitors, beta-blockers and antiplatelets. In the event of coronary spasms observed during the coronarography, calcic inhibitors may be considered. Given the main pathophysiological hypothesis considered in this pathology (an excess of catecholamines), it seems preferable to avoid using amines and beta-agonists. In the event of hemodynamic failure or cardiogenic shock, dobutamine must be used cautiously, and a hemodynamic mechanical support

(extra corporal membranous oxygenation) must be considered rapidly in case of serious dysfunction. The treatment of Takotsubo syndrome complications is symptomatic: diuretics, heparin, anti-arrhythmics, etc.… In the acute phase, patients must benefit from a continuous monitoring in intensive care unit or in resuscitation, along with the help of echocardiographic supervision.

Evolution

Takotsubo syndrome myocardial kinetics anomalies are transient, with a return to a normal primary state within a few days or weeks (3–6). Only the E.C.G. can retain a trace of this event through non-specific signs (repolarization or conduction troubles, lengthening of QT interval). However, short-term prognosis can be clouded by serious, indeed fatal, complications, such as a cardiogenic shock, a left ventricle thrombus, a trouble of ventricular rhythm or of conduction, a mechanical complication.

The death rate is very low (around 1–2 %), even if the clinical picture is worrying by requiring heavy duty resuscitation [4]. The risk of relapse is equally low.

Pathophysiology

Takotsubo syndrome pathophysiology remains little known. A recent stressful event or an important emotional burden appear to be trigger factors for this pathology. The presence of catecholamines at peak level following that stress could well be responsible for a systemic inflammatory reaction and left ventricle fraction [7]. The link between the discharge of catecholamines and ventricular dysfunction is already observed in the meningeal hemorrhage and in pheochromocytoma. The hypothesis of catecholamines released during stress having a toxic and direct influence onto cardiomyocytes is thus plausible [7]. Models based on the use of animals have permitted to copy electrocardiographic modifications and left ventricle kinetics troubles in a rat subjected to a physical stress (forced immobilization). Nevertheless, the concentration of catecholamines released in patients with Takotsubo syndrome is not always high. A microvascular spasm or an intraventricular blocking are other hypotheses put forward, and a multi-factor origin cannot be excluded.

Conclusion

Takotsubo syndrome is a rare and recent concept, most often affecting elderly female patients who have suffered an intense stress. In its acute form, it presents as a particular cardiogenic failure, mimicking a preliminary myocardial infarctus.

Emergency department physicians and anesthetists should familiarize themselves with it, so as to define a quick diagnosis and adapt the required therapies. The evolution is often positive but impredictible, and sometimes strewn with complications. Treatment is empirical and pathophysiological mechanisms are still to be established.

References

1. Sato H, Tateishi H, Uchida T et al (1990) Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M (eds) Clinical aspect of myocardial injury: from ischemia in heart failure (in Japenese). Kagakuhouronsya Co, Tokyo, pp 56–64
2. Marron BJ, Towbin JA, Thiene G et al (2006) Contemporary definitions and classification of the cardiomyopathies: an American heart association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. Circulation 113:1807–1816
3. Gianni M, Dentali F, Grandi AM et al (2006) Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J 27:1523–1529
4. Bybee KA, Kara T, Prasad A et al (2004) Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med 141:858–865
5. Dib C, Asirvathan S, Elesber A et al (2009) Clinical correlates and prognostic significance of electrocardiographic abnormalities in apical ballooning syndrome (takotsubo/stress-induced cardiomyopathy). Am Heart J 157:933–938
6. Leurent G, Larralde A, Boulmier D et al (2009) Cardiac MRI studies of transient left ventricular apical ballooning syndrome (takotsubo cardiomyopathy): a systematic review. Int J Cardiol 135:146–149
7. Morel O, Sauer F, Imperiale A et al (2009) Importance of inflammation and neurohumoral activation in takotsubo cardiomyopathy. J Card Fail 15:206–213

Brugada Syndrome

D. Lena, A. Mihoubi, H. Quintard and C. Ichai

Key Points

- Brugada syndrome is responsible for 20 % of sudden cardiac death in apparently normal hearts.
- This syndrome is an autosomal dominant gene abnormality disease.
- This syndrome associates an ST segment elevation in the right precordial leads and a history of ventricular arrhythmogenic events, syncope or a familial history of sudden cardiac death.
- If uncertain, this syndrome may be confirmed by testing the efficiency of a type I antiarrhythmic drug or by inducing a ventricular tachycardia/fibrillation during electrophysiological assessment.
- The treatment consists to equip the patient with an automatic defibrillator.

Introduction

Brugada syndrome was first described in 1992 by Josep et Pedro Brugada [1]. This syndrome is characterized by electrocardiographic abnomalities which are at risk of sudden death due to ventricular fibrillation in apparently normal heart.

D. Lena · H. Quintard · C. Ichai (✉)
Service de Réanimation médicochirurgicale, Faculté de Médecine de Nice,
Hôpital Saint-Roch, 5 Rue Pierre Dévoluy 06000 Nice, France
e-mail: ichai@unice.fr

A. Mihoubi
Service de Cardiologie, Institut Arnaud Tzanck, Rue Maurice Donat 06700,
Saint Laurent du Var, France

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_3,

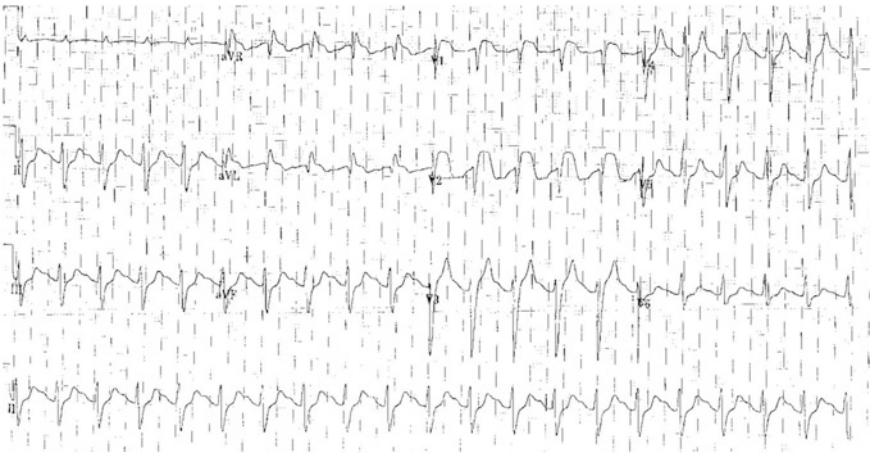

Fig. 1 Electrocardiogram after cardiocirculatory restoration: ST elevation in V1–V2

Mrs G, 41 year-old, with a history of several syncopes, is hospitalized in the intensive care unit for a cardiorespiratory arrest related to a ventricular fibrillation. The questions to the family revealed cocaine acute intoxication. After restoration of a spontaneous cardiocirculatory activity, an ST segment elevation on V1 and V2 precordial leads associated with a right bundle branch block was present on the electrocardiogram (ECG) (Fig. 1). The coronarography showed no abnormalities of coronary arteries and left ventricular function was normal. Accordingly, we made the hypothetic diagnosis of a Brugada syndrome. The genetic assessment allowed us to identify a mutation in the MOG1 gene which was probably responsible for the Brugada syndrome. A familial survey was further performed.

Epidemiology

The prevalence of Brugada syndrome is about 1 à 5/10,000 habitants [2]. This syndrome is responsible for 4 % of all sudden death and for 20 % of sudden death in apparently normal hearts. This frequency is highly variable according to the geographic situation: in south-east Asia, Brugada syndrome also named "unexplained sudden death syndrome" is considered to be endemic because it represents the first cause of mortality in males under 50 years. Rhythm abnormalities are more frequent in male than in female and the diagnosis is made at mean age of 42 ± 22 years.

Physiopathology

Genetic Aspects

The Brugada syndrome is an autosomal dominant inheritance illness showing a variable expression. In 1998, the SCN5A gene mutation, the gene encoding the α-subunit of the cardiac sodium channel, was identified to be responsible for the Brugada syndrome. These sodium channels are strongly implicated for initiating cardiomycytes depolarization. More than 80 other mutations of this gene were further identified, but they are really implicated in only 20–25 % of cases. The role of a new gene which is localized on the chromosome 3 has been, recently questioned.

Pathophysiological Notions

Mutations induce an inactivation of sodium channel leading to a decrease in sodium trafficking observed at the early phase of the action potential [3]. Consequently, the inverse potassium trafficking I_{to} increases during phase 1 of the action potential. This current Ito is responsible for a transmural gradient (between the epicardium and the endocardium) during ventricular activation, which is expressed by an elevated J point on the ECG. The epicardic cells of the right ventricule loss the phase 2 (dome part) of the action potential reflected by an ST segment elevation which is more pronounced in the right precordial leads. Electrophysiologically, this abnormality leads to an heterogenous repolarization of the epicardic surface which is responsible of the arrhythmogenicity observed in this syndrome: ventricular fibrillation are triggered by a phase 2 reentry phenomenon.

Diagnosis

Diagnosis Criteria

The ECG abnomalities which can be observed in the Brugada syndrome are presented in Fig. 2:

- A convexe ST elevation above 0.2 mV (2 mm) with a progressive slope, present at least on one right precordial lead (V1–V3), with a "dome" aspect of the QRS and negative T waves: this is the *type 1* ECG.
- *Type 2* ECG is characterized by a persistent top-concave ST segment elevation above 2 mm giving the typical aspect of a "horse saddle" and which is followed by a positive biphasic T wave.
- *Type 3* ECG is characterized by a top-concave ST segment elevation with the terminal part lower than 1 mm, always in the right precordial leads.

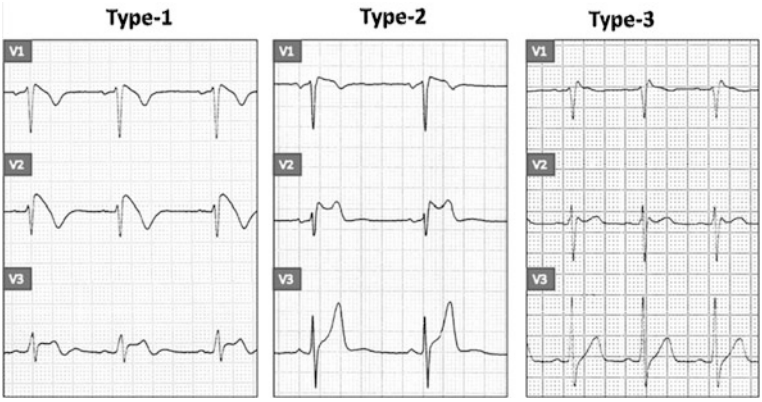

Fig. 2 Possible abnormal aspects of ECG in the Brugada syndrome

The European Consensus Conference which has been elaborated by the European Rhythm Society has defined the Brugada syndrome in 2005 [2] as follow:

- The association of a type 1 ECG (in the absence of any previous cardiopathy) and at least one of these criteria:
  - A history of documented ventricular fibrillation or a polymorphic ventricular tachycardia,
  - A familial history of sudden death before 45 year-old,
  - syncope,
  - malaise in the night with a stertorous breathing (these symptoms appear more frequently at rest).
- Or a type 2 or 3 ECG which becomes a type 1 following the administration of a antiarrhythmic drug of class I which blocks the sodium channels (ajmaline, flécaïnide, procainamide, pilsicainide) (Table 1). This pharmacological test is completed by an electrophysiological assessment aiming to stimulate ventricules in order to evaluate the myocardium excitability. This test can increase arrhythmogenicity and so must be performed during a short hospitalization with an ECG monitoring.

Precipitating Factors

Some factors can favor arrhythmogenicity of patients with a Brugada syndrome such as hyperthermia, hyperkalemia, hypokalemia, hypercalcemia, alcohol and cocaine absorption.

Some drugs induce Brugada-like ST segment elevation and should be avoid in this pathology. There is no published definitive list of contra-indicated drugs, but some of them have been listed by the European Consensus Conference in 2005 [2] (Table 1).

Table 1 Drugs possibly responsible for a Brugada-like ST elevation [2]

1. Antiarrhythmics
a. *Sodium channels blockers*
• classe Ic: flecaïnide, pilsicaïnide, propafenone
• classe Ia: ajmaline, procaïnamide, disopyramide, cibenzoline
b. Calcium inhibitors: verapamil
c. β blockers
2. Drugs against cardiac angor
a. Calcium inhibitors: nifedipine, diltiazem
b. Nitrate derivates: dinitrate d'isosorbide, nitroglycerin
c. Potassium opening channels: nicorandil
3. Psychotropes
a. Tricyclic antidepressors: amytriptylin, nortriptylin, desipramin, clomipramin
b. Tetracyclic antidepressors: maprotylin
c. Phenothiazin: perphenazin, cyamemazin
d. Serotonin reuptake inhibitors: fluoxetin

Differential Diagnoses

An ST segment elevation on ECG can be observed in many pathologies but must be differentiate from the Brugada syndrome: myocardial infarctus, acute pericarditis, myocarditis; hemopericardium, pulmonary embolism, aortic dissection, Duchenne myopathy, Friedreich ataxia, left ventricular hypertrophy, arrhythmogenic right ventricular cardiomyopathy, pectus excavatum, early repolarization syndrome of athletes, severe hypothermia, autonomic or central nervous system abnormalities (especially in case of subarachnoid hemorrhages).

Genetic Tests

Diagnosis Test

The SCN5A gene mutation [4] is responsible for 20–25 % of the Brugada syndromes. Accordingly, there is no interest to detect systematically this abnormality in a general population. On the other hand, it can be useful in patients presenting only partial diagnosis criteria or during familial surveys. These tests are performed only in rare specialized laboratories for research protocols. A test for SCN5A gene has a real diagnosis value only if positive. Other gene mutations are still actively researched, especially concerning the gene encoding the MOG1 protein.

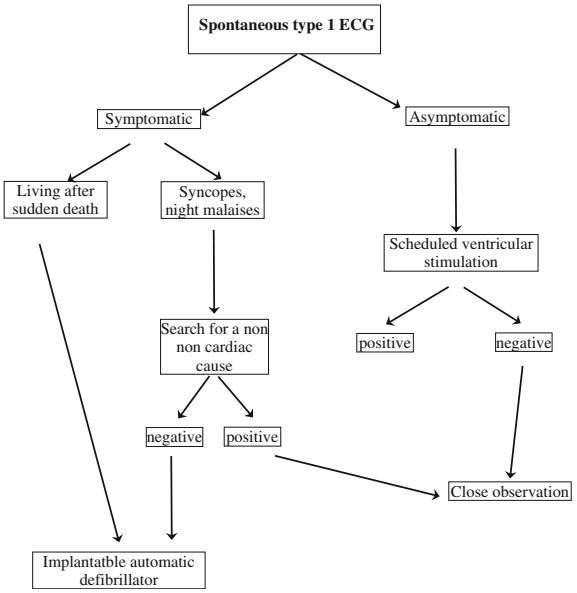

Fig. 3 Indications of automatic defibrillator implantation according to ECG abnormalities (spontaneous and class I antiarrhythmic drugs-induced type 1 ECG)

Prenative Test

Considering the non negligible consequences of this syndrome in term of severity and of the recommended preventive treatment (implantable automatic defibrillator) for children, a prenative test can be discussed. However, possible late manifestations, relative good performance of prognosis tests and efficient preventive treatment do not favor this position. Finally, the indication of a prenative test must be discussed for each case with a pluridisciplinar team.

Genetic Advices

A familial survey must be proposed for closers of patients presenting a Brugada syndrome [2]. This includes an ECG, a blood sample for a genetic survey, a pharmacological test in case of normal ECG and a scheduled ventricular stimulation in case of electrical abnormalities.

Treatment

The treatment options depend on the risk of sudden death. In patients having previously presented an episode of sudden death, the risk to develop a new episode is between 17 and 62 %, according studies. This risk reach 19 % in the following

3 years, in patients having syncope and a type 1 ECG. Data are less precise in asymptomatic patients, but several poor risk factors may help to orientate the treatment such as a spontaneous type 1 ECG, a male sex, the development of ventricular arrhythmogenicity after a scheduled electrical stimulation.

Presently, the sole efficient treatment is the implantation of an automatic defibrillator which permits to prevent ventricular arrhythmias-related deaths [2]. Indications of such a treatment are summarized in the Fig. 3 guidelines.

Among pharmacological drugs, it has been reported that quinidine could prevent sudden death by blocking the I_{to} current and thus normalizing the ST segment abnormalities and preventing the phase 2 reentry phenomenons. However, data showing a real efficiency of this drug in clinical trial are still not sufficient.

Conclusion

The Brugada syndrome is an autosomal genetic illness which is responsible of cardiac sudden death in young patients with apparently healthy hearts. The diagnosis is based on the ECG potential abnormalities as well as previous episodes of sudden death or syncope in the patient or in the familial history. The treatment is essentially preventive based on the implantation of an automatic defibrillator.

References

1. Brugada P, Brugada J (1992) Right bundle branch block, persistent ST segment elevation and suddden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. J Am Coll Cardiol 20:1391–1396
2. Antzelevitch C, Brugada P, Borggrefe M et al (2005) Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 111:659–670
3. Leenhardt A, Milliez P, Messali A et al (2007) Syndrome de Brugada, mise au point. Réanimation 16:285–289
4. Benito B, Brugada R, Brugada J, Brugada P (2008) Brugada syndrome. Prog Cardiovasc Dis 51:1–22

Cardiovascular Disease: Calcium Channel Anomalies

Christopher Hurt, David Montaigne, Pierre-Vladimir Ennezat, Stéphane Hatem and Benoît Vallet

Key Points

A better comprehension of cardiac physiology and more specifically cardiomyocyte calcium movements and concentration variations has led to increased understanding of calcium channel anomalies and their role in various congenital or acquired cardio-vascular diseases.

Ever increasing understanding in this area should lead to the development of treatments targeting specific malfunctions leading to or playing a role in the evolution of heart failure or atrial fibrillation, which affect a vast number of patients.

C. Hurt
Pôle de Cardiologie, Clinique Cardiologique, Hôpital Cardiologique, CHRU de Lille, Boulevard du, Professeur Jules Leclercq 59037 Lille, France

D. Montaigne
Faculté de Médecine, Service d'Explorations Fonctionnelles Cardio-Vasculaires, CHRU de Lille, Département Universitaire de Physiologie, Université de Lille 2, 59000 Lille, France

P.-V. Ennezat
Pôle de Cardiologie, Soins Intensifs Cardiologiques, Hôpital Cardiologique, CHRU de Lille, Boulevard Pr J Leclercq 59037 Lille, France

S. Hatem
Faculté de Médecine, UMRS 956. INSERM/UPMC-Paris 6, Institut du Cœur, Hôpital Pitié-Salpêtrière, Pierre et Marie Curie, 91, Boulevard de l'Hôpital 75634 Paris Cedex 13, France

B. Vallet (✉)
Pôle d'anesthésie Réanimation, CHRU de Lille, Hôpital Huriez, Rue Polonovski 59037 Lille, France
e-mail: Benoit.VALLET@CHRU-LILLE.FR

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_4,

Introduction

Calcium ions (Ca++) are major actors in cardiomyocyte electric and contractile functions as well as in adapting energy supply to metabolic demand. Calcium metabolism is often impeded in acquired or congenital cardiomyopathies. This is especially true in genetic calcium channel abnormalities, which can cause severe arrhythmias and sudden death syndrome.

Cardiomyocyte Calcium Homeostasia

L type calcium channels allow inward calcium movement during the cardiomyocyte membrane action potential (Fig. 1). This entering calcium flux is the main contributor to sustaining the action potential "plateau" phase (phase 2). In the adult heart, the resulting calcium cytosolic concentration is insufficient to activate sarcomeric activation but sparks the excitation contraction coupling. Calcium entering through the voltage-dependant calcium channels is detected by ryanodine receptors (RyRs) situated on the membrane of the sarcoplasmic reticulum. These RyRs open, releasing massive quantities of Ca^{2+} stored in the sarcoplasmic reticulum in a positive feedback physiological response, thereby producing a major increase in cytosolic calcium concentration, from a few nM to 1 μM during systole. This calcium increase facilitates calcium dependent actine-myosine cross-bridging and sarcomere shortening. This mechanism was first described by Françoise et Alexandre Fabiato in the 1980s and has since then been known as "calcium-induced calcium release". Other sources of cytosolic calcium increase have a negligible impact in this setting. Contraction is transient and is followed by a relaxation phase due to the cytosolic calcium decrease brought on by three mechanisms:

Sarcoplasmic reticulum calcium uptake by its Ca++-ATPase (SERCA), responsible for approximately 60 % of the calcium outflow

(1) calcium outward movement through the cellular membrane Na/Ca++ exchanger (NCX). This is a ion cotransporter depending not on ATP but on transmembrane sodium and calcium gradients and membrane potential. Responsable for 30 % of calcium outflow, this cotransporter is electrogenic and plays its main role during the depolarization phase.
(2) the remaining 10 % are extracted by slower systems such as membrane Ca++-ATPase and the calcium mitochondrial uniporter (mCU).

In a stable setting, all calcium transmembrane uptake is subsequently expelled. When transmembrane calcium inward movement increases, so do sarcoplasmic reticulum calcium concentrations (e.g. rapid pacing, catecholaminergic stimulation), mainly through enhanced activation of the sarcoplasmic reticulum calcium pump (SERCA). Strength of contraction primarily depends on the quantity of calcium freed by the sarcoplasmic reticulum.

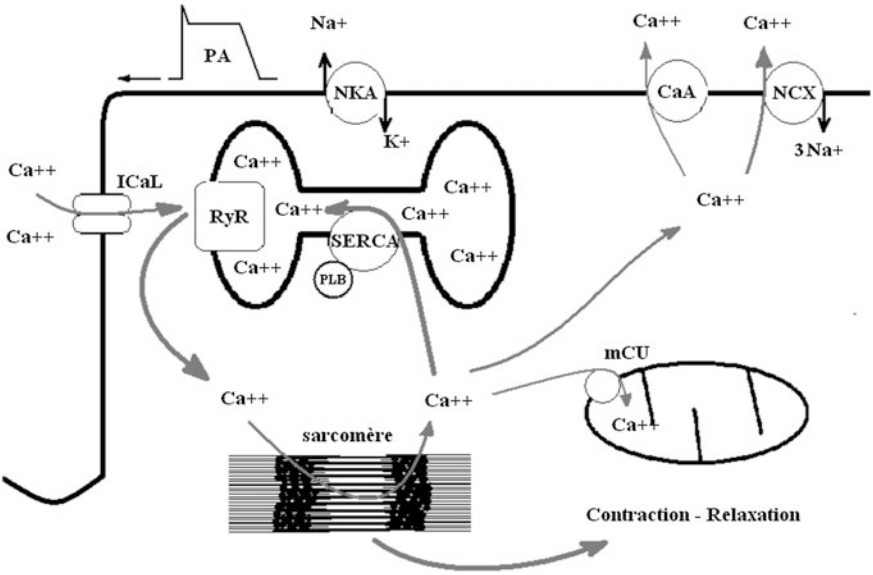

Fig. 1 Schematic illustrating cardiomyocyte calcium in and outflows and the excitation–contraction coupling

Calcium intake through the calcium mitochondrial uniporter (mCU) plays a small role in the total reabsorption of cytosolic calcium and mainly serves to adapt mitochondrial energy production according to the increased metabolic cellular demand, expressed in the form of a heightened calcium transient. This modulation is obtained through activation of enzymes implicated in the Krebs cycle by calcium ions.

Calcium kinetics and its cellular consequences in the cardiomyocyte environment are regulated by kinase-dependent signalization pathways:

- adrenergic stimulation leads to protein kinase A activation, which in turn phosphorylates L-calcium channel opening thereby prolonging its opening and calcium spark intensity
- SERCA activity is modulated by an adjacent regulating protein named phospholomban. This regulation is depends on calmoduline kinase and protein kinase A mediated phospholomban phosphorylation.

AP: action potential; ICal: L type calcium channel current; RyR: Ryanodine receptor; SERCA: sarcoendoplasmic reticulum (SR) calcium transport ATPase; PLN: phospholamban; MCU: mitochondrial calcium uniporter; NAK: sodium/potassium ATPase; NCX: sodium/calcium exchanger.

Acquired Cardiac Disease and Calcium Remodeling

Heart Failure

Heart failure related calcium homeostasis alteration explains cardiomyocyte contractile dysfunction, ventricular remodeling and the generation of ventricular arrhythmias.

SERCA activity is reduced due to:

- diminished myocardial content of this protein linked to the absence of SERCA gene induction during hypertrophy
- reduced phospholomban phosphorylation, consequence of increased phosphatase activity, which thereby inhibits SERCA function

The loss of SERCA activity is in part compensated by an increase in the NCX membrane exchanger but this compensation is obtained at the cost of lengthened relaxation and therefore altered adaptation to heart rate modifications through loss of the frequency-dependant acceleration of relaxation. NCX upregulation also results in lengthened action potential duration, and increased risk of arrhythmia.

Another consequence of heart failure is "porous" RyR with non calcium-induced sarcoplasmic reticulum calcium leaks. Phosphodiestérase and phosphatase regulation anomalies bring about an increased activation of Protein kinase A, which in turn excessively phosphorylates calstabine (FKBP12.6) dissociating it from RyR, leading to it's tendency to leak calcium. The resulting cytosolic calcium overload leads to overactivity of NCX, which exchanges one cytosolic calcium ion for three extra-cellular sodium cations thereby generating arrhythmogenic inward early diastolic sodium currents known as late after-depolarizations (LAD). These LADs may trigger severe ventricular arrhythmias such as ventricular tachycardia (VT) or fibrillation (VF).

NO synthase expression alterations also modify calcium movement. NOS 1 is relocalized from the sarcoplasmic reticulum to sarcolemma caveolin-3 near L-type calcium channels. Reduced NOS 1 near SR results in reduced RyR_2 NO-mediated regulation and altered excitation–contraction coupling whereas NOS 1-induced NO concentration increase near I_{Cal} inhibits calcium inward movement and therefore genesis of the cardiac cycle.

Myocardial Infarction

Added to the calcium homeostasis modifications associated with heart failure, specific alterations can be observed in cardiomyocytes bordering infarct zones. Inward calcium movement impairment result in reduced I_{Cal} current, SERAC expression is lessened and calcium micro domains coupling Ryr2 to L-type calcium channels are disorganized. These modifications lead to the reduced

amplitude and slower reversal of the calcium transient. RyR2 related calcium leaks may also increase causing potential arrhythmogenic situations.

Atrial Fibrillation

Atrial fibrillation (AF) is associated with action potential duration shortening due to a reduction of over 70 % of the I_{Cal} current for which the explanation is twofold:

- lessened L-type channel phosphorylation due to increased GMPc and phosphatase activity
- lessened L-type channel protein expression due to chronic activation of the signalization "calcium/calmodulin, calcineurin" cascade.

This reduced I_{Cal} current also leads to atrial tissue contractile dysfunction more easily observed after arrhythmia reversal. Alterations of calcium homeostasis thereby facilitate arrhythmia recurrence or persistence.

Congenital Calcium Channel Disease

Some calcium channel genetic anomalies lead to clinical syndromes associating severe cardio vascular symptoms such as syncope and sudden death syndrome linked to ventricular arrhythmias to resting or effort EKG anomalies. These congenital diseases are often found in infants and young adults.

Long QT Syndrome

The Timothy Syndrome or long QT syndrome type 8, is a rare form of congenital lo,g QT syndrome mainly affecting children, and described as a prolonged QTc longer than 440 ms and T wave electric variation, associated with syncopes and sudden death caused by "torsades de pointe" or ventricular fibrillation. Arrhythmia related mortality has been reported as high as 60 % before the age of 2 years and a half. Other possible but inconstant anomalies have been described such as severe atrio-ventricular blocks, immune deficiency, autism and abnormal cerebral development. Genotyping studies revealed voltage-dependent L-type calcium channel gene mutations, causing abnormally slow channel inactivation resulting in a persistent inward calcium current and therefore prolonged cardiomyocyte action potential phases 2 and 3 and EKG QT duration.

Type 4 long QT syndrome (LQT4) is related to the mutation of a gene coding the ankyrin B protein which serves to deploy ion channels and exchangers that play a role in the excitation–contraction coupling. Ankyrin B may therefore be

indirectly implicated in the pathophysiology of the QT segment and ventricular arrhythmias. Of note, LQT4 mutated gene carriers often present with sinus dysfunction and atrial fibrillation.

Short QT Syndrome: Brugada Syndrome

A congenital loss of function of l-type calcium channels has recently been described in a syndrome associating syncopes and sudden death caused by ventricular arrhythmias and a baseline EKG presenting with repolarization anomalies found in the Brugada and the short QT syndromes (respectively V1 to V3 ST segment elevation and a QTc shorter than 360 ms). Ventricular tachycardias in this setting are caused by heterogeneous distribution of repolarizing currents and especially the phase 1 potassium channel related I_{to} current within the myocardial muscle. This heterogeneous distribution creates an epicardial-endocardial repolarization gradient amplified by failures in the inward depolarizing currents especially I_{Cal}.

Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) presents as stress-related syncopes or sudden death in children and young adults, often during physical exercise. The VT are often polymorphic as the name lets on. Bidirectional tachycardias alternating two alternating ventricular morphologies are more often linked to a mechanism mimicking that of digoxin intoxication meaning cytosolic calcium overload responsible for the onset of late after-depolarizations (LADs). The heart of patients suffering from CPVT does not present with morphological or baseline EKG abnormalities but stress testing whether physical or through the administration of catecholaminergic drugs, EKG monitoring shows the onset of polymorphic ventricular extrasystoles followed by short non-sustained runs of ventricular tachycardia eventually leading to full out ventricular fibrillation. These arrhythmias are successfully treated using beta-blockers.

CPVT is linked to functional abnormalities of the RyR protein complex: mutations of the RyR channel itself, of its stabilizing protein FKBP12.6 or of intrasarcoplasmic calsequestrin lead to calcium leaking out of the sarcoplasmic reticulum, especially when the RyR complex is phosphorylated by Protein kinase A following adrenergic stimulation. Increased cytosolic calcium concentrations upregulates NCX function responsible for rest ing membrane potential oscillations facilitating the triggering of LADs.

Congenital Atrio-ventricular Block (AVB)

Congenital AVB is an auto-immune disease that affects fetuses or newborns of lupus-affected mothers: Anti-Ro/La antibodies present in the blood of these mothers directly interact with the L-type calcium channel α1C and α1D proteins and with the T-type calcium channel leading to reduced I_{Cal} and I_{CaT} (inward calcium based current found in cardiomyocytes capable of automatic activity).

Arterial Hypertension in Renal Polycyctosis

Ciliary polycystin-2 is a endothelial cell mechanosensitive calcium channel capable of reacting to vascular shear stress. Anomalously localized or expressed polycyction-2 calcium channels in renal polycyctosis affected patients might explain the development of arterial hypertension due to lessened sensitivity to shear stress and reduced endothelial NO synthesis.

Pulmonary Arterial Hypertension in Intensive Care Unit

Laurent Muller, Christian Bengler, Claire Roger, Robert Cohendy and Jean Yves Lefrant

Key Points

- In critically ill patients, the diagnosis of pulmonary arterial hypertension (PAH) is difficult as it can easily be confounded with other forms of pulmonary hypertension (PH).
- PAH is a form of PH. On the opposite, PH does not automatically imply PAH.
- The main cause of PH in ICU is left cardiac failure, followed by chronic pulmonary disease and chronic thromboembolic disease.
- Idiopathic is the most frequent cause of PAH, but PAH can also be associated with scleroderma, HIV infection, anorexigen toxicity, thyroid disease, cirrhosis.
- Pulmonary vasodilators allow a significant improvement of the prognosis in outpatient. In ICU, pulmonary vasodilators should be only a part of a general management including: treatment of triggering factors, optimization of fluid balance, decrease of RV afterload by using pulmonary vasodilators while maintaining cardiac output and mean arterial pressure.
- The early contact of PH referral center or specialized physician is of particular importance.

Introduction

Pulmonary arterial hypertension (PAH) is a rare, severe and complex disease. When the diagnosis is suspected, a multidisciplinary approach involving at least a PAH-

L. Muller (✉) · C. Bengler · C. Roger · R. Cohendy · J. Y. Lefrant
Intensive Care Units—Nîmes University Hospital, Groupe Hospitalo-Universitaire Caremeau—Place du Pr R. Debré 30029 Nîmes cedex 9, France
e-mail: laurent.muller27@orange.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_5,

specialized physician is recommended as highly specific treatment (in particular pulmonary vasodilators) can be indicated. In the absence of specific treatment, death occurs in the 3 years following diagnosis [1]. For the intensive care unit (ICU) physician, the diagnosis of pulmonary arterial hypertension (PAH) is difficult as it can easily be confounded with other forms of pulmonary hypertension (PH). The key issue is that PAH is a form of PH. On the opposite, PH does not automatically imply PAH. Pulmonary arterial hypertension must be differentiated from other causes of PH that are frequently seen in ICU. It was recently emphasized that pulmonary veno-occlusive disease (PVOD) must be differentiated from PH and PAH.

In critically ill patients, acute PH is frequently observed, especially in case of severe hypoxia due to acute respiratory distress syndrome or severe pulmonary embolism (PE) [2, 3]. In this case, acute PH is due to reflex and reversible hypoxic pulmonary vasoconstriction. The second cause of acute PH in ICU patient is acute left ventricle failure that increases left atrial pressure and, as a consequence, pulmonary artery pressure ("post capillary" PH). Acute PH is a reversible phenomenon when hypoxia and/or left atrial pressure are rapidly controlled. This should be differentiated from chronic PH that can be due to various chronic diseases. In ICU patients, chronic PH is also frequently seen in the evolution of chronic obstructive pulmonary disease (COPD), thromboembolic disease or chronic left heart failure. Beyond these three mains causes of chronic PH, the intensivist have to keep in mind that PH can be associated to rare chronic diseases that should not be under diagnosed because they imply a specific treatment. The more frequent of these rare diseases is PAH. The accurate diagnosis of PAH is of crucial importance since it implies a specific treatment by selective pulmonary vasodilators.

The diagnosis of PAH in ICU is a triple challenge. *First*, acute pulmonary hypertension must be distinguished from chronic pulmonary hypertension. *Second*, when chronic PH is diagnosed, a systematic screening of all potential causes of PH must be performed in order to exclude or diagnose PAH because PAH implies a specific treatment with pulmonary vasodilators. *Third*, when PAH is suspected, the last challenge is to test the clinical response to pulmonary vasodilators and to choose the best pharmacological class. In case of respiratory symptoms worsening after administration of pulmonary vasodilators, a PVOD should be suspected.

In the present text, we will only discuss clinical and therapeutic features of PAH and PVOD in ICU patients that correspond to the Class 1 and 1′ of the actual PH classification [4].

Definition and Classification

Pulmonary hypertension is the main sign of PAH. Pulmonary hypertension is a wide syndrome defined as a non-specific elevation of the pulmonary artery pressure at rest, whatever the etiology [5]. Pulmonary hypertension is defined as

a mean PAP (mPAP) >25 mm Hg as assessed by right heart catheterization (RHC). Echocardiography is very useful to screen patients with suspected PH but it cannot replace RHC. The criterion based on systolic pulmonary pressure (sPAP) >35 mm Hg should be abandoned. The criterion based on exercise PAP values (mPAP >30 mm Hg on exercise) should no longer be used, as they are not supported by strong published data. Moreover, on exercise, healthy individuals can reach much higher of mPAP values [5].

The first classification of PH published in 1973 by the World Health Organization (WHO) [6] stated that PH should be divided in two categories: secondary or primary PH. This pragmatic approach is apparently well adapted to critically ill patients but it nowadays appears as too simple. As evoked in introduction section, in ICU patients, "secondary" chronic PH is frequently observed as a final consequence of chronic diseases as left ventricle failure (post capillary chronic PH), chronic thromboembolic pulmonary disease or severe chronic obstructive pulmonary disease (COPD). In 1973, primary PH referred to PH with no obvious cardiovascular or pulmonary cause. It was further demonstrated that "primary" PH was a complex and non-homogeneous group of diseases that could be primary (idiopathic), but also associated with various diseases ranging from connective tissue disease or cirrhosis to drug toxicity or human immunodeficiency virus (HIV) infection. Therefore, the risk of the original classification was to under-diagnose rare causes of PH that needs a specific treatment. Then, a more complex classification was proposed in 1998 (*Evian* classification [7]) and updated in 2003 (*Venice* classification [8]) and 2008 (*Dana point* classification, published in 2009 [5]). The actual classification (*Dana point*) is shown in Table 1. The three main evolutions of the new classification were (1) to stop the use of primary/secondary HP classification, (2) to separate PH from pulmonary arterial hypertension (PAH), (3) to separate PAH from veno-occlusive pulmonary disease and/or hemagiomatosis [4, 5, 9]. The evolution of clinical classification of PH during the 3 past decades is summarized in Table 1. Pulmonary arterial hypertension (PAH = Class 1) refers to a heterogeneous group of non-cardiac, non-pulmonary diseases characterized by a chronic PH. The main causes of PAH are: idiopathic, heritable, drug-induced, associated (HIV infection, connective tissue disease, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia) and persistent PH of the newborn. In this classification, pulmonary hypertension refers to a PH due to an obvious pulmonary or cardiac cause. The three mains causes of PH are cardiac (severe congestive left heart failure, Class 2), pulmonary (COPD, Class 3) and thromboembolic (Class 4) (Table 1). A fourth cause of PH is proliferative diseases as hematologic diseases, storage diseases or anatomical obstruction of pulmonary vessels by fibrosis or tumor (Class 5). These four PH classes represent the "secondary" PH of the original classification. Finally, an intermediate class (Class 1′) is a direct pulmonary vessels disease called pulmonary veno-occlusive disease (PVOD) and/or capillary hemangiomatosis. The diagnosis of PVOD may be difficult because since it can mimics left ventricle failure.

Table 1 Updated clinical classification of pulmonary hypertension (Dana Point 2008) [5]

1 Pulmonary arterial hypertension (PAH)
This class refers to "primary" PH of the initial classification (1973)
1.1 Idiopathic (IPAH)
1.2 Heritable *(formerely familial—2003)*
1.2.1 BMPR2
1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Drugs and toxins induced: fenfluramine derivatives, aminorex, rapeseed oil
1.4 Associated with (APAH)
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease: Eisenmenger's syndrome[a], Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts[b], adult pulmonary arterial hypertension with small defect[c], Pulmonary arterial hypertension after corrective cardiacsurgery[d]
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis.
This class refers to "primary" PH of the initial classification (1973)
This class was separated from class 1 as compared to the 2003 classification
2 Pulmonary hypertension (PH) due to left heart disease
This class refers to "secondary" PH of the initial classification (1973)
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3 PH due to lung diseases and/or hypoxia
This class refers to "secondary" PH of the initial classification (1973)
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4 Chronic thromboembolic pulmonary hypertension (PH)
This class refers to "secondary" PH of the initial classification (1973)
5 PH with unclear and/or multifactorial mechanisms
This class refers to "secondary" PH of the initial classification (1973)
5.1 Haematological disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis

(continued)

Table 1 (continued)

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 activin receptor-like kinase 1, *APAH* associated pulmonary arterial hypertension, *BMPR2* bone morphogenetic protein receptor, type 2, *HIV* human immunodeficiency virus, *PH* pulmonary hypertension

Italics: comparison with previous classifications (1973 and 2003)

[a] Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present

[b] Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts. In these patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest

[c] Adult pulmonary arterial hypertension with small defects : in cases with small defects (usually ventricular septal defects, 1 cm and atrial septal defects, 2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH

[d] Pulmonary arterial hypertension after corrective cardiac surgery. In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery

Epidemiology

Pulmonary artery hypertension is characterized by a progressive increase of pulmonary artery resistances and chronic right ventricle failure. Chronic right heart failure is the main prognostic factor of PAH. The prevalence is probably underestimated because of the poor specificity of clinical signs. In a population of patients evaluated by echocardiography for dyspnea, the prevalence of PH was about 10 %. On the population of patients with PH echocardiographic signs, about 80 % had left heart failure, 10 % had chronic pulmonary disease and hypoxia, 4 % had PAH, 0.6 % had thromboembolic disease [10]. The prevalence of PAH ranges from 15 to 50/million adult population [11]. Idiopathic PAH (IPAH) is the most common cause of PAH. In a population of patient with documented PAH, 39.2 % of patients has IPAH and 3.9 % had family history of PAH. In the subgroup of associated PAH, 15.3 % had connective tissue disease, 11.3 % had congenital heart disease, 10.4 % had portal hypertension, 9.5 % had anorexigen-associated PAH and 6.2 % had HIV infection [12]. Pulmonary artery hypertension is a severe and insidious disease. The non-specific signs of PAH are associated with a delayed diagnosis that worsens prognosis. Before 2000, there were few specific treatment and few specialized teams for PAH care. At that time, the mean survival time was low (2.8 years following diagnosis) with survival rates of 68, 48, and 34 % at 1, 3, and 5 years, respectively [1]. Since the introduction of specific vasodilators (in particular epoprostenol) and specialized teams, the prognosis significantly improved as the reported survival at 1, 3, and 5 years was 87.8, 76.3, and 62.8 % in USA registry and 87, 76 and 67 % in the French registry, respectively [1, 13]. If these results are encouraging, the prognosis remains severe, especially when ICU

admission is required. In ICU, the prognostic of PH or PAH is considered as poor but few data are available. Therefore, no strong recommendation for PH or PAH treatment in ICU patients can be done [14, 15]. In a population of 82 septic ICU patients with history of PH mainly due to pulmonary disease, the mortality was related to the severity of PH. In mild, moderate or severe PH, the mortality was 28, 67 and 80 %, respectively [16]. Therefore, in patients with end-stage PH in whom all available treatment options have been exhausted, limitations on advanced treatment and/or ICU admission should be discussed [15].

Physiopathology Insights

Pulmonary arterial hypertension is characterized by the progressive increase in pulmonary arterioles (500 microns diameter) resistance. This induces right ventricle failure that is strongly associated to death. Right ventricle tolerance to PH is highly variables among subjects. As numerous chronic severe diseases, PAH mechanisms are multiple, complex and not well identified [5]. Genetic factors have been identified in PAH. Heritable PAH represents less than 10 % of cases. Heritable PAH is an autosomal dominant disease with incomplete penetrance. Mutations of *transforming growth factor beta* (TGF-β) receptors genes were identified as responsible of heritable but also sporadic cases. In particular, mutations of *bone morphogenetic protein recepetor*-2 (BMPR2) or *activin-like receptor* 1 (ALK-1) were shown to be associated with PAH and hereditary hemorrhagic telangiectasia, respectively (Class 1, 2, Table 1). The three mains pathophysiologic findings reported in autopsy studies are (1) abnormal vascular cell proliferation (low apoptosis/proliferation ratio) inducing arteriolar remodeling, (2) excessive vasoconstriction and (3) partial thrombotic phenomenon. Pregnancy should be discouraged since it can worsen PAH.

Diagnosis

Clinical Diagnosis of PAH [4, 5, 8, 12]

The first step of diagnosis approach is to eliminate clinical signs of COPD (or other chronic pulmonary parenchymal disease), of congestive left heart failure and of thromboembolic disease. If such signs are present, the diagnosis of PAH is unlikely and Class 2, 3 and 4 PH should be suspected and explored. The presence of signs of hematologic, malignant, vasculitis or storage disease is unlikely in PAH. In this case, a class-5 PH (Table 2) must be suspected and explored.

If no signs of class 2, 3, 4 and 5 PH are present, PAH can be suspected. The onset of disease is insidious, with low specific functional signs. The most common symptom is breathlessness, particularly on exercise (60 %), followed by fatigue

(19 %), syncope (8 %), angina (7 %), lipothymia (5 %), leg edema (3 %) [17]. Data obtained from the French national registry published in 2006 shows the following characteristics [12]. The female/male sex ratio is 1.9. The mean age is 50 ± 15 years. Body mass index (BMI) is usually normal. A BMI above 30 is observed in 15 % of the cases, similar to the adult French population. The delay between onset of symptoms and diagnosis is 27 months. A majority (75 %) of patients had severe symptoms at presentation, with a New York Heart Association (NYHA) functional class III or IV (class I = 1 %, class II: 24 %). Exercise capacity is tested through a 6-minute walk test, which was abnormal (329 ± 109 m) in most patients. The six-minute walk distance is correlated with NYHA functional class.

In PAH Symptoms at rest are seen only in advanced cases. The physical examination shows left parasternal lift, accentuated pulmonary component of second heart sound, systolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency and right ventricle third sound. In the more advanced states, functional symptoms are present at rest and physical examination shows jugular vein distension, hepatomegaly, peripheral edema, ascites, and cool extremities. Lung sounds are usually normal in PAH. The presence of basal crackles may point towards interstitial lung disease or left cardiac failure. Nevertheless, physicians have to keep in mind that basal crackles can be seen in PVOD. A cyanosis can be seen in 20 % of IPAH cases and suggests right-to-left shunting and severe reduction of cardiac output. Digital clubbing is not frequent in IPAH but when present, a congenital heart disease or a PVOD should be suspected. Telangiectasia, digital ulceration, and sclerodactily are seen in scleroderma. Finally, clinical examination tries to identify or exclude stigmata of chronic liver disease.

The diagnosis of POVD should be suspected in case of symptoms worsening after administration of selective pulmonary vasodilator. The presence of pulmonary edema signs associated with RV failure without evidence of LV failure is also highly suggestive of POVD. In the evolution of PAH, low cardiac output can be associated with bacteremia due to gut bacteria translocation that can lead to death.

Electrocardiography

Electrocardiography is classically normal at the early stage of IPAH. Electrocardiograpm has low sensibility (55 %) and specificity (70 %) and cannot be used alone as a screening tool for the diagnosis of PH or PAH. The association of right axis deviation, pulmonary P wave, R/S wave ratio >1 in V1 lead and R wave >0.5 mV has a 90 % specificity for RV failure. This is of poor prognosis during PAH. Ventricular arrhythmias are rare. Supraventricular arrhythmias may be present in advanced stages (in particular atrial flutter and atrial fibrillation) and always leads to further clinical deterioration.

Table 2 World Health Organization (WHO) functional classification of pulmonary hypertension modified after the New York Heart Association (NYHA) functional classification

Class I
Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
Class II
Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class III
Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class IV
Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

Biology

There is no specific biomarker of PAH. The brain natriuretic peptide (BNP) is elevated due to right atrial and/or ventricle dilation. The BNP value is correlated to prognosis. Liver tests may be abnormal either in case of RV failure or in case of PAH associated with cirrhosis. Differentiating one from the other cause may be difficult. In this case, clinical evaluation and morphologic hepatic evaluation are of paramount importance. Serologic tests for HIV infection and hepatitis are mandatory. Thyroid tests are also useful (Class5 PH). When a connective tissue disease (CTD) is suspected, auto immunity tests should be performed. Antinuclear antibodies are not specific of CTD-APAH. About 40 % of patients with IPAH have elevated anti-nuclear antibodies, usually in low titre (1:80). Scleroderma is the CTD with the highest prevalence of PAH. Anti-centromere antibodies are typically positive in limited scleroderma as are other anti-nuclear antibodies including dsDNA, anti-Ro, U3-RNP, B23, Th/To, and U1-RNP. In the diffuse variety of scleroderma, U3-RNP is typically positive. In case of systemic lupus erythematosus, anti-cardiolipin antibodies may be found. Thrombophilia screening (antiphospholipid antibodies, lupus anticoagulant, and anti-cardiolipin antibodies) should be performed when chronic thromboembolic PH is suspected [5].

Chest X Ray

The main interest is to eliminate obvious sign of PH associated with chronic pulmonary (COPD, emphysema or interstitial disease) or left cardiac failure (infiltrates associated with congestive heart failure). However, Chest X ray is

usually abnormal at the time of PAH diagnosis. The typical findings are central pulmonary artery dilation which contras with peripheral vascular loss. The enlargement of right atria and ventricle are seen in advanced cases.

Echocardiography

Echocardiography is the best tool for PAH screening when suspected. Transthoracic echocardiography (TTE) is usually sufficient to diagnose PH and assess RV function that remains the main prognostic factor in PAH. Echocardiography does not exclude the need for RHC, which remains mandatory in all suspected cases of PAH. Echocardiography is nowadays widely available in ICU [18] and plays a fundamental role in cardiac and hemodynamic assessment in critically ill patients [19, 20], especially in case of RV failure or PH [21]. Figure 1 shows an example of severe IPAH in a patient admitted to ICU for a septic shock due to invasive diarrhea.

First Step: Echocardiography Diagnosis of PH, Estimation of Systolic PAP Value

Because patients with PAH admitted in ICU are usually at advanced stage of the disease, echocardiography findings are usually easy to diagnose. The first difficulty is to separate acute from chronic PH. In case of acute PH, sPAP value is rarely more than 40 mm Hg. Above such value, RV cannot compensate acute afterload increase and right cardiac output (CO) decreases. The subsequent low CO limits the sPAP increase, which rarely reaches more than 40–45 mm Hg. The consequence of acute RV failure is a rapid (few hours) dilation of RV. As pericardium is not distensible in a short period of time, the biventricular volume is constant. Therefore, the hemodynamic consequence of acute RV dilation is LV compression, which limits LV filling and subsequently worsens low cardiac output. For those reasons, when a sPAP value is more than 40 mm Hg, a chronic PH is likely. In chronic PH, the simplest way to assess sPAP is to record tricuspid regurgitation (TR) flow on a four-chamber apical view (Table 3). The maximal velocity of TR is correlated to the pressure gradient between pulmonary artery and RV (Table 3). This approach can also be applied to pulmonary regurgitation that require a trained operator. Pulmonary regurgitation flow allows evaluation of mean and diastolic pulmonary artery pressure (Table 3). The sum of right atrial pressure or central venous pressure (RAP, CVP) value and right ventriculo-arterial gradient represent sPAP (Table 3). Evaluation of RAP value by TTE is summarized in Table 4. A semiquantitative approach of sPAP can be done on the basis of gradient only (Table 3). The acceleration time of pulmonary ejection flow allows a semi-quantitative assessment of sPAP for trained operators when TR is not recordable. (Table 3)

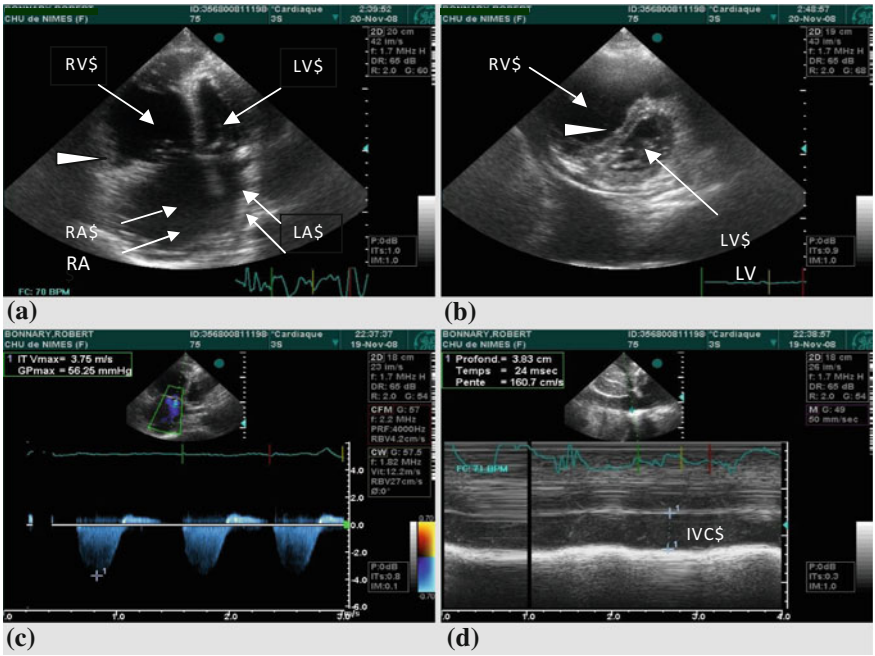

Fig. 1 Echocardiography diagnosis of pulmonary hypertension. Idiopathic pulmonary arterial hypertension with chronic right ventricle failure in a 68 years-old patient admitted in ICU for septic shock in intensive care unit. **a** Four chambers apical view showing a major right atrial and ventricle (RV) dilation. The RV free wall is thickened (white triangle) due to a chronic adaptation to chronic pulmonary hypertension. **b** Parasternal short axis view. Paradoxical septum (white triangle) with typical left ventricle of "D sign". In physiological condition, LV shape is circular ("O sign"). **c** Tricuspid regurgitation recoeder by continuous Doppler. Maximal velocity (Vmax) = 3.75 which correspond to a RV/PA gradient equal to 56 mm Hg ($\Delta P = 4\ V^2$). **d** Recording of inferior vena cava (IVC) by M mode in a subcostal view. The IVC diameter is 38 mm and no respiratory variation is observed. The RAP value is over than 20 mm Hg (See Table 3). In this case, systolic pulmonary artery pressure is 56 + 20 = 76 mm Hg. This was consistent with the value measured by pulmonary artery catheter (80 mm Hg)

Second Step: Eliminating Left Systolic and/or Diastolic Failure, Advanced Valvular Disease and Screening for Eisenmeger's Syndrome

As mentioned in epidemiology section, left heart failure is the main cause of PH. One of the main roles of TTE is to exclude systolic or diastolic LV dysfunction. The quantification of systolic function is usually simple, visually or by LV ejection fraction measurement. Assessing diastolic function can be more difficult. Clinical and echocardiography criteria for suspecting PH secondary to LV failure (especially diastolic) are summarized in Table 5. The intensivist can perform them. It includes LV ejection fraction, Mitral inflow Doppler pattern, tissue Doppler pattern at the lateral and medial mitral annulus, pulmonary venous flow. The intensivist can also perform the diagnosis of advanced valvular disease. However, diagnosis of

Table 3 Echocardiography assessment of pulmonary artery pressure by echocardiography

Evaluation of sPAP by tricuspid regurgitation velocity in apical four chamber view (simple technique)
Pressure gradient between RV and PA: $\Delta P = 4. (RT\ Vmax)^2$
$sPAP = \Delta P + RAP$
Semiquantitative assessement of sPAP by tricuspid regurgitation velocity in apical four-chamber view assuming a RAP value of 5 mm Hg (the simplest technique)
Echocardiographic diagnosis: PH unlikely
Tricuspid regurgitation velocity = 2.8 m/s, PA systolic pressure = 36 mm Hg
No additional echocardiographic variables suggestive of PH
Echocardiographic diagnosis: PH possible
Tricuspid regurgitation velocity = 2.8 m/s, PA systolic pressure = 36 mm Hg
Presence of additional echocardiographic variables suggestive of PH
Tricuspid regurgitation velocity = 2.9–3.4 m/s, PA systolic pressure = 37–50 mm Hg
With/without additional echocardiographic variables suggestive of PH
Echocardiographic diagnosis: PH likely
Tricuspid regurgitation velocity = 3.4 m/s, PA systolic pressure = 50 mm Hg
With/without additional echocardiographic variables suggestive of PH
Exercise Doppler echocardiography is not recommended for screening of PH
Evaluation of sPAP by pulmonary ejection flow acceleration time in short axis view (for trained operators, when TR is not recordable)
Tacc <100 ms = PH, Tacc <60 ms = severe PH
Evaluation of sPAP by pulmonary regurgitation flow (for trained operators, when TR is not recordable)
Pulmonary regurgitation flow have a maximum velocity that evaluates mPAP (mPAP = 4.Vmax2 + RAP) and a minimum velocity which correspond to dPAP. The sPAP is obtained by the following formula: sPAP = 3 mPAP–2 dPAP

Vmax maximal velocity, *PAP* pulmonary artery pressure, sPAP *systolic PAP*, *mPAP* mean PAP, *dPAP* diastolic PAP, *RAP* right atrial pressure, *Tacc* pulmonary ejection acceleration time, *PH* pulmonary hypertension, *ΔP* pressure gradient between right ventricle and pulmonary artery

Table 4 Echocardiographic assessment of right atrial pressure (RAP) by analysis of inferior vena cava (IVC) diameter and its respiratory variations (collapsibility of IVC: cIVC)

IVC diameter	cIVC (%)	RAP (mm Hg)
Low: <15 mm	>50	0–5
Normal: 15–25 mm	>50	6–10
	<50	11–15
High: >25 mm	<50	16–20
	None	>20

Eisenmenger's syndrome is difficult and must be done by a cardiologist specialized in such diseases.

Third Step: Assessment of Right Ventricle Function

The main sign of RV failure is dilation. The RV dilation can be visually assessed [22] or by calculation of RV/LV end diastolic area (Fig. 2). In chronic RV failure,

Table 5 Clinical and echocardiography criteria for the diagnosis of PH related to of left ventricular systolic or diastolic dysfunction. Adapted from [5]

Clinical features
Age >65
Elevated systolic blood pressure
Elevated pulse pressure
Obesity, metabolic syndrome
Hypertension
Coronary artery disease
Diabetes mellitus
Atrial fibrillation
Echocardiography
LVEF <40 %, visually or by Simpson approach. The S wave velocity at the lateral mitral annulus can also be used (Normal >8 cm/s, equivalent to LVEF >50 %) in the absence of regional severe wall motion anomaly.
Left atrial enlargement
Concentric remodelling of the LV
LV hypertrophy
Presence of echocardiographic indicators of elevated LV filling pressure: E/A ratio >2, E wave velocity >90 cm/s, E/E′ ratio >15, S/D ratio of pulmonary venous flow <1.
Evaluation over time
Symptomatic response to diuretics
Exaggerated increase in systolic blood pressure with exercise
Concomitant decrease of sPAP and LV filling pressure after diuretics
Re-evaluation of chest radiograph consistent with heart failure

LVEF left ventricle ejection fraction, *LV* left ventricle, *sPAP* systolic pulmonary artery pressure

the RV free wall is thickened (normal value <6 mm). The RV systolic function can be evaluated by the tricuspid annulus plane systolic excursion (TAPSE) in M-mode. The normal value of TAPSE is 16–25 mm. A TAPSE value inferior to 15 mm is of poor prognosis [5]. This index represents the maximal anterior systolic displacement of tricuspid annulus. This simple and reproducible index is correlated with RV ejection fraction (RVEF). An analogous method could be applied to tissue Doppler at the lateral tricuspid annulus. The maximal velocity of S (systolic) wave recorded by tissue Doppler at the lateral tricuspid annulus is correlated to RVEF. A S velocity value inferior to 11 cm/s correlates with altered RVEF whereas a value inferior to 9 cm/s is correlated with sever alteration of RV systolic function. The existence of pericardial effusion is associated with bad prognosis [5].

Thoracic CT Scan

Performing CT scan is of mandatory for the diagnosis of PAH, especially in order to exclude pulmonary, cardiac or thromboembolic cause of PH. Contrast CT angiography of the pulmonary artery show the typical angiographic findings in

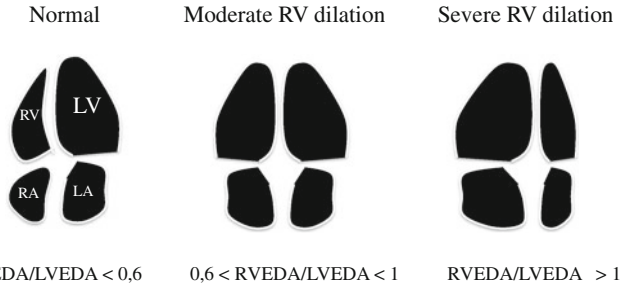

Fig. 2 Echocardiography visual assessment of right ventricle dilation. The main sign of right ventricle failure is dilation. *RVEDA* right ventricle end diastolic area, *LVEDA* left ventricle end diastolic area

chronic thromboembolic PH (Class 4) such as complete obstruction, bands and webs, and intimal irregularities as accurately and reliably as conventional angiography. High-resolution CT scan gives important informations on lung parenchyma. It can easily identify interstitial lung disease, advanced COPD and emphysema. It can also be helpful in case of clinical suspicion of PVOD. The presence of interstitial edema with diffuse central ground-glass opacification and thickening of interlobular septa suggest PVOD. In this disease, CT scan may also show lymphadenopathy and pleural effusion. A diffuse bilateral thickening of interlobular septa associated with small centrilobular poorly circumscribed nodular opacities can help to diagnose pulmonary capillary hemangiomatosis.

Right Heart Catheterization

Outside the ICU

A right heart catheterization is obligatory to confirm the diagnosis of PAH. It allows to exclude other causes of PH, in particular post capillary PH. It is the sole way to test the vasoreactivity of pulmonary vessels to selective pulmonary vasodilators in order to evaluate the usefulness of subsequent chronic treatment. In outpatients, the complication rate of RHC is low in experienced centers [23]. In a study evaluating 7218 RHC procedures, the complication rate was 1.1 % (IC 0.8–1.3), related to difficult vascular access, arrhythmias or hypotension. Four death were reported but only one was directly attributable to RHC. RHC must record staged measurement of SaO2, RAP, RV pressure, PAP (systolic, diastolic and mean), PA wedge pressure (that reflects left atrial pressure), cardiac output, cardiac index and pulmonary vascular resistances. The RHC criteria for PAH are summarized in Table 6. At the time of diagnosis, mPAP value is 50 ± 17 mm Hg NYHA class I–II patients and 56 ± 15 mm Hg NYHA III–IV class patients [12].

Table 6 Right heart catheterization criteria for PAH diagnosis

mPAP at rest >25 mm Hg
Pulmonary artery wedge pressure (PAwP) <15 mm Hg
Pulmonary vascular resistances ([mPAP-PAwP]/CO) >3 Wood units
A PawP >15 mm Hg associated with a dPAP—PawP gradient >10 mm Hg is seen in PAH from arterial and venous origin

mPAP mean pulmonary arterial pressure, *dPAP* diastolic pulmonary artery pressure

The RHC can be useful for the diagnosis of PVOD. When the catheter extremity is in wedge position, a saline flush leads to a marked pressure increase followed by a very slow pressure decrease. This phenomenon is due to a trapping of saline between the catheter and the occluded veins. If a wedge pressure can be recorded (this may be difficult), a low value is classical whereas capillary pressure is high. This can be indirectly assessed by the difference between dPAP and PAwP.

The vasoreactivity test must be performed in every cases of suspected PAH. This test aims to identify patients that can benefit from selective or non selective pulmonary vasodilators. A positive response to vasoreactivity test is more frequent in IPAH than in other categories of PAH. The test is performed during the RHC procedure. It can use IV epoprostenol IV at a dose ranging from 2 to 10 ng/Kg/min (incremental dose of 2 ng/Kg/min every 15 min), or IV adenosine at a dose ranging from 50 to 250 mcg/Kg/min (incremental dose of 50 mcg/Kg/min every 2 min), or inhaled nitric oxide (NO) at a dose ranging from 10 to 80 ppm (fixed dose, no incremental administration needed). Inhaled NO is the best pharmacological agent because of a strong selectivity for pulmonary vessels. In clinical practice, inhaled NO is administered at a dose of 24 to 40 ppm over 5 min. At that time, new RHC measurements are performed, with ongoing NO administration. A positive response is defined as a 10 mm Hg mPAP decrease associated with an absolute value below 40 mm Hg with no concomitant cardiac output decrease. For non IPAH, the probability of positive response is low. This test can be harmful in case of elevated left filling pressure.

In the Context of ICU

The RHC can be dangerous in decompensated patients. Moreover, decompensated patients may have transient elevated PA pressure. Therefore, pressure criteria must be difficult to interpret. In such case, the positivity of vasoreactivity test is more important than absolute PAP value. In ICU, right heart catheterization can be difficult in case of severe PAH [24]. Despite these restrictions, RHC is mandatory for IPAH diagnosis in ICU patients when diagnosis is suspected.

Table 7 Determinants of poor prognosis in PAH

Clinical evidence if right ventricle failure
Rapid rate of progression of symptoms
Syncope
NYHA functional class = III–IV
Six minutes walk test <300 m
Peak O_2 consumption <12 mL/min/Kg
High elevated BNP or NT-proBNP plasma levels
Echocardiography findings: TAPSE <15 mm and/or pericardial effusion
Right heart catheterization findings : RAP >15 mm Hg or CI <2 L/min/m^2

NYHA New York Heart Association, *BNP* brain natriuretic peptide, *TAPSE* tricuspid annulus plane systolic excursion, *RAP* right atrial pressure

Prognosis (Table 7)

The prognosis depends on the severity of RV failure and the etiology. The worse prognosis is seen in PAH associated with scleroderma. Whatever the cause, treatment by a selective pulmonary vasodilator (when indicated) has a favorable impact on outcome [25].

Traitement (Fig. 3)

Outside the ICU

General measures: oxygen therapy, diuretics in case of edema and/or RV failure, anticoagulants and digoxin in case of arryhtmias. Pregnancy, altitude travel, important exercise are classically contra-indicated.

Specific treatments (Table 8): calcium blockers, selective endothelin inhibitors (ERA), prostacyclin analogous, phosphodiesterase type 5 inhibitors (IPDE). Riociguat, a soluble guanylate cyclase stimulator, has been show in a phase III study (PATENT-1 trial) to significantly improved exercise capacity by week 12. This molecule improved the 6-minute walk distance both in patients who were receiving no other treatment for the disease and in those who were receiving endothelin-receptor antagonists or prostanoids. There were significant improvements in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to clinical worsening, and dyspnea score [26]. Encouraging results were also recently reported with riociguat in case of thromboembolic PH [27]. In the past, most studies involving the therapies listed in Table 8 were short-term trial with exercise capacity as a primary end point. Macitentan is a new oral dual (ETA and ETB) Endothelin Receptor Antagonist (ERA). Recently, the phase III SERAPHIN trial enrolled a total of 742 patients comparing placebo to Macitentan 3 mg and Macitentan 10 mg in a long-term trial. It is the largest PAH prospective

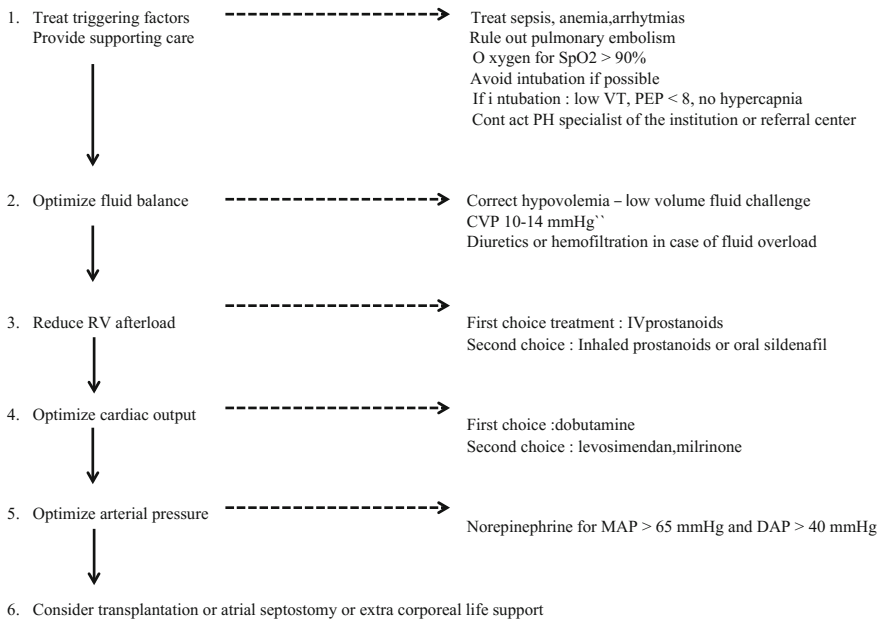

Fig. 3 General approach of decompensated PAH in ICU patients. Adapted from [15]. *CVP* central venous pressure, *VT* tidal volume, *IV* intravenous, *PEP* positive expiratory pressure, *MAP* mean arterial pressure, *DAP* diastolic arterial pressure

study to date. In this study, Macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension [28].

In the Context of ICU (Fig. 3)

The main objective is to prevent and to treat RV failure. The principles are reduction of PVR by vasodilators, limitation of pulmonary hypoxic vasoconstriction by oxygen, preservation of coronary output by control of systemic arterial pressure, use of inotropes, arrhythmia control. No algorithm was validated in ICU patients. Each therapeutic option must be individually tested. Anemia should be treated (>10 g/dL).

Mechanical ventilation may be deleterious since it can increase PVR. High levels of PEP (positive expiratory pressure) also increase PVR, RV afterload and PAP. On the opposite, hypercapnia may induce a 50 % increase of PVR. If the patient is intubated, mechanical ventilation adjustments are crucial but difficult. The principles are that low levels of tidal volume and PEP (3–8 cm H2O) are necessary whereas hyperpania should not be tolerated

Hypovolemia should not be tolerated but volemia assessment is difficult in this context. Evaluation of fluid responsiveness by fluid challenge with low fluid

Table 8 Recommendations for efficacy of specific drug therapy, balloon atrial septostomy, and lung transplantation for pulmonary arterial hypertension (class 1) according to WHO functional class. Adapted from [5]

Measure/treatment	Classes of recommendation–level of evidence		
	WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers	I–C[a]	I–C[a]	–
Endothelin receptor antagonists (ERA)			
Ambrisentan	I–A	I–A	IIa–C
Bosentan	I–A	I–A	IIa–C
Sitaxentan[b]	IIa–C	I–A	IIa–C
Macitentan—promising results in PAH and thromboembolic PH	No actual recommendation		
Phosphodiesterase type-5 inhibitors			
Sildenafil	I–A	I–A	IIa–C
Tadalafil	I–B	I–B	IIa–C
Prostanoids			
Beraprost	–	IIb–B	–
Epoprostenol (intravenous)	–	I–A	I–A
Iloprost (inhaled)	–	I–A	IIa–C
Iloprost (intravenous)	–	IIa–C	IIa–C
Treprostinil (subcutaneous)	–	I–B	IIa–C
Treprostinil (intravenous)	–	IIa–C	IIa–C
Treprostinil (inhaled)	–	I–B	IIa–C
Soluble guanylate cyclase stimulator			
Riociguat—promising results in PAH	No actual recommendation		
Initial drugs combination therapy	–	–	IIa–C
Sequential drugs combination therapy	IIa–C	IIa–B	IIa–B
Balloon atrial septostomy	–	I–C	I–C
Lung transplantation	–	I–C	I–C

[a] Only for positive vasoreacivity test
[b] Sitaxentan was withdrawn on 2010 due to severe unpredictable side effects (hepatic toxicity)

volume is logical but not demonstrated. Dynamic indices cannot be used in case of PH [29]. The optimal value for central venous pressure is 10–14 mm Hg [30].

In order to maintain cardiac output, the concomitant use of vasopressors and inotropes are frequently necessary. Dobutamine is the most inotrope studied in PH. Low doses (5 mcg/Kg/min) decrease PVR and PAP and moderately increase cardiac output. Higher doses are not recommended as they induce tachycardia without decreasing RVP. Systemic vasodilation is frequently observed in decompensated PH, due to systemic inflammatory response syndrome. This phenomenon can be worsened by sepsis. Systemic vasodilation is characterized by low diastolic pressure, which is the main determinant of coronary pressure. Therefore, a low diastolic pressure (>40–50 mm Hg) [31] may induce functional myocardial ischemia that may worsen RV function. In this case, Norepinephrine is the agent of choice since it induces systemic vasoconstriction without alteration of coronary

Table 9 Pulmonary vasodilators that may reduce PVR in ICU setting. Adapted from [14]

Drug	Dose	Duration of action	Side effects
Intravenous			
Prostacyclin (Epoprostenol, Flolan®)	Start at 1 ng/kg/min 2-ng/kg/min increments according to effect	3–5 min	Systemic hypotension, worsening oxygenation, antiplatelet effect, headache, flushing, nausea, diarrhea
Iloprost	1–5 ng/kg/min	30 min	Idem Flolan
Inhaled			
Prostacyclin (Epoprostenol, Flolan®)	0.2–0.3 ml/min of 10–20 μg/ml nebulized into inspiratory limb of ventilator circuit (30–40 ng/kg/min)	3–5 min	Less hypotension, better oxygenation
Iloprost	2.5–5 μg 6–9 times/day, 1 mg/ml into the ventilator circuit or via face mask at 0.2–0.3 ml/min for 10–20 min	30 min	As above, plus bronchospasm
NO	5–80 ppm, continuously	15–30 s	Methemoglobinemia
Oral			
Sidenafil	0.25–0.75 mg/kg/4 h	3–4 h	Few hypotension Few paradoxical hypoxia

blood flow. The objective of MAP is classical, 65–75 mm Hg [32]. Levosimendan can be used but may be individually tested as there is a risk of systemic hypotension. Intravenous milrinone has limited indications because of hypotension.

The use of selective pulmonary vasodilators in order to decrease RV afterload is logical in decompensated PAH [14]. The agents that can be used, their dose, duration of action and side effects are summarized in Table 9.

Endothelin receptor antagonist has not been tested in the context of ICU. Intravenous administration can induce severe hypotension that limits their use in unstable patients.

Inhaled NO decreases PAP and increases RV performance at a dose ranging from 5 to 40 ppm. It has some limitations: rebound effect, methemoglobinemia, and price. Moreover, the beneficial effect is not sustained by 72 h in ARDS patients [33]. This diminution in the beneficial effect of NOi may be due to the fact that NO also has proinflammatory activityand prolonged exposure can result in oxidative injury and the nitrosylation of proteins. To date, at our knowledge, no long term evaluation of NOi was performed for PAH patient.

Inhaled epoprostenol (Flolan®) induces significant pulmonary vasodilation without systemic effect. Continuous infusion of epoprostenol via an automatic syringe in a nebulization device at a dose of 12.5–50 ng/Kg/min in the inspiratory circuit or mask is feasible. Intravenous epoprostenol is started at the dose of 1 ng/

kg/min and titrated upward in 2 ng/kg/min increments according to clinical effect. The use of intravenous forms of prostanoids is limited in ICU since they have severe systemic effects: hypotension, paradoxical worsening oxygenation, nausea, headache, flush, diarrhea, antiplatelet effects.

Intravenous ilomedin (Iloprost®) has been used in post-operative ICU patient at a dose of 2 $\mu g.kg^{-1}$ over 20 min. Its efficacy and side effects are comparable to epoprostenol. One study suggest short duration of hemodynamic effects (20 min) limiting its use [34], whereas one other found sustained effect other 2 h but in ARDS patients [35]. A recent study in eight patients with PAH functional class IV with right heart failure, four of them candidates for lung transplantation, suggest the association inhaled Iloprost plus oral Sildenafil as an alternative to Epoprostenol [36].

The use of sildenafil was reported as efficacious in ICU patients in several case reports at a dose of 25–50 mg followed by 25 mg/8 h. The effects are seen after 15 min of oral intake and the peak efficacy is observed between 30 and 60 min. Intravenous Sildenafil administered at infusion rate of 2 and 9 mg/h for 20 min each to achieve plasma levels of 100 and 300 ng/l respectively (equivalent to peak plasma levels of 25 and 50 mg of oral sildenafil therapy) led to significant reductions in mPAP (−7.4 mm Hg or—16.9 % (9.2) p <0,001) and PVR (−188.8 dyn/s/cm^5 or—25.1 % (11.4) p <0,001) [37].

The treatment of the cause of acute exacerbation is fundamental, especially sepsis. In case of failure of medical treatment, septostomy, extra corporeal life support and transplantation should be discussed with referral center only in a highly selected population since the mortality is very high in this context.

Conclusion

The prognosis of PAH was consistently improved in the ten past years by introduction of selective pulmonary vasodilators and management by highly specialized medical teams. In ICU patients, PAH remains a severe disease with a high mortality rate. When PAH is suspected, a systematic diagnosis approach is of particular importance in order to rapidly eliminate left cardiac, thromboembolic and pulmonary causes of PH. Left cardiac disease is the most common cause of PH. Early recognition of PAH allows a rapid introduction of selective pulmonary vasodilators that can improve outcome. Idiopathic PAH is the most frequent cause but it can also be associated with scleroderma, HIV infection, anorexigen toxicity, thyroid disease, cirrhosis. Pulmonary vasodilators should be only a part of a general management including treatment of triggering factors, optimization of fluid balance, decrease of RV afterload by using pulmonary vasodilators while maintaining cardiac output and mean arterial pressure. The early contact of PH referral center or specialized physician is of particular importance.

References

1. McLaughlin VV, Shillington A, Rich S (2002) Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 106:1477–1482
2. Vieillard-Baron A, Price LC, Matthay MA (2013) Acute cor pulmonale in ARDS. Intensive Care Med 39:1836–1838
3. Jardin F, Vieillard-Baron A (2009) Acute cor pulmonale. Curr Opin Crit Care 15:67–70
4. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R (2009) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54:S43–S54
5. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30:2493–2537
6. Hatano S, Strasser T (1973) Primary pulmonary hypertension. Report on a WHO meeting. World Health Organization, Geneva, 15–17 Oct 1973
7. Fishman AP (2001) Clinical classification of pulmonary hypertension. Clin Chest Med 22:385–391, vii
8. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman A (2004) Clinical classification of pulmonary hypertension. J Am Coll Cardiol 43:5S–12S
9. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, Harrington RA, Anderson JL, Bates ER, Bridges CR, Eisenberg MJ, Ferrari VA, Grines CL, Hlatky MA, Jacobs AK, Kaul S, Lichtenberg RC, Lindner JR, Moliterno DJ, Mukherjee D, Pohost GM, Rosenson RS, Schofield RS, Shubrooks SJ, Stein JH, Tracy CM, Weitz HH, Wesley DJ (2009) ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation 119:2250–2294
10. Gabbay E, Reed A, Williams TJ (2007) Assessment and treatment of pulmonary arterial hypertension: an Australian perspective in 2006. Intern Med J 37:38–48
11. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S (2007) An epidemiological study of pulmonary arterial hypertension. Eur Respir J 30:104–109
12. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G (2006) Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 173:1023–1030
13. Humbert M, Sitbon O, Yaici A, Montani D, O'Callaghan DS, Jais X, Parent F, Savale L, Natali D, Gunther S, Chaouat A, Chabot F, Cordier JF, Habib G, Gressin V, Jing ZC, Souza R, Simonneau G (2010) Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 36:549–555
14. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ (2010) Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Crit Care 14:R169
15. Hoeper MM, Granton J (2011) Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med 184:1114–1124
16. Tsapenko MV, Herasevich V, Mour GK, Tsapenko AV, Comfere TB, Mankad SV, Cartin-Ceba R, Gajic O, Albright RC (2013) Severe sepsis and septic shock in patients with

pre-existing non-cardiac pulmonary hypertension: contemporary management and outcomes. Crit Care Resuscitation 15:103–109
17. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK et al (1987) Primary pulmonary hypertension. A national prospective study. Ann Intern Med 107:216–223
18. Quintard H, Philip I, Ichai C (2011) French survey on current use of ultrasound in the critical care unit: ECHOREA. Ann Fr Anesth Reanim 30:e69–e73
19. Joseph MX, Disney PJ, Da Costa R, Hutchison SJ (2004) Transthoracic echocardiography to identify or exclude cardiac cause of shock. Chest 126:1592–1597
20. Mayo PH, Beaulieu Y, Doelken P, Feller-Kopman D, Harrod C, Kaplan A, Oropello J, Vieillard-Baron A, Axler O, Lichtenstein D, Maury E, Slama M, Vignon P (2009) American College of Chest Physicians/La Societe de Reanimation de Langue Francaise statement on competence in critical care ultrasonography. Chest 135:1050–1060
21. Vieillard-Baron A (2009) Assessment of right ventricular function. Curr Opin Crit Care 15:254–260
22. Vieillard-Baron A, Charron C, Chergui K, Peyrouset O, Jardin F (2006) Bedside echocardiographic evaluation of hemodynamics in sepsis: is a qualitative evaluation sufficient? Intensive Care Med 32:1547–1552
23. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, Barst RJ, Ghofrani HA, Jing ZC, Opitz C, Seyfarth HJ, Halank M, McLaughlin V, Oudiz RJ, Ewert R, Wilkens H, Kluge S, Bremer HC, Baroke E, Rubin LJ (2006) Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 48:2546–2552
24. Lefrant JY, Muller L, Bruelle P, Pandolfi JL, L'Hermite J, Peray P, Saissi G, de La Coussaye JE, Eledjam JJ (2000) Insertion time of the pulmonary artery catheter in critically ill patients. Crit Care Med 28:355–359
25. Galie N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A (2009) A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 30:394–403
26. Ghofrani HA, Galie N, Grimminger F, Grunig E, Humbert M, Jing ZC, Keogh AM, Langleben D, Kilama MO, Fritsch A, Neuser D, Rubin LJ (2013) Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 369:330–340
27. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C (2013) Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 369:319–329
28. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G (2013) Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 369:809–818
29. Mahjoub Y, Pila C, Friggeri A, Zogheib E, Lobjoie E, Tinturier F, Galy C, Slama M, Dupont H (2009) Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. Crit Care Med 37:2570–2575
30. Tsapenko MV, Tsapenko AV, Comfere TB, Mour GK, Mankad SV, Gajic O (2008) Arterial pulmonary hypertension in noncardiac intensive care unit. Vasc Health Risk Manage 4:1043–1060
31. Benchekroune S, Karpati PC, Berton C, Nathan C, Mateo J, Chaara M, Riche F, Laisne MJ, Payen D, Mebazaa A (2008) Diastolic arterial blood pressure: a reliable early predictor of survival in human septic shock. J Trauma 64:1188–1195
32. Antonelli M, Levy M, Andrews PJ, Chastre J, Hudson LD, Manthous C, Meduri GU, Moreno RP, Putensen C, Stewart T, Torres A (2006) Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27–28 Apr 2006. Intensive Care Med 33:575–590

33. Griffiths MJ, Evans TW (2005) Inhaled nitric oxide therapy in adults. N Engl J Med 353:2683–2695
34. Schenk P, Petkov V, Madl C, Kramer L, Kneussl M, Ziesche R, Lang I (2001) Aerosolized iloprost therapy could not replace long-term IV epoprostenol (prostacyclin) administration in severe pulmonary hypertension. Chest 119:296–300
35. Sawheny E, Ellis AL, Kinasewitz GT (2013) Iloprost improves gas exchange in patients with pulmonary hypertension and ARDS. Chest 144:55–62
36. Lopez-Meseguer M, Berastegui C, Monforte V, Bravo C, Domingo E, Roman A (2013) Inhaled iloprost plus oral sildenafil in patients with severe pulmonary arterial hypertension delays the need for lung transplantation. Transplant Proc 45:2347–2350
37. Suntharalingam J, Hughes RJ, Goldsmith K, Doughty N, George P, Toshner M, Sheares KK, Pepke-Zaba J (2007) Acute haemodynamic responses to inhaled nitric oxide and intravenous sildenafil in distal chronic thromboembolic pulmonary hypertension (CTEPH). Vascul Pharmacol 46:449–455

Part III
Infectious Diseases

Strongyloidiasis in Intensive Care

Laurent Zieleskiewicz, Laurent Chiche, Stéphane Donati and Renaud Piarroux

Key Points

- Strongyloidiasis is a pandemic disease with a probably underestimated prevalence due to is asymptomatic character.
- Disseminated "malignant" strongyloidiasis is associated with up to 80 % mortality rate.
- This particular form can be related to all immune deficiencies but mostly to corticotherapy because of it direct effect on the Nematode biology.
- Initiation of corticotherapy is probably risky in a patient who is possibly asymptomatically infected with Strongyloides, even at low doses and after anti-parasitic treatment.
- Ivermectin is the treatment of choice for decontamination and for disseminated strongyloidiasis.

L. Zieleskiewicz (✉)
Service d'anesthésie réanimation, Hôpital Nord chemin des Bourrely, 13915 Marseille cedex 20, France
e-mail: laurent.zieleskiewicz@ap-hm.fr

L. Chiche
Service de médecine interne, Centre de compétence des Maladies auto-immunes et vascularites systémiques, PACA-OUEST, CHU de la Conception, 147, boulevard Baille 13385 Marseille Cedex 5, France

S. Donati
Service de réanimation polyvalente, Hôpital Sainte Musse, Centre hospitalier intercommunal de Toulon-La-Seyne-sur-Mer BP 1412, 83056 Toulon, France

R. Piarroux
Service de parasitologie et mycologie, Hôpital de la Timone, Assistance Publique-Hôpitaux de Marseille, 264, rue Saint-Pierre 13385 Marseille, France

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_6,

Introduction

Strongyloidiasis is a parasitic disease caused by *Strongyloides stercoralis*, a human intestinal nematode infecting several million individuals worldwide. Although, in the majority of cases, the infection is asymptomatic, it may transform to a fulminant form in certain clinical situations. For the intensivist, it is necessary to know how to recognise this "malignant" form, which frequently causes death, despite treatment. Above all, intensivists should prevent its occurrence in patients hospitalised in intensive care (IC) when they are chronic carriers of the parasite. Due to the fact that there is a direct parasitic cycle without obligatory passage through an external vector, a contaminated patient can remain an asymptomatic carrier for the whole of their life and a single trip to a tropical area is sufficient for infestation. Taking into account the increasing mobility of individuals, the increase in migratory flow and the large number of circumstances that can lead to a lowering of immunity, it is important that the intensivist takes into account the risks linked to this parasite in his/her therapeutic decisions.

Epidemiology and Parasitic Cycle

Classically limited to equatorial zones, foci of strongyloidiasis have also been described in temperate zones such as the Spanish Mediterranean coast. Humans are usually infected via the transcutaneous route, by walking barefooted on soil contaminated with human faeces and harbouring larvae of *S. stercoralis*. Ingestion or bathing in contaminated water has also been incriminated in the mechanisms of infection. *S. stercoralis* uses several pathways to complete its life cycle (Fig. 1). In effect, the life cycle of this parasite may include a free phase in the external environment, where a sexual phase of multiplication can even take place, but in contrast, the cycle may take place entirely in humans where the larvae released in the intestine may directly cross the intestinal mucosa and skin around the anus to pass into the circulation. The existence of this short cycle is manifest as repeated reinfestations and explains the possibility of chronic carriage of the parasite in patients who left the endemic area decades previously. A patient can therefore remain infected and pauci-symptomatic all their life until an eventual lowering of their immunity and the triggering of a disseminated infection.

Definitions and Clinical Forms

During a primo-infection, the most common signs are cutaneous (around the site of entry), digestive and respiratory. The chronic form is most often asymptomatic but digestive, respiratory (pseudo-asthma), cutaneous (larva migrans) and biological

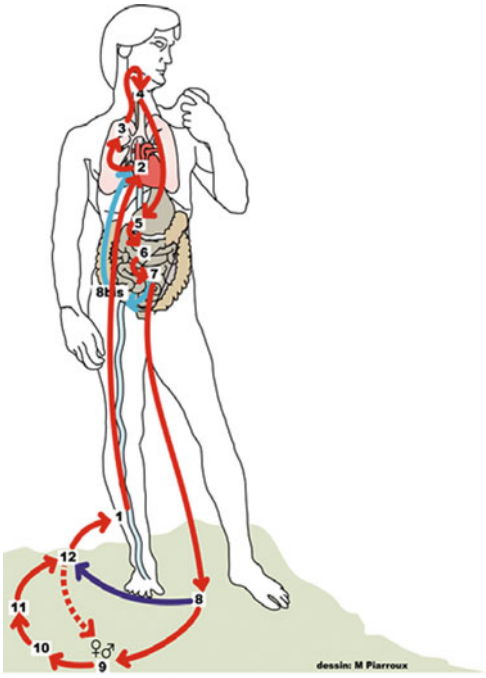

Fig. 1 The different steps in the life cycle of *Strongyloides.* 1. *Strongyloides* larvae (filariform) penetrate the skin and then enter the circulation. 2. *Strongyloides* larvae (filariform) arrive in the right side of the heart. 3. *Strongyloides* larvae (filariform) pass into the aveoli and are expelled by coughing. 4. *Strongyloides* larvae (filariform) arrive at the aerodigestive junction and are swallowed. 5. *Strongyloides* larvae (filariform) transform into parthenogenetic females after having crossed the pylorus. 6. The parthenogenetic females lay their eggs in the intestine. 7. These eggs evolve into "first generation" rhabditoid larvae. 8. The "first generation" rhabditoid larvae are released into the external environment (in the faeces), or 8b: the "first generation" rhabditoid larvae transform into filariform larvae in the intestine and these then cross the intestinal wall and enter the circulation. 9. The "first generation" rhabditoid larvae transform into sexual adults (male and female). 10. The pregnant females lay their eggs in the external environment. 11. These eggs evolve into "second generation" rhabditoid larvae. 12. The "second generation" rhabditoid larvae transform into filariform larvae. The different cycles of strongyloidiasis. External sexual cycle of strongyloidiasis (heterogonic). Sexual multiplication in the external environment: the *Strongyloides* larvae can transform into sexual adults without passage through a human. External asexual cycle: the "first generation" rhabditoid larvae released in the faeces can transform directly into filariform larvae, which are infective to humans if the external environment is unfavourable, or develop into sexual adults. Cycle of endogenous asexual auto-reinfestation: the "first generation" rhabditoid larvae can transform directly into filariform larvae in the intestine and pass into the circulation. This cycle explains the persistence of the disease

(hypereosinophilia) signs may be observed. Disseminated ("malignant") strongyloidiasis occurs in different circumstances when corticotherapy is prescribed or there is a lowering of cellular immunity principally, but sometimes humoral, as all

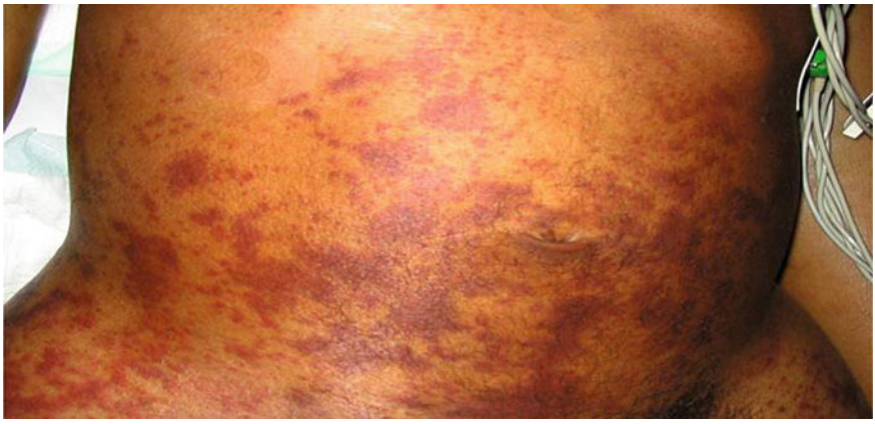

Fig. 2 Periumbilical purpura, a sign of disseminated strongyloidiasis

types of immunity are involved in the fight against the parasite. This is the most severe form of the disease with nearly 80 % mortality, characterised by larval invasion of organs that do not usually participate in the parasitic cycle. There are many clinical manifestations depending on the organs affected. In terms of the abdomen, in addition to the classic functional signs digestive haemorrhages, ulcers of the small intestine or colon, occlusive syndromes and malabsorption have been described. From a respiratory perspective, the symptoms corresponding the phase of tissue migration of *Strongyloides* larvae can extend to severe acute respiratory distress syndrome (ARDS) with intra-alveloar haemorrhages. Cutaneous involvement is seen as periumbilical purpura, which is a pathognomic clinical sign of disseminated strongyloidiasis (Fig. 2).

Cases of meningitis or meningoencephalitis, aseptic or bacterial, have been described. Many other organs such as the liver, bladder, pancreas and kidneys can be infected by the parasite. Bacteriaemia is often associated with disseminated strongyloidiasis as translocation of bacteria accompanies translocation of the parasites.

Risk Factors for Disseminated Strongyloidiasis

Both humoral and cellular immunity are involved in controlling infection by the parasite, but cellular immunity mediated by T-lymphocytes and type 2 T-helper cells plays a predominant role. The role played by glucocorticoids is only partially linked to their immunosuppressive effect because they also act directly on the metabolism of the parasite by inducing the production of infectious *Strongyloides* larvae (filariform) in the intestine of patients (direct activation of the parasite and transformation of rhabditoid larvae by the action of steroid receptors present on the parasite).

Glucocorticoids are therefore the most frequent triggering factor. These may be endogenous or exogenous corticoids. The duration of treatment and the doses vary, but cases have been described for durations of treatment less than 10 days and very low doses. In addition to their direct effect on the parasite, glucocorticoids can act on the defences of the host by inhibiting the production of polynuclear eosinophils, reducing lymphocyte activation and inducing apoptosis of T-helper cells. Thus, the use of corticoids may be considered as a specific risk factor depending on the background of the patient. The use of hydrocortisone at a substitutive dose in septic shock presents a large potential theoretical risk and it should be used with some precautions: screening, decontamination with ivermectin. Many immunosuppressive chemotherapies have been incriminated in the genesis of disseminated strongyloidiasis (vinca-alkaloids, cyclophosphamide, methotrexate). However, in most cases they were associated with corticotherapy. Cyclosporine does not appear to be associated with an increase in the incidence of disseminated forms of the disease. Some authors even attribute anti-parasite properties to cyclosporine.

Infection with HTLV-1 is frequently associated with strongyloidiasis, with disseminated forms and with treatment failures. This is probably due to an alteration of type 2 T-helper cells. In contrast, with only about 40 cases of co-infection reported in the medical literature, it is difficult to confirm that HIV predisposes to disseminated strongyloidiasis. These two diseases have the same endemic areas and their association should be more frequent. Furthermore, many patients with HIV are treated with corticotherapy for pneumocystosis without developing disseminated strongyloidiasis. Finally, some cases of disseminated strongyloidiasis have been described in the absence of severe immunosuppression. These may be favoured by diabetes or malnutrition.

Screening of Carriers of the Disease Before Exposing them to an At-Risk Situation

In IC, the risk consists mainly of corticotherapy, irrespective of the dose. Given the urgency of the initiation of these treatments in IC, the clinician does not usually have time to wait for the results of biological examinations. The decision should therefore take into account the benefit/risk ratio of treatment and the probability of contamination of the patient bearing in mind his/her ethnic origin, travel, way of life and digestive symptomatology. For example, in an at-risk patient, the expected benefit of substitutive opotherapy with hydrocortisone in the case of septic shock does not appear to be favourable given the risk of inducing disseminated strongyloidiasis. Serology, blood counts for the detection of eosinophilia and parasitological examination of stools are among the examinations classically used to diagnose chronic infection. Hypereosinophilia in a high risk patient has a sensitivity and specificity of 93 % and the speed of diagnosis makes this a useful examination for the intensivist. Specific techniques should be used for the parasitological examination of stools or the diagnosis may be missed. It is therefore very important

to indicate 'detection of *Strongyloides*' at the start of the examination so that the laboratory uses adequate methods such as the detection of larvae in stools using the Baermann technique. Serology can be carried out by ELISA or GPIA (gelatin particle indirect agglutination) with sensitivities ranging from 70–98 % and a specificity close to 100 %, including immunosuppressed patients.

Diagnosis of Disseminated Strongyloidiasis

Disseminated strongyloidiasis should be suspected in a patient at risk of chronic carriage (stay in an endemic area, even a long time ago) presenting with risk factors for disseminated disease (essentially corticotherapy) who presents with an evocative clinical picture of exceptional severity. To make the diagnosis of disseminated strongyloidiasis, it is necessary to document the presence of parasites outside of organs normally colonised during the parasitic cycle (i.e. lungs, intestine). Multiple specimens should be taken and examined for larvae: bronchoalveolar lavage, urine, gastric fluid, stools and biopsies of cutaneous lesions. Hypereosinophilia is not constant but appears to be associated with a better prognosis. Intestinal biopsies and fibroscopy specimens are rarely carried out in current practice.

Treatment

It is necessary to completely eradicate the parasite to prevent the development of disseminated disease. Persistence of a single larva could lead to the development of disseminated strongyloidiasis in some circumstances (Fig. 3).

Drugs Available

The azoles, notably thiabendazole, are the first drugs to have been used. Prescribed at a dose of 25 mg/kg twice a day for 3 days, it is effective in approximately 70 % of cases. It is necessary to repeat treatment after 2 weeks to obtain complete eradication of the parasite. Thiabendazole is sometime effective in disseminated strongyloidiasis, particularly when administered via the intrarectal (IR) route. Side-effects such as nausea, malaise, hallucinations and neuropsychiatric problems are common (>95 % of cases). Albendazole at a dose of 400 mg/day for 3 days has a comparable efficacy and tolerance.

Ivermectin appears to be at least as effective as thiabendazole with better clinical tolerance and a shorter duration of treatment (2 days) in the case of chronic disease. The usual dose is 200 μg/kg as one single dose. This treatment has also been used

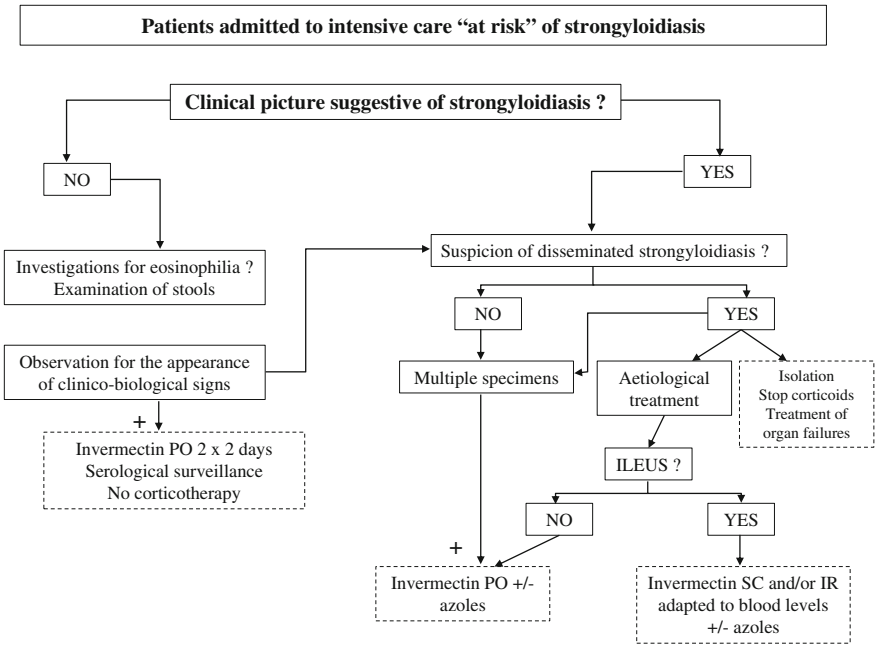

Fig. 3 Strongyloidiasis in intensive care, algorithm and management

successfully in disseminated forms. However, in the case of paralytic ileus (common in disseminated disease), intestinal absorption is minimal or even nil.

There is no parenteral antihelminthic form. Its use via the IR route [2] has sometimes given good results. Recently, some authors [1] have used veterinary forms of ivermectin via the parenteral route (subcutaneous) in patients with disseminated strongyloidiasis. While this type of treatment is judicious, notably in cases of paralytic ileus, treatment failures have already been described and the pharmacokinetics of this route of administration are unknown. The creation of a galenic parenteral form therefore appears urgent.

Therapeutic Strategies

Patient Infected or Possibly Infected Before Undergoing Corticotherapy

Many parameters should be taken into account, particularly the expected benefit of corticotherapy and its level of urgency. Complete eradication of the parasite sometimes requires several courses of antihelminthics and verification of the efficacy of treatment by blood counts to reveal a decrease in number of eosinophils

and by parasitological examination of stools repeated at least three times. The whole of the process of decontamination may therefore take several weeks. Starting anti-parasitic treatment just before corticotherapy gives the false impression of security because cases of disseminated forms have been described after treatment. If corticotherapy is not essential in a patient at risk, the wisest option is to prescribe an anti-parasitic treatment, to monitor its efficacy and to defer or abandon corticotherapy. Persistence of a single larva could lead to the development of disseminated strongyloidiasis in a patient treated with corticotherapy.

Patient with Disseminated Strongyloidiasis

There are no formal recommendations or randomised studies on the subject. Our proposals are therefore based on published clinical cases and physiopathology. Initial treatment depends on repeated and prolonged doses of ivermectin. The cycle of auto-infection lasts 2 weeks and some authors recommend continuing treatment until clinical improvement and negativity of specimens over 15 days.

In the case of malabsorption, ileus or curarisation (e.g. in ARDS), the IR or subcutaneous route has been used. The subcutaneous route appears to be the most effective. However, there is a risk of neurotoxicity [3] and the patient should be monitored for signs of this (mydriasis, ataxia, shaking, coma). It is important to monitor blood concentrations of ivermectin. Ivermectin may be associated with an azole in the case of treatment failure. Probabilistic antibiotherapy active against *Enterobacter* and adapted secondarily to specimens should be initiated. Meningitis should be investigated and treated if present. Corticotherapy should be interrupted. The patient should be isolated (healthcare personnel to wear gloves and masks for protection). The patient's family should be tracked down and receive decontamination. The other associated organ failures are not specific and the patient should receive standard symptomatic treatments. The interest of activated protein C has not been clearly established due the side-effects described.

References

1. Marty FM, Lowry CM, Rodriguez M et al (2005) Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. Clin Infect Dis 41:5–8
2. Tarr PE, Miele PS, Peregoy KS, Smith MA, Neva FA, Lucey DR (2003) Case report: rectal administration of ivermectin to a patient with Strongyloides hyperinfection syndrome. Am J Trop Med Hyg 68:453–455
3. Turner SA, Maclean JD, Fleckenstein L, Greenaway C (2005) Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. Am J Trop Med Hyg 73:911–914

Dengue in the Intensive Care Unit

Frédéric Potié, Olivier Riou and Marlène Knezynski

Key Points

- Dengue is a tropical viral disease which has seen a worldwide resurgence in the past 25 years.
- Severe forms of the disease include haemorrhagic dengue and dengue shock syndrome, which presents as fever, haemorrhaging with thrombopenia, and a state of shock due to capillary leak.
- There is no effective aetiological treatment for this disease.
- Treatment consists essentially of the management of shock and correction of haemorrhagic problems.

Introduction

Dengue is a tropical viral disease which has seen a worldwide resurgence over the past 25 years. Geographic spread of the mosquito vector and the virus has led to an exponential increase in number of cases of the disease since the first cases identified in the 1950s in Bangkok and Manila.

F. Potié (✉)
International SOS, Suite 105, Kunsha Building 16 Xinyuanli, Chaoyang District, Beijing 100027, China
e-mail: frederic.potie@internationalsos.com

O. Riou
Service anesthésie réanimation, Centre Hospitalier Gabriel Martin, Rue Labourdonnais 97460 Saint Paul Reunion, France
e-mail: oriou@msn.com

M. Knezynski
Service de Gériatrie, Centre hospitalier Universitaire Nord Réunion, Allée des Topazes, 97400 Saint Denis Reunion, France
e-mail: marleneknez@hotmail.com

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_7,

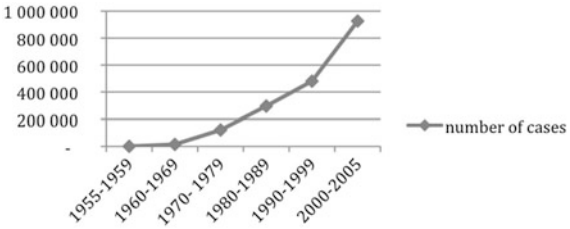

Fig. 1 Annual number of cases of dengue worldwide reported to WHO

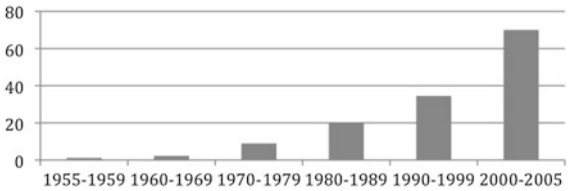

Fig. 2 Number of countries reporting cases of dengue to WHO

Although this disease usually presents as a benign fever, two more severe forms of the disease may also occur, namely haemorrhagic dengue and dengue shock syndrome, which are associated with a high mortality rate, particularly in children, and justify hospitalisation in an intensive care unit (ICU). In emergency departments or ICUs, a diagnosis of dengue should be evoked in a patient who has stayed in an endemic area and presents with a combination of fever and thrombopenia [2].

Over the past decade, dengue has become one of the major international public health problems. Moreover, it is considered to be a "neglected tropical disease" justifying a specific plan of action by the World Health Organisation (WHO). In 2002, the annual number of cases of dengue was estimated as more than 100 million worldwide, with 250,000 cases of haemorrhagic dengue and 25,000 deaths. Furthermore, the number of reported cases has continued to increase exponentially over the past few years. Mortality is higher in children.

The areas of geographic predilection for dengue are linked to its vector, the *Aedes* mosquito, which develops in urban, peri-urban and rural areas in tropical and subtropical regions. This corresponds to a zone including more than 100 countries. Dengue therefore represents a danger to public health for more than 2.5 million individuals worldwide. Furthermore, more than half of the world's population live in these endemic areas and the risk of infection is 30-times higher in individuals <50-years of age (Figs. 1 and 2). Global warming has led to fears of an expansion of the habitat of this mosquito. Likewise, globalisation and an increase in population migration will increase the risks of spread of the virus.

Dengue affects both adults and children with a predominance in the latter. The overall rate of mortality is estimated to be approximately 1 %, but is higher for severe forms of the disease like dengue shock syndrome where it ranges from 0.1 to 10 %.

Physiopathology

Transmission of the Virus

Dengue is caused by an arbovirus and is transmitted by an arthropod vector, a mosquito of the genus *Aedes* (*A. aegypti, A. albopictus*). Humans are the main reservoir of the virus although some primates can also be infected. The virus belongs to the family of Flaviviridae and has four different serotypes (DEN1, DEN2, DEN3 and DEN4).

Immunity

Infection confers long-lasting immunity, but only to the serotype concerned. There is no long-lasting cross-immunity between the four different serotypes. Furthermore, successive infections with different serotypes increase the risk of severe forms of the disease. The greater severity of "secondary" forms of dengue has been suggested to be due to the presence of facilitating antibodies acquired during the first infection. In endemic areas, the majority of the adult population is immunised and the risk of dengue is highest in children. Conversely, in non-endemic areas, dengue affects both adults and children. Both humoral immunity (secretion of IgM and IgG) and cellular immunity (via the production of cytokines, which have a major role in capillary permeability) play a role. The long-term hope for the management of this disease lies in the development of a recombinant vaccine, which is currently undergoing clinical trials in humans.

Dissemination of the Virus

Like all arboviruses, the dengue virus has a tropism for the small vessels and central nervous system. When the virus is inoculated into the blood via a mosquito bite it multiplies in the reticular endothelial system and then disseminates throughout the body. The most significant physiopathological manifestations are thrombopenia, on the one hand, linked to depression of platelet synthesis or the secretion of anti-platelet antibodies, and an increase in endothelial permeability, on the other, which is immunological in origin.

Leakage of plasma due to increased capillary permeability is caused by over-production of a secreted metalloproteinase enzyme following inflammation by target dendritic cells infected with the virus.

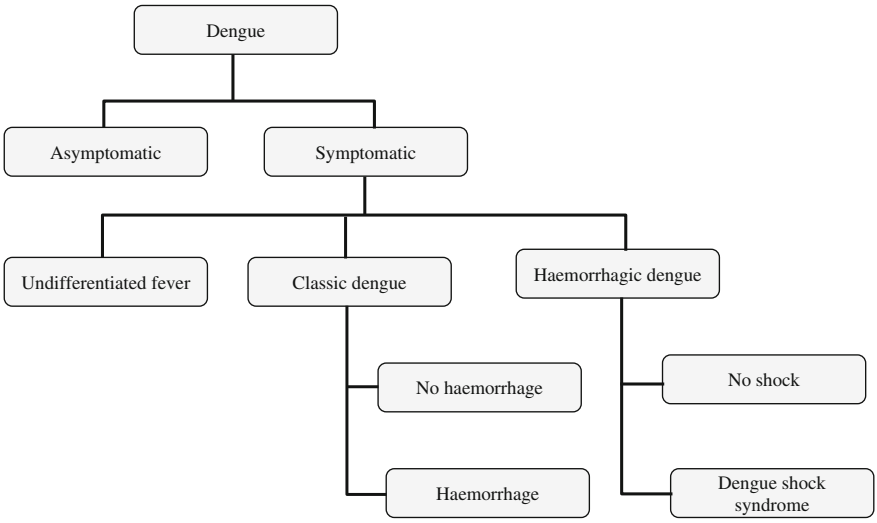

Fig. 3 Clinical presentation of the different forms of dengue

Clinical Presentation

Clinical Symptoms

Most of the time, dengue (dengue fever) is a benign disease characterised by an acute painful fever with a favourable spontaneous evolution. It can sometimes even be asymptomatic (Fig. 3). The incubation period of dengue can range from 3 to 14 days, but in general is between 4 and 7 days. Acute symptoms then appear in the form of an influenza-type syndrome: intense fever (≥39–40 °C), asthenia, prostration, severe headaches, occasionally meningeal syndrome, shivering, myalgia and arthralgia, diffuse adenopathies, macular erythematous rash, hepatomegaly.

However, a number of forms can present more severely and can even be fatal. These severe forms consist of haemorrhagic dengue (dengue haemorrhagic fever) and dengue shock syndrome. These two clinical forms of dengue generally appear after a period of remission, of variable duration. Clinical signs reveal problems with coagulation or haemostasis (bleeding in the nose or gums, purpura, haematemesis or melena).

The WHO recommends that these problems are evaluated using the tourniquet test (Table 1). However, there are also signs of circulatory failure (hypotension with narrow pulse pressure, tachycardia, mottling of the skin, etc.) or plasma leakage (pleural effusion, ascites). Rarer complications such as myocarditis, pericarditis, hepatitis, severe neurological problems (encephalopathy, neuropathy) and rhabdomyolysis can also occur.

Table 1 WHO classification of different forms of dengue

Clinical forms	Stage	Symptoms	Biology
Simple dengue		Fever associated with two or more of the following signs: headaches, myalgia, arthralgia, retro orbitar pain	Leukopenia—occasional Thrombopenia—possible No evidence of plasma leakage
Haemorrhagic dengue	I	Previous signs plus positive tourniquet test	Thrombopenia <100,000 Increased Ht ≥20 %
Haemorrhagic dengue	II	Previous signs plus spontaneous bleeding	Thrombopenia <100,000 Increased Ht ≥20 %
Dengue shock syndrome	III	Previous signs plus circulatory failure (rapid weak pulse, narrowing of pulse pressure <20 mmHg, neurological signs)	Thrombopenia <100,000 Increased Ht ≥20 %
Dengue shock syndrome	IV	Major shock with undetectable blood pressure	Thrombopenia <100,000 Increased Ht ≥20 %

Tourniquet test this test is carried out by applying a blood pressure cuff to the arm and inflating it to a pressure intermediate between systolic and diastolic pressure for 5 min. The test is considered positive if ≥10 petechiae/2.5 cm^2 appear on the forearm

Biological Anomalies

Although biological parameters may be normal in asymptomatic or moderate forms of the disease, the biological anomalies typically found comprise: thrombopenia, leukopenia with neutropenia or lymphopenia, a moderate increase in liver enzymes and LDH, hyponatraemia, etc.

Classification

The association of clinical and biological signs has enabled the WHO to establish a classification of different forms of dengue according to their severity (Table 1). This simple classification has been designed to be applicable in care structures with modest equipment which are predominant in endemic areas. However, some authors have recently pleaded for a new, more appropriate classification, modifying the thresholds for thrombopenia.

Evolution of the Disease

Typically, dengue progresses through a phase of high fever lasting around 4 days, followed by a rapid drop in body temperature (defervescence) where complications can occur (Fig. 4).

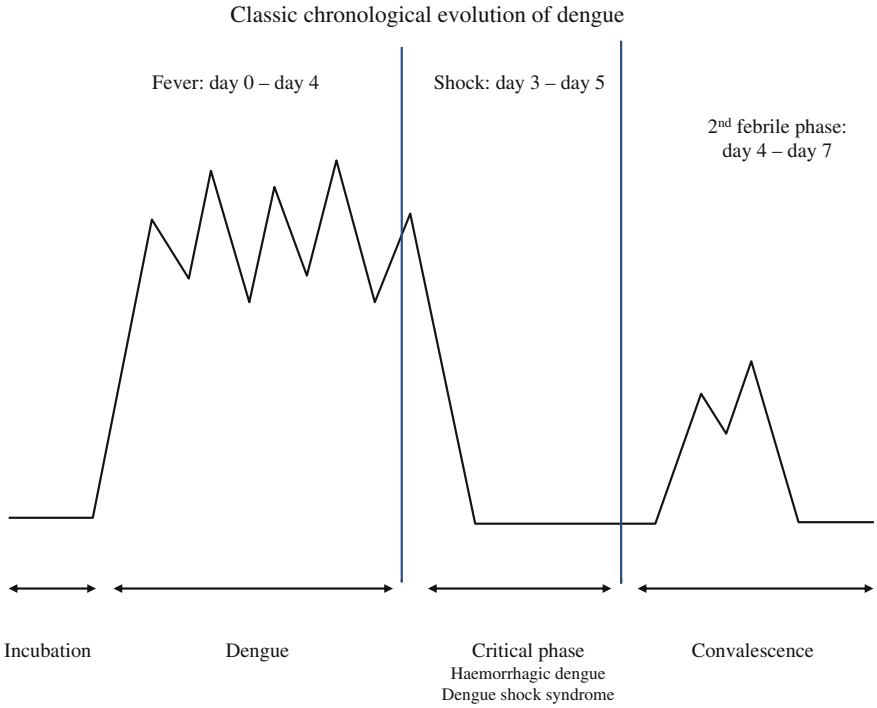

Fig. 4 Chronology of the different phases of dengue

Diagnosis

The diagnosis of dengue is confirmed by culture of the virus, PCR or serological tests. The first two tests are not generally used in clinical practice. The diagnosis is therefore based on serology. Serological tests detect IgM and IgG by ELISA, as well as the more recent detection of NS1 antigenaemia. Detection of IgM by ELISA is most often used, but requires certain precautions. This test is negative in the initial phase of the disease and should only be carried out after the 4th or 5th day following the onset of symptoms. It should be repeated in the case of an unclear clinical picture. Primary infections are characterised by an increase in IgM on the 4th or 5th day whereas IgG do not increase until after 7–10 days. In secondary dengue, the rate of increase in IgM is slower but IgG increase more rapidly than in primary infections. False positives have been described in cases of associated rheumatoid factor or infection by flavivirus.

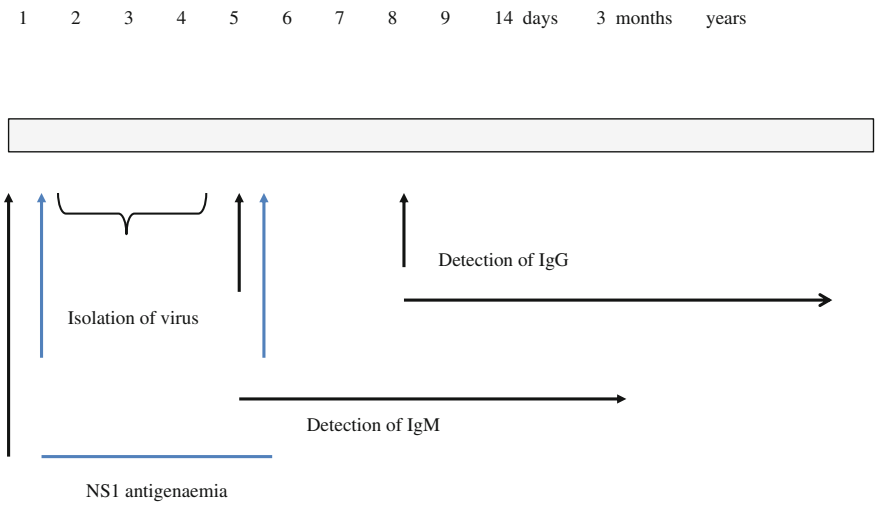

Fig. 5 Chronology of the serological diagnosis of dengue

NS1 Antigen

The *NS1* gene encodes a glycoprotein produced by all flaviviruses and involved in viral replication. This protein is produced by infected mammalian cells, but not by those of insects. It appears in the first days after the appearance of fever and then decreases to become undetectable by the 5th or 6th day. Measurement of NS1 antigenaemia by ELISA is therefore recommended for the early diagnosis of dengue (Fig. 5).

Treatment

Overall, the management of dengue consists of three main actions: (i) eradication of the mosquito (*Aedes)*; (ii) vaccination and (iii) specific medical treatment. The first two subjects are not discussed here as they are beyond the scope of the current article, but they are nevertheless important areas studied by international bodies or the subject of pharmaceutical research, particularly vaccine development. Concerning the third subject, there is currently no effective specific antiviral medical treatment against dengue. No antiviral drugs or treatments such as corticoids or carbazochrome (potentially active on capillary permeability) have been proven to be effective to date. Symptomatic treatment is therefore the basis of management.

Simple Forms of Dengue

Antipyretic treatment based on paracetamol and avoiding aspirin and non-steroidal anti-inflammatory drugs, rehydration and rest are the main approaches to treatment of dengue types I and II.

Rehydration should preferentially be carried out via the oral route or intravenously if oral rehydration is not possible or is insufficient. Vital signs (pulse, blood pressure, differential blood pressure, urine output) as well as the capillary haematocrit have been proposed by WHO for clinical monitoring of treatment. Cristalloids are recommended at a rate of 6 ml/kg/h during the first 3 h and can then be reduced to 3 ml/kg/h over the following 6–12 h in the case of improvement or conversely increased to 10 ml/kg/h for 1 h in the case of deterioration [4–6].

Complicated Forms of Dengue

Haemorrhagic dengue and dengue shock syndrome, that is to say dengue stages II, III and IV (Table 1), require hospitalisation in an ICU. Due to the severity of the disease and the development of haemodynamic and haematological complications, usually at the time of defervescence, it is important not to relax surveillance of these patients at this time.

Haemodynamic Management

The WHO has put forward a number of recommendations concerning volaemic expansion (Fig. 6). These have the advantage of feasibility and reproducibility, even if some authors have criticised them as being based on empiricism rather than any real scientific evidence. They are aimed at harmonising the haemodynamic management of patients in geographic regions where great differences in means and levels of hospital structure may exist from one area to another. The scheme proposed by WHO recommends the use of cristalloids initially and proposes dextrans in patients where there is no improvement in shock.

A study comparing three types of solutes (Ringer lactate®, dextran 70® and amidon) in dengue shock syndrome [3] has shown that Ringer® is most beneficial in the initial phase of hypovolaemic shock, but that if colloids are required amidon is slightly superior and has fewer side-effects than dextran. The other approaches to the treatment of shock do not differ from usual measures (monitoring, use of vasopressor amines or isotropics, etc.).

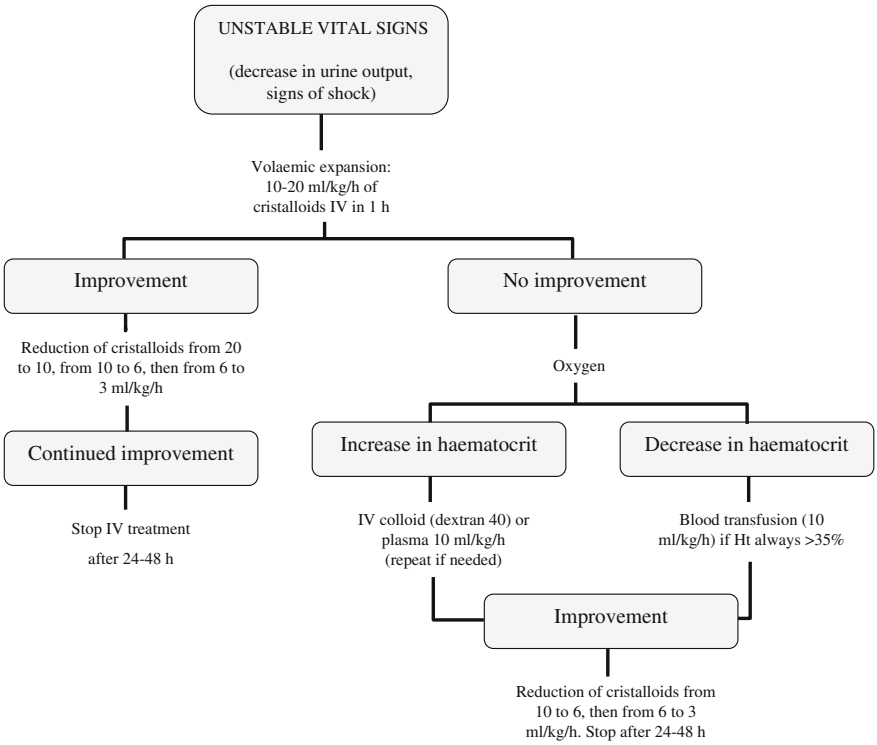

Fig. 6 Scheme for volaemic expansion proposed by WHO for patients with haemorrhagic dengue stages III and IV

Ventilation

The management of respiratory decompensation, whether due to real acute respiratory distress syndrome or to excess filling, does not differ from other causes of respiratory distress. Non-invasive ventilation has been tested effectively in children compared to oxygenation with a simple mask.

Mechanical ventilation, when necessary, will follow the protocols used in each service.

Haematological Management

Platelet transfusions are indicated according to the usual transfusion criteria, that is to say, according to the appearance of clinical signs of bleeding rather than on isolated values. The plan not to transfuse platelets unless there is thrombopenia <30 G/L in the case of bleeding and <10 G/L in the absence of bleeding may be

used as the basis for discussion. Similarly, the use of packed red blood cells, plasma and other blood products should be adapted to the state of each patient. It has been reported that anti-D immunoglobulins have been used successfully in severe forms of haemorrhagic dengue. It is not recommended to use corticoids to limit thrombopenia even though some authors have reported their efficacy in children with thrombopenia [1]. Likewise, agents which may have a favourable action on coagulation or haemostasis such as activated recombinant factor VII, desmopressin or tranexamic acid are not recommended.

Other Measures

Dengue shock syndrome be associated with a number of clinical complications such as myocarditis, encephalitis, liver failure, renal failure, disseminated intravascular coagulation or multiorgan failure, and the treatment of these complications in the ICU should be adapted on a case by case basis.

Although transmission of the virus between humans requires, in theory, a mosquito vector, cases of interhuman transmission through wounds or exposure to blood from an infected subject have been described. The usual measures for the protection of health personnel should therefore be taken.

References

1. Panpanich R, Sornchai P, Kanjanaratanakorn K (2006) Corticosteroids for treating dengue shock syndrome. Cochrane Database Syst Rev 19:3CD003488
2. Wilder-Smith A, Schwartz E (2005) Dengue in travelers. N Engl J Med 353:924–932
3. Wills BA, Nguyen MD, Ha TL et al (2005) Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med 353:877–889
4. World Health Organization (1997) Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/print.html . Accessed 13 Feb 2013
5. World Health Organization (1999) Guidelines for treatment of dengue fever/dengue haemorrhagic fever in small hospitals. http://www.searo.who.int/LinkFiles/Dengue_Guideline-dengue.pdf . Accessed 13 Feb 2013
6. World Health Organization (2006) Scientific working group report on dengue 1-5 October Geneva Switzerland. http://apps.who.int/tdr/svc/publications/tdr-research-publications/swg-report-dengue . Accessed 13 Feb 2013

Chikungunya in the Intensive Care Unit

Olivier Riou, Marlène Knezynski and Frédéric Potie

Key Points

- Chikungunya is an infectious tropical disease caused by an arbovirus. The zone of distribution may also extend to the southern Europe and the United State
- Mortality from the disease is estimated at 1/1,000
- Severe forms of the disease include meningo-encephalitis, Guillain-Barré syndrome, hepatitis and myocarditis.
- The treatment is purely symptomatic.
- A vaccine for the prevention of this disease is currently under development.

Introduction

Chikungunya is an infectious tropical disease caused by an arbovirus of the genus Alphavirus, from the family Togaviridae. It is transmitted by mosquitoes of the genus *Aedes*. The name of the disease comes from the Makonde language and

O. Riou (✉)
Service anesthésie réanimation, Centre Hospitalier Gabriel Martin, Rue Labourdonnais, 97460 Saint Paul, Reunion, France
e-mail: oriou@msn.com

M. Knezynski
Service de Gériatrie, Centre hospitalier Universitaire Nord Réunion, Allée des Topazes, 97400 Saint Denis, Reunion, France
e-mail: marleneknez@hotmail.com

F. Potie
International SOS, Suite 105, Kunsha Building 16 Xinyuanli, 100027 Chaoyang District, Beijing, China
e-mail: frederic.potie@internationalsos.com

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_8,

means “disease that bends the bones” or “bent man disease” because Chikungunya gives infected patients a characteristic bent appearance.

Epidemiology

Chikungunya virus was first identified during an epidemic in Tanzania in 1952. The classic endemic area for Chikungunya includes Africa, India and South–East Asia. In 2005–2006, all of the islands in the Indian Ocean were affected by the intense dissemination of this virus. In 2006, an epidemic developed in India which affected more than 1.4 million individuals. For the first time in 2007, an epidemic developed in a non-tropical zone, in Italy, from an index case originating from India and involving *Aedes albopictus*, which can be found in the south of France and in some areas of America, suggesting a possible expansion of the zone of infestation [2].

Transmission

Vector Transmission

Several species of mosquito can transmit Chikungunya, but to date only *Aedes aegypti* and *Aedes albopictus* have been identified as vectors of epidemics as a result of their adaptation to areas of human habitation. The female *Aedes* mosquito becomes infected by biting an infected human or animal during the phase of viraemia (which starts 5 days before and lasts until 7 days after clinical diagnosis). The mosquito is a diurnal vector with a peak of activity at the beginning and the end of the day.

Nosocomial Transmission

Nosocomial transmission is possible via blood transfusions or transplants. A hospital case has been described after accidental exposure to blood.

Materno-Foetal Transmission

This has been observed during epidemics on La Reunion Island [3] and in India. The risk is particularly high if the birth takes place during the phase of viraemia.

Physiopathology

The virus replicates in macrophages, but can be isolated from many organs: bronchial lining, glial cells, cardiac myocytes, Kupffer cells, biliary canal, kidneys. The virus also infects "adherent" cells such as endothelial cells, epithelial cells, fibroblasts, etc.

Chikungunya virus can mutate, facilitating its development in the vector cycle or favouring the attack of specific organs (neurovirulence, hepatitis, etc.).

Clinical

Asymptomatic forms of the disease may occur, estimated at 13 % of cases in seroprevalence studies carried out on La Reunion Island and in Mayotte in 2006, and at 35 % in Thai studies.

Classic Clinical Picture

Typically, after an incubation period of 2–10 days, a high fever develops, sometimes above 40 °C, which lasts for 3–5 days. Polyarthralgia develops 2–5 days after the start of fever and affects many joints (>10). This attack of the joints is symmetrical in 70 % of cases and preferentially involves the peripheral joints: wrists, ankles (50 %) and hands (60 %). Headaches, severe myalgia (80 %) and a maculopapular rash on the trunk and limbs (55 %), which is sometimes pruriginous (35 %), are also frequently found. Benign haemorrhages such as gingivorrhagia, epistaxis or purpura may also be observed, particularly in children (20 % of cases) [4].

More rare symptoms, which demonstrate the ubiquitous localisation of the virus in the body, include: digestive manifestations such as abdominal pain, vomiting, diarrhoea and hepatitis; neurosensory manifestations such as hypoacusis, epilepsy, meningitis, encephalomyeloradiculitis and neuromyopathy; ocular attacks such as chorioretinitis, conjunctivitis, iridocyclitis; interstitial nephritis; or episodes of transient hypoxemia of unknown mechanism [4].

The most frequent laboratory anomalies are lymphopenia, thrombopenia, elevation of hepatic enzymes (2–3-fold increase in transaminases) and creatine phosphokinase.

The acute phase of infection by Chikungunya virus lasts on average 5–10 days. The spontaneous evolution is usually favourable but can, in some cases, lead to prolonged asthenia and chronic relapsing joint pain (>50 % of patients at 6 months to 12 % at 5 years).

Complicated Forms

The epidemic in La Reunion was associated with a disease related mortality of 1/1,000 infected cases [3]. Two-hundred and forty-six patients were admitted to intensive care, with a mortality of 50 %. In Ahmedabad in India, overmortality was observed during the 4 months of the peak of the epidemic in 2006. These severe complications particularly involve frail patients (three-quarters of cases aged $\geq$70-years), patients with polygenetic defects and neonates. Several cases of sudden death have been described in patients without any previous history. However, the connection with Chikungunya is often unclear, even if there is proof of infection, and the aetiology of the death remains hypothetical: acute coronary syndrome, arrhythmia, shock, etc.

In the intensive care unit (ICU) the following clinical presentations may be observed: serious neurological forms, essentially progressive meningo-encephalitis with serious sequellae in half of cases with loss of autonomy, chronic coma and Guillain-Barré type polyradiculoneuritis [5] requiring respiratory assistance; necrotising hepatitis, specifically in chronic alcoholic patients, leading to discussions about a liver transplant; myocarditis and pericarditis responsible for cardiac decompensation.

However, in most patients admitted to the ICU, infection with Chikungunya virus is itself a comorbidity or decompensation factor favouring: opportunistic infections and septic shock through viral immunosuppression; acute renal failure by frequent dehydration secondary to digestive problems, fever, problems with consciousness, a state of shock and/or the use of non-steroidal anti-inflammatory drugs; decompensation of preexisting diseases: coronaropathy, heart failure, kidney failure, liver failure, diabetes, etc.

The disease in neonates infected by late materno-foetal transmission has a particularly severe symptomatology in one-half of cases. Three to seven days after the birth, encephalopathy is observed with cerebral oedema, haemodynamic problems secondary to severe sepsis, thrombocytopenia in 90 % of cases, occasional haemorrhagic complications (disseminated intravascular coagulations), extensive bullous dermatosis and problems with feeding [3].

Differential Diagnosis

Except for polyarthralgia, the symptoms are non-specific and many other arbovirus infections have similar symptoms: fever, jaundice, Rift valley fever, dengue, other Togaviruses, as do bacterial and parasitic infections such as malaria, rickettsiosis, leptospirosis, bacterial meningitis, typhoid fever, etc.

Diagnostic Tools

The viral genome can be demonstrated in the body by RT-PCR during the viraemic phase: 5 days before until 7 days after the clinical diagnosis. Immunoglobulin M antibodies (IgM) appear towards the 5th day of the illness and persist for several months. IgG then appear from the 15th day, which persist for several years, or even decades, and protect from a new Chikungunya infection.

Treatment and Prevention

There is no virucidal treatment available. There is no proof of efficacy of chloroquine in vivo. In vitro, ribavirin and alpha-interferon appear to have activity against viral replication [1]. Treatment is therefore exclusively symptomatic. Typical medical management consists of antipyretic and analgesic treatment. Corticotherapy may be necessary in patients with chronic painful joints. There is no specific management in the ICU setting and treatment consists of adapted organ support.

Prevention of this infection is both collective, depending on vector control, and individual (insect repellents, mosquito nets, etc.). Patients should be isolated in order to limit the spread of the disease. Infected humans are the main reservoirs of the disease. An experimental vaccine was developed by the US Army Institute of Research in 1980 and is in the process of being requalified in France under the aegis of INSERM.

References

1. Briolant S, Garin D, Scaramozzino N et al (2004) In vitro inhibition of Chikungunya and Semliki Forest viruses replication by antiviral compounds: synergistic effect of interferon-alpha and ribavirin combination. Antiviral Res 61:111–117
2. Charrel RN, de Lamballerie X, Raoult D (2007) Chikungunya outbreaks—the globalization of vectorborne diseases. N Engl J Med 356:769–771
3. Gérardin P, Barau G, Michault A et al (2008) Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Reunion. PLoS Med 5:e60
4. Queyriaux B, Simon F, Grandadam M et al (2008) Clinical burden of chikungunya virus infection. Lancet Infect Dis 8:2–3
5. Wielanek AC, Monredon JD, Amrani ME et al (2007) Guillain-Barré syndrome complicating a chikungunya virus infection. Neurology 69:2105–2107

Snakebite Envenoming

Jean-Pierre Bellefleur and Jean-Philippe Chippaux

Keypoints

- Ophidian envenoming represents a public health problem in tropical countries.
- Faced to a snakebite, the practitioner has to confirm the envenoming in order to use immunotherapy.
- The new generation of purified immunoglobulins are actually effective and safe.
- The reference centres where are located banks of antivenoms should be known.

Introduction

In tropical countries, especially in Africa and Asia, envenoming remains a critical public health problem due to high incidence (up to 5 million bites resulting in more than 125,000 deaths annually) and poor management [1]. In contrast, in

J.-P. Bellefleur (✉)
Service d'anesthesie et de reanimation, Hopital Nord, Assistance Publique-Hopitaux de Marseille, Chemin des Bourrely, 13915 Marseille Cedex 20, France
e-mail: bellefleur.jpm@gmail.com

J.-P. Chippaux
Institute of Research for Development (IRD—UMR 216 "Mother and child facing tropical diseases"), 08 BP 841 Cotonou, Bénin
e-mail: jean-philippe.chippaux@ird.fr

J.-P. Chippaux
Sorbonne Paris Cité, Faculté de Pharmacie, University Paris Descartes, Paris, France

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_9,

developed countries, particularly in Europe, the incidence is low (about 300 bites in France a year), as well as the case fatality rate due to lower toxicity of the venom and better management. Regarding epidemiology, accidental bites due to autochthonous vipers, are opposed to "illegitimate" bites occurring during animal manipulation, which increase with the new fashion of exotic pet. If the management of the first ones is now well codified, clinicians are generally unprepared for the diversity and severity of the latters, resulting in inflammation, necrosis and often uncontrollable coagulopathy, the evolution of which leads to multiple complications or sudden paralysis and respiratory paralysis.

Venom Composition

The snake venoms are composed primarily of proteins belonging to two functional groups whose characteristics are quite distinct regarding pharmacological, clinical and therapeutic characteristics, namely toxins and enzymes. Toxins generally have low molecular weight. They bind to cellular receptors inducing the inhibition or disruption of their working. The specific toxicity is directly proportional to the number of receptors affected, and consequently to the amount of inoculated toxin. Toxins rapidly diffuse in the organism, involving deep tissues explaining quick toxicity. Toxins generally have good immunogenicity despite their small size. On the other hand, the enzymes convert a substrate as long as it remains. As a consequence, the toxicity of enzymes is less directly related to their quantity than their persistence in the organism. They are highly immunogenic. However, the antibodies bind to the enzyme without necessarily interrupting its activity. In addition, the product obtained after enzyme digestion could be not neutralised by the antibodies.

Elapid Venoms

Elapid venom contains neurotropic low molecular weight toxins. Among them, the α-neurotoxins present in the venom of cobras and mambas, bind selectively to cholinergic receptors of the postsynaptic membrane. They quickly reach their target to block nerve impulses, causing paralysis. In mamba venoms, the dendrotoxin increases the release of acetylcholine and the fasciculin inhibits cholinesterase; both potentiate pharmacological action of acetylcholine. Finally, muscarinic toxins, also present in mamba venom, bind specifically to muscarinic receptors in the neuromuscular junction, leading to muscarinic syndrome very early during the envenoming. Phospholipases A_2, also called β-neurotoxins although they are high molecular weight enzymes, are found in the venoms of *kraits (Bungarus)*, Australian elapids and some American rattlesnakes or Old World vipers. They block the release of acetylcholine at the presynaptic plate level, which also produce paralysis.

However, their enzymatic activity can cause paralysis, particularly myolysis. Cytotoxins, which are found in large amount in the venom of spitting cobras, induce cell destruction resulting in focal necrosis.

Viper Venoms

Viper venoms lead to pathophysiological changes due to the production of pro-inflammatory cytokines, similar to those found in cases of severe trauma [2]. Venoms of vipers are inflammatory, haemorrhagic and necrotising. The processes involved in the bleeding disorders are complex, due to frequent and conflicting interactions. Two phenomena are distinct. In a first step, haemorragins cause damage to blood vessel walls resulting in localised or diffuse bleedings. Then, other venom factors disrupt the coagulation. *Echis* and some Australian elapid venoms contain a prothrombin activator. Most of other Viper venoms have thrombin-like enzymes that act like natural thrombin to hydrolyse fibrinogen, various substances active on platelets and enzymes activating fibrinolysis. According to the venom, thrombin-like enzymes induce specific compound distinct from natural fibrin resulting in a clot variable in size and stability [3]. The susceptibility of the newly formed clot to fibrinolytic enzymes, particularly to plasmin, will also be different, as well as the neutralising capacity of heparin or hirudin. Hypercoagulable phase duration varies in length according to the venom. It results in a syndrome of diffuse vascular thrombosis which may favour certain visceral complications. Strongly marked after the bite from few American vipers (e.g. *Bothrops lanceolatus*), this phenomenon has never been described after Asian or African viper bites. Following *Echis* bite, the clinical manifestations of haemorrhagic syndrome are delayed with respect to biological signs, which appear usually very early. In viper envenoming, necrosis is mainly due to the presence of proteolytic enzymes that destroy tissue organisation

Venom Toxicokinetics

Toxicokinetics of *Vipera aspis* venom has been studied in rabbits after intravenous or intramuscular injection [4]. Intravenously, the half-life is approximately 12 h. Three days after administration, it remains less than 3.5 % of the venom initial dose. The volume of distribution is greater than the plasma volume, indicating that the venom is also present in the cellular compartment. After intramuscular injection of venom, the venom absorption process lasts over 72 h maintaining high plasma concentrations of venom over a long period. Similarly, Elapid venoms spread into the deeper tissues where they are in concentration two to three times

higher than in blood. In the deeper tissues, the venom peak is reached within 1–2 h depending of the venoms. This explains the rapid onset of clinical disorders between 15 min and 1 h. Then, a phenomenon of redistribution of venom is observed from deep tissue toward the blood compartment, explaining recurrent venom antigenaemia and coagulopathy.

Clinical Symptoms

It is conventional to oppose elapid envenoming, primarily neurotoxic, and viper envenoming, dominated by necrosis and haemorrhagic syndrome. In practice, the distinction should be qualified.

Elapid Envenoming

Invasion of elapid envenoming is fast. It is immediately dominated by neurological symptoms. Venom inoculation is usually painless, although mamba and some cobra bites are deemed painful. From the first minutes, paraesthesia are described by the victim, like stinging or tingling around the bite site, linked to local anaesthesia, which quickly radiate along the limb. Anxiety clearly dominates the clinical picture associated with epigastric pain, thirst and dryness of mucous membranes, nausea, tinnitus, phosphenes, dysphonia and dysgeusia; the latter can last for several weeks. In 15–30 min, highly evocative physical signs occur. Hypotension can evolve into shock. Vomiting and drowsiness suggest the involvement of the central nervous system by the venom. Lacrimation, photophobia, salivation, sweating and diarrhoea are present in most elapid envenoming but are particularly intense after a mamba bite, which muscarinic effects are very evocative. Muscle tremors can be joined to cramps or spasms. Bilateral palpebral ptosis and gape (paralysis of the mandible in semi-open mouth position) are pathognomonic of elapid envenoming; these latter signs confirm the involvement of the central nervous system and require artificial ventilation. Muscular paralysis, without loss of consciousness precedes the death by asphyxia. The progression to death can take 2–10 h depending on the amount of injected venom and the size of the victim.

Local symptomatology is often mild. However, the pain is intense in *Dendroaspis* bites. Necrosis, usually dry and somewhat extensive, occurs in some *Naja* bites, especially *N. nigricollis*, *N. mossambica* and *N. naja*. The necrotic area involves superficial tissues, and heals slowly.

Envenoming by the elapids does not cause neurologic sequel. Besides the local necrosis, complications are iatrogenic or nosocomial.

Viper Envenoming

Venom injection is deep because of the configuration of the fangs of the viper, and very painful resulting from the penetration of the venom in the body. Most often, the pain increases, radiating to the whole limb. However, a few envenomings by *Echis ocellatus* have been reported similar to the prick of a thorn, which may mislead the diagnosis. Inflammatory syndrome is generally associated. Oedema appears within a few minutes, gradually invading the surrounding areas. It may extend to the entire half of the body within a few hours. Necrosis, often wet, oozing, rapidly extends in surface and sometimes in depth.

Haemorrhagic syndrome appears gradually. In general, due to haemorragins, local bleedings at the wound site last during several days. Epistaxis, haematuria, massive purpura, sometimes haemoptysis or gastrointestinal bleeding occurs secondarily. After a bite by *Echis*, the haemorrhagic syndrome will manifest late (sometimes after 2–3 days), by hypovolemic shock or subarachnoid haemorrhages, which frequently cause death. However, biological signs appear earlier, namely a rapid fibrinogen decrease, associated with a gradual lowering of clotting factors.

Sequels are common. They are related to necrosis which can eventually require amputation, while a thrombotic syndrome may cause visceral infarction away from the site of the bite, particularly after *Bothrops lanceolatus* bite (Martinique). Renal lesions are the most numerous. They occur between 12 h and 2 weeks after the bite, even though the clinical evolution seems favourable. The renal ischemia may be the cause of early tubular or cortical necrosis. Extracapillary proliferative glomerulonephritis, which pathogenesis is more complex, occur later.

Severity–Progression–Prognosis

Most of snake bites are not followed by severe envenoming. First, the severity of the envenoming has to be confirmed and evaluated. Numerous factors influence the severity of envenoming. The species responsible for the bite is probably the most important, but the size of the snake, amount of inoculated venom, the site of the bite and the health condition of the victim (chronic disease, such as diabetes), age or circumstances (pregnancy) will also have a significant role in the progression of the envenoming. The severity of envenoming is determined by clinical and biological criteria which allow classifying the bite into four grades (Table 1). Envenomings in Europe are mainly from European vipers (*Vipera aspis* and *V. berus*) which severity is usually grade 1 or 2 [5].

The time between the bite and the onset of symptoms vary from a few seconds to 3 h. Actually, 1 h after the patient's arrival, it is usually possible to determine whether the envenoming is obvious [1]. However, it is preferable to extend this period to 6 h for additional security.

Table 1 Clinic and biological classification of envenoming severity

Grade	Viper envenoming		Elapid syndrome	General symptoms	Hemostasis disorders
	Local syndrome local	Bleedings			
0	Mild pain fang marks	0	0	0	0
1	Intense pain, swelling not exceeding the elbow or knee	0	Ptosis	Anxiety	Biological abnormalities: platelets (G/L): 100< to <150 G/L fibrinogen (g/L): 1 to 2
2	Swelling above the elbow or knee—minimal necrosis	Moderate bleeding(bite, puncture, haematuria)	Trismus dysphagia	Vomiting, diarrhoea, hypotension, oliguria	Mild coagulopathy: platelets (G/L): 50 < 100 fibrinogen (g/L) <1 TP (%): 50 to 65
3	Swellingat or above the limb extensive necrosis	Major bleeding (epistaxis, haemoptysis, hematemesis, melena)	Respiratory distress	Acute renal failure, coma, shock	Major coagulopathy: platelets (G/L): < 50 TP (%): <50 fibrinogen (g/L) < 0, 5

Following a bite from Elapidae, a fatal outcome can occur quickly (3–8 h on average). Following viper bite, including *Echis*, evolution is slower. It is common to observe life-threatening complications by 3–6 days after the bite.

Management

Management begins before reaching the hospital by telephone advice: keep quiet, reassuring surroundings, disinfect the wound, tight bandage with crepe strip (but preserving the bloodstream), immobilise the limb in a functional position, begin analgesic treatment at levels 1 and 2, but avoiding salicylates and non-steroidal anti-inflammatory drugs. It must be stressed at this stage the importance of not harming: avoid cauterisation, amputation, debridement, suction and tight tourniquet. It is important to identify the snake by its Latin name, especially when exotic species are involved.

Initial Management

At presentation in hospital, snakebite management takes place in an emergency ward where clear protocols are available. Note the time of onset of symptoms and the delay for treatment which both impact the evolution of the envenoming and the occurrence of complications. Laboratory tests, in particular a complete haemostasis, are carried out in emergency. The plasma level of venom is not yet routinely performed.

Symptomatic treatment is urgently administered upon arrival: installing an intravenous access, filling hypertonic macromolecules, compressing the site (if accessible) in case of active bleeding, and oxygen in case of respiratory distress. The wound is cleaned; tetanus vaccination is checked and updated if necessary. Anxiolytic treatment is administered; analgesia is adapted to the pain by the use of analgesics at level 3. Anaesthesia by nerve block may be considered in the absence of major disturbance of haemostasis.

A decision algorithm is applied according to the clinical and biological grades of the envenoming (Fig. 1). Envenoming can be eliminated in bitten patient showing no symptoms and normal coagulation 6 h after the bite. The patients can be discharged from the hospital with advice to return if they develop alarming symptoms. Alternatively in case of doubt, they can be offered a 24-h hospitalisation. All symptomatic patients are hospitalised in intensive care unit to begin immunotherapy.

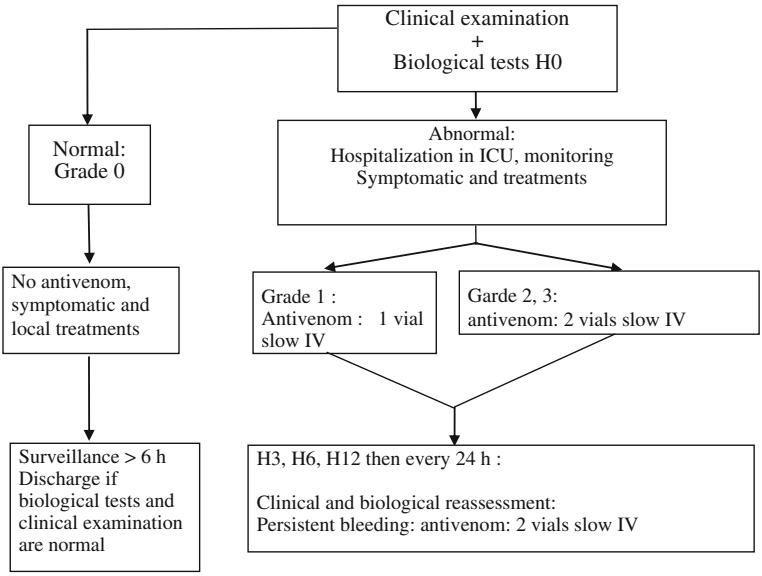

Fig. 1 Decision algorithm to snakebite management

Symptomatic Treatment

In Intensive care unit, the patient is clinically reassessed and continuous monitoring is implemented in particular hemodynamic, in the best with direct blood pressure measurements. An ECG is recorded in search of arrhythmias or depolarisation. The management of organ failure is not specific. In case of respiratory distress, oxygen therapy should begin by face mask or mechanical ventilation, afteroro-tracheal intubation and sedation. An antagonism by atropine and Prostigmin® is suggested by some authors in case of neuromuscular symptoms [6]. Its actual efficacy is controversial and probably depends on the venom characteristics. Regarding the hemodynamic management, it should be emphasized on respect of dosages of starches, the excess of which can induce renal failure or coagulation disorders. Erythrocyte transfusion is guided by the assessment of haemorrhage, clinical tolerance of anaemia and laboratory findings. The use of vasopressors is necessary in case of persistent hemodynamic failure. The treatment of coagulation disorders is primarily based on haemorrhage aetiology. Transfusion of coagulation factors, platelet concentrate and/or fibrinogen is indicated as a rescue measure in case of active or potential bleedings (e.g. invasive therapeutic procedure) associated with major disorders of haemostasis. However, the effectiveness of these transfusions is conditioned by a prior immunotherapy in order to avoid a relapse of the consumption process of coagulation factors. There is no instruction for PPSB or heparin. The treatment of renal failure is primarily the restoration of good renal perfusion. Recourse to haemodialysis is sometimes necessary.

Immunotherapy

Immunotherapy is the only aetiological treatment, using highly purified $F(ab')_2$ fragments of immunoglobulins (IgAV) (Table 2). They are efficient and very well tolerated. New generation IgAV show few adverse reactions, in only 2–11 % of patients. Severe anaphylactic schoks, the treatment of which remains the adrenaline, seem to be exceptional [7]. Premedication with antihistamines and/or corticosteroids is no longer necessary. The IgAV should be administered as early as possible but seem beneficial even after 24 h [8]. Its indications are broad: Grades 2–3 of envenoming (Fig. 1). The prescription, dosage and feedback are empirical and guided by the severity and progression of the envenoming. The clinical and biological evolution should be reassessed at H3, H6, H12 and H24. In case of persistent or recurrent bleedings, new administrations are performed (Fig. 1). At biological level, the aim of immunotherapy is not to normalise at all costs the coagulation disorders but obtain clinical significant improvement [9]. It does not seem necessary to perform more than three injections using two vials each [7]. In case of viper envenoming, immunotherapy stops bleedings in less than 2 h in 60 % of patients and 24 h in 80 % (Fig. 2). The clinical efficacy IgAV is related to a sharp drop in the plasmatic concentration of venom (venomaemia) after administration of IgAV. The venomaemia drops sharply in less than 2 h after injection of IgAV, often completely and durably [7]. In case of elapid envenoming, immunotherapy reduced the time of mechanical ventilation to 48 h while it extends up to 2 months without treatment [10]. Immunotherapy reduces the duration of ICU and hospital stays.

Local Treatment

The treatments are carried out with strict compliance to asepsis: clean the wound and bandage daily at the beginning, then every 2 days, immobilise the limb in a functional position.

The effectiveness of systematic antibiotics remains unproven; they induce an additional cost and the development of bacterial resistance [11]. Locally, envenoming may be complicated by compartment syndrome causing extensive tissue anoxia and a high risk of gangrene. The creatine-phosphokinase rates should be measured regularly. The measurement of the intracompartmental pressure is used to evaluate the risk of tissue anoxia and cost benefit of surgical treatment. Surgical debridement should be avoided as it increases the risk of superinfection and induces unacceptable disabling sequels. It remains indisputable that at gangrene stage, amputation should be performed as a rescue. In case of superinfection of the wound, antibiotic of choice is amoxicillin-clavulanic acid.

Table 2 Main available antivenoms

Manufacturer	Name	Areas	Species	Registration in France
Sanofi pasteur (France)	Viperfav ®	Europe	*Viperaaspis, viperaberus*	AMM
	Fav-afrique ®	Afria	*Bitis*, *echis*, *naja, dendroaspis*	ATU
	Bothrofav ®	Martinique	*Bothropslanceolatus*	ATU (Martinique)
Bioclon (Mexico)	Antivipmyn ®	America	*Crotalus*, *bothrops*	ATU
	Antivipmyn-tri ®		*Crotalus*, *bothrops*, *lachesis*	ATU
	Coralmyn ®		*Micrurus*	ATU
Inosan (Mexico)	Inoserp ® Pan-african	Africa	*Bitis*, *echis*, *naja, dendroaspis*	ATU

AMM autorisation de mise sur le marché; *ATU* autorisation temporaire d'utilisation

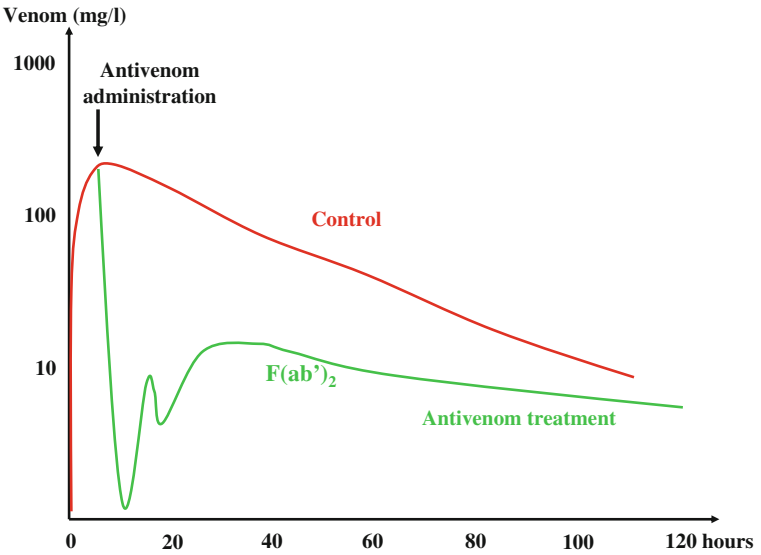

Fig. 2 Normalisation of clinical (•) and biological (x) haemorrhagic syndromes after administration of an average of 3.8 vials of IgAV in 289 patients showing Viper syndrome, according to Rivière et al. [4]

Antivenom Accessibility

The quality, availability and cost of IgAV remain a major problem for the management of envenoming. Indeed, the purification process of IgAV is very costly and can lead to industrial choices which performance is likely to be low, resulting in a significant reduction of safety. Protocols for patient management should

contain contact data with poison control centers (CAP) in order to determine and locate suitable antivenoms. Routinely and for the best, hospitals keep in stock only Viperfav ® (and Bothrofav ® in Martinique). For other antivenoms, the CAPs are in relation to banks of antivenoms (BSA). IgAV are stored in limited quantities and transported to the final destination using the civil and military means. We can mention several BSA: CAPs of Angers and Marseilles, in France (www.centre-Poison@chu-angers.fr), BSA in Basel, Switzerland (www.toxi.ch) and Munich, Germany (Mavin: www.toxinfo.org/antivenoms). It should be noted that in France there is no registration of Asian and Australian IgAV, which are not available.

Conclusion

Faced to snakebite, the practitioner should confirm the severity of the envenoming and evaluate the necessity of immunotherapy. This remarkably effective treatment is no longer a safety issue with new generation of purified fragments of immunoglobulins. However, their availability remains problematic and should be resolved by the use of reference centres where are established banks of antivenoms.

References

1. Chippaux JP (1998) Snake-bites: appraisal of the global situation. Bull World Health Org 76:515–524
2. Avila-Agüero ML, París MM, Hu S et al (2001) Systemic cytokine response in children bitten by snakes in Costa Rica. Pediatr Emerg Care 17:425–429
3. Chippaux JP (2002) Venins de serpent et envenimations. IRD, Coll Didactiques, Paris, p 288
4. Rivière G, Choumet V, Saliou B et al (1998) Absorption and elimination of viper venom after antivenom administration. J Pharmacol Exp Ther 285:490–495
5. Warrel DA (2005) Treatment of bites by adders and exotic venomous snakes. BMJ 331:1244–1247
6. Gold BS, Dart RC, Barish RA (2002) Bites of venomous snake. N Engl J Med 347:347–356
7. Chippaux JP, Massougbodji A, Stock RP et al (2007) Clinical trial of an F(ab')2 polyvalentequine antivenom for African snake bites in Benin. Am J Trop Med Hyg 77:538–546
8. Bentur Y, Zveibel F, Adler M et al (1997) Delayed administration of Vipera xanthina palaestinae antivenin. J Toxicol Clin Toxicol 35:257–261
9. Ruha AM, Curry SC, Beuhler M et al (2002) Initial postmarketing experience with crotalidae polyvalent immune Fab for treatment of rattlesnake envenoming. Ann Emerg Med 39:609–615
10. Agarwal R, Aggarwal AN, Gupta D et al (2005) Low dose of anti-snake venom is as effective as high dose in patients with severe neurotoxic snake envenoming. Emerg Med J 22:397–399
11. Jorge MT, Malaque C, Ribeiro LA et al (2004) Failure of chloramphenicol prophylaxis to reduce the frequency of abscess formation as a complication of envenoming by Bothrops snakes in Brazil: a double-blind randomized controlled trial. Trans R Soc Trop Med Hyg 98:529–534

Part IV
Respiratory System

Diffuse Interstitial Lung Disease and Pulmonary Fibrosis

Jean-Marie Forel, Carine Gomez, Sami Hraiech and Laurent Chiche

Key points

Diffuse interstitial lung disease (DILD):

- Eliminate pulmonary infection (intracellular pathogens, Pneumocystis, viruses) and cardiogenic involvement by history, clinic, thoracic TDM, peripheral microbiological specimens, echocardiography and bronchoalveolar lavage (cytology and microbiology) when possible.
- Eliminate drug- or environment-associated toxicity, carcinomatous lymphangitis, connective tissue disease and granulomatosis by the analysis of

J.-M. Forel (✉) · S. Hraiech
Réanimation des Détresses Respiratoires et des Infections Sévères, Hôpital Nord, Assistance Publique—Hôpitaux de Marseille, Chemin des Bourelly, 13015 Marseille, France
e-mail: jean-marie.forel@ap-hm.fr

S. Hraiech
e-mail: sami.hraiech@ap-hm.fr

J.-M. Forel · C. Gomez · S. Hraiech
Aix-Marseille Université, URMITE UMR CNRS 7278, Marseille, France
e-mail: carine.gomez@ap-hm.fr

C. Gomez
Pneumologie, Maladies Rares Respiratoires, Mucoviscidose, Equipe de Transplantation Pulmonaire, Hôpital Nord, Assistance Publique—Hôpitaux de Marseille, 13015 Marseille, France

L. Chiche
Médecine Interne, Hôpital de la Conception, Assistance Publique—Hôpitaux de Marseille, 13006 Marseille, France
e-mail: laurent.chiche@ap-hm.fr

L. Chiche
Centre d'Immunologie de Marseille-Luminy (CIML), Aix Marseille Université, INSERM U 1104, CNRS UMR7280, Marseille, France

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_10,

history, extrapulmonary signs, HD-thoracic TDM, BAL cytology, and immunological investigations before concluding an idiopathic cause. Multidisciplinary discussion is necessary before lung biopsy.
- Non-invasive ventilation is rarely effective, but can help in carrying out BAL. Invasive ventilation must be protective.
- Antibiotic treatment (consider anti-intracellular pathogens, Pneumocystis) is usually prescribed before microbiological results.
- Corticotherapy has poor efficacy outside connective tissue diseases, granulomatosis, eosinophilic pneumonia, histiocytosis and cryptogenic organising pneumonia.
- The prognosis is extremely poor in patients with established pulmonary fibrosis.

Introduction

Diffuse interstitial lung disease (DILD) is a heterogeneous group of lung disorders characterised histologically by diffuse inflammation and fibrosis affecting predominantly, but not exclusively, the pulmonary interstitium. Pulmonary fibrosis is a progressive feature of many lung disorders and more than 200 diseases can present in the form of DILD [1]. Several types can be distinguished: (i) idiopathic DILD [2]; (ii) DILD of known cause; and (iii) DILD associated with connective tissue disease or granulomatosis [1]. Figure 1 summarises the main types of DILD. Faced with a clinico-radiological picture of DILD compatible with pulmonary fibrosis, the main problem is to identify the aetiologies accessible to curative treatment. The therapeutic (e.g. anti-infective agents vs. corticotherapy) and prognostic (e.g. high probability of recovery from an infectious cause vs. terminal progression of idiopathic pulmonary fibrosis (IPF)) implications require rigorous diagnostic and therapeutic approaches which are usually invasive (bronchoalveolar lavage, lung biopsy).

Diagnostic Strategy

Principal Diffuse Interstitial Lung Diseases of Interest to the Intensivist

The most frequently encountered DILDs in intensive care, except for cardiogenic oedema, are: infectious DILD (pneumocystosis, intracellular bacteria, viruses, tuberculosis), IPF, non-specific interstitial lung disease (NSILD, which should lead

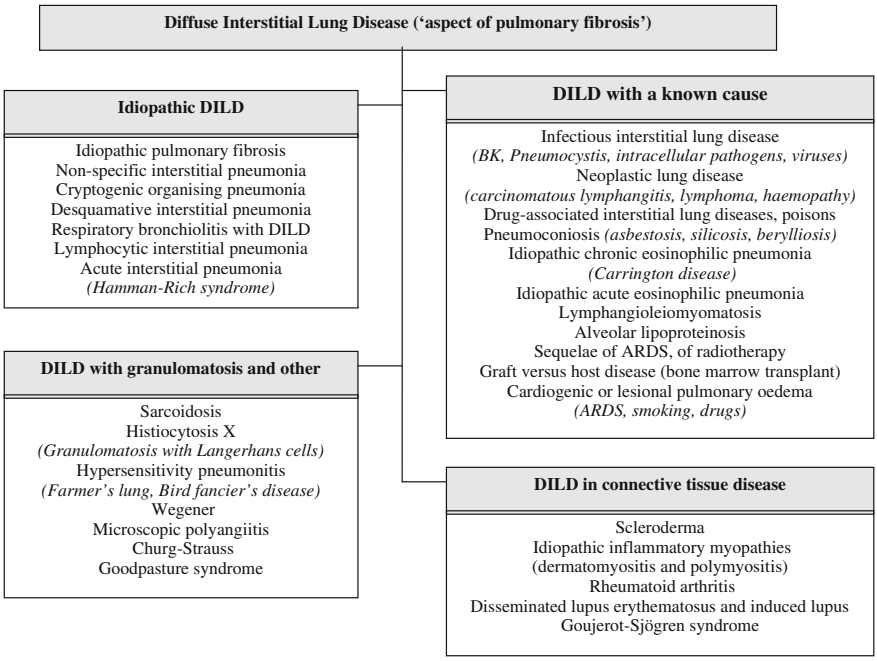

Fig. 1 Classification of diffuse interstitial lung disease (DILD) (according to the American Thoracic Society—European Respiratory Society)

to investigations for connective tissue disease), neoplastic DILD, DILD associated with connective tissue disease or granulomatosis, drug-associated and toxic DILD, and acute interstitial lung disease. Tables 1 and 2 show the main characteristics of idiopathic DILD and DILD associated with connective tissue disease. Lung disease with intra-alveolar haemorrhage is not discussed in this chapter (Goodpasture, Churg-Strauss syndrome, Wegener, microscopic polyangiitis). For the intensivist, acute respiratory failure (ARF) in relation to DILD may present as one of two clinical scenarios: (i) previously known DILD. The patient is admitted with ARF, sometimes in the context of chronic restrictive respiratory failure. An aggravating factor should be investigated (heart disease, pulmonary embolus, pneumothorax, infection, drug toxicity) before concluding that it is an exacerbation of the known lung disease. This is a diagnosis of exclusion; (ii) previously unknown DILD. The diagnostic process is focused on identifying the aetiology of DILD.

Previously Known Diffuse Interstitial Lung Disease

Figure 2 outlines the diagnostic procedure when a DILD has been identified previously. The aim of the diagnostic approach is to demonstrate a curable acute

Table 1 Characteristics of the main idiopathic diffuse interstitial lung diseases (DILD)

	Idiopathic pulmonary fibrosis	Nonspecific interstitial pneumonia	Acute interstitial pneumonia	Desquamative interstitial pneumonia	Cryptogenic organising pneumonia
Clinical	Age > 50 years (65 years) Smoking + Insidious onset >3 months Few general signs Digital clubbing Crackles/rales "velcro" Absence of other causes	Age: 45–50 years Less insidious onset General signs (AEG) Inspiratory squeaks Look for associated connective tissue disease ++	Age: 50 years Acute onset General signs Pseudo-influenza syndrome Picture of ARDS	Age: 50 years Smoking +	Age: 55 years Subacute onset General signs and pseudo-influenza syndrome
Frequency in idiopathic DILD	55 %	25 %	<1 %	15 %	3 %
Relative frequency in idiopathic DILD in intensive care	+++	+++	++ (Picture of ARDS, Hamman-Rich syndrome)	+	+
High-definition TDM	Bi-basal and sub-pleural reticular opacities Sub-pleural pseudo-cysts (honeycomb) Traction bronchiectasis	Bi-basal and sub-pleural 'frosted glass' opacities Reticular opacities Rare sub-pleural pseudo-cysts (honeycomb)	Alveolar condensations Reticular opacities Antero-superior parenchymal distortion Honeycomb (aspect of ARDS)	Bi-basal and sub-pleural 'frosted glass' opacities Basal reticular opacities Centrolobular emphysema of the apexes	Parenchymal condensations with sub-pleural, peribronchial air bronchogram 'Frosted glass' opacities Migratory opacities

(continued)

Table 1 (continued)

	Idiopathic pulmonary fibrosis	Nonspecific interstitial pneumonia	Acute interstitialpneumonia	Desquamative interstitial pneumonia	Cryptogenic organising pneumonia
BAL	Hypercellularity (neutrophils)	Hypercellularity (lymphocytes > 20 %) Alveolitis "mottled"	Hypercellularity (neutrophils ± lympho.) Siderophages Atypical pneumocytes	Moderate hypercellularity Brown pigmented macrophages	Hypercellularity (lymphocytes > 20 %) Alveolitis "mottled"
Treatment (except for transplantation)	Discuss corticosteroids ± an immunomodulator ± N-acetylcysteine, Pirfenidone	Corticoid ± azathioprine or cyclophosphamide	Corticoid	Corticoid Stop smoking	Corticoid
Mortality	90 % at 10 years (median survival = 3 years)	30 % at 10 years	>50 % at 3 months	30 % at 10 years	Rare

Table 2 Characteristics of the main diffuse interstitial lung diseases (DILD) associated with connective tissue disease

	Scleroderma	Rheumatoid arthritis	Idiopathic inflammatory myopathies (dermatomyositis or polymyositis)	Goujerot-Sjögren syndrome	Disseminated lupus erythematosus (particularly if induced lupus)
Associated extra-pulmonary attacks	Raynaud syndrome Cutaneous sclerosis Telangiectasis Renal attack Digestive attack Cardiac attack	Deforming arthritis Rheumatoid nodules	Raised CPK Purple rash on eyelids Myalgia Picture of "myopathy" Myocardiopathy Polyarthritis Problems swallowing Hyperkeratosis of hands	Dry syndrome (Xerostomia, Xerophthalmia) Arthralgia	Erythema, Raynaud, Arthritis, Nephrotic syndrome, Pericarditis, Endocarditis, Haemolytic anaemia, Leuco-thrombopenia Dry syndrome Convulsions, Psychosis Livedo
Associated pulmonary attacks	Nonspecific interstitial pneumonia (NSIP) PAH Mediastinal adenopathies	NSIP Pleurisy Bronchial dilation	NSIP (precedes extrapulmonary signs) Cryptogenic organising pneumonia Inhalation pneumonia	Chronic cough Lymphocytic ILD Pulmonary lymphoma	Pleurisy PAH (APLS) Intra-alveolar haemorrhage Lupic pneumonia Shrinking lung syndrome
Frequency of DILD in connective tissue disease	50–70 % (especially if anti-SCL70 Ab)	20 % (particularly in males)	10–20 % (especially if anti-Jo-1 Ab)	10–20 %	<10 %
Paraclinical	Anti-SCL70 Ab Anti-centromere Ab	Rheumatoid factor Anti-CCP Ab	Anti-Jo-1 Ab (anti-synthetase syndrome) Raised CPK (polymyositis)	Anti SSA(Ro) Ab	Complement consumption Anti-native DNA Ab Anti-Sm Ab Anti-histone Ab in induced lupus
BAL	Nonspecific	Hypercellularity (neutrophils)	Nonspecific	Hypercellularity (lymphocytes ++)	Frequent intra-alveolar haemorrhage (siderophages > 30 %)

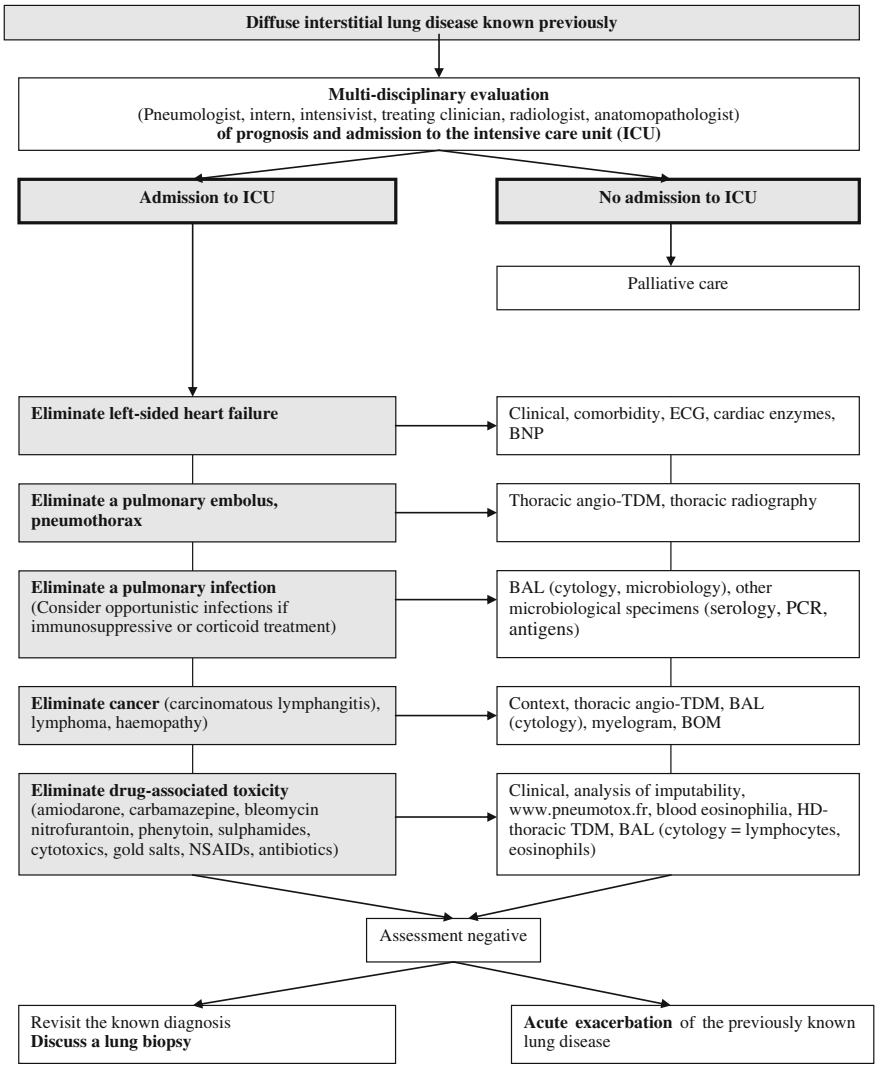

Fig. 2 Management of acute respiratory failure when diffuse interstitial lung disease (DILD) has been identified previously

disease complicating the DILD. The initial approach consists of looking for a cardiac aetiology by measuring Brain Natriuretic Peptide (BNP), troponin Ic, carrying out electrocardiography (ECG), cardiac echography, and even right-sided catheterisation to determine left and/or right haemodynamic participation. Angio-TDM may reveal a pneumothorax or pulmonary embolus (particularly if pulmonary arterial hypertension (PAH), vasculitis or anti-phospholipid antibodies (Ab) are present). Bronchopulmonary infection should also be eliminated (clinical, hyper-leukocytosis, inflammatory syndrome, raised C-reactive protein, procalcitonin),

particularly as the immunosuppressive and corticoid treatment received by these patients increases the risk of infection. Bronchial specimens, BAL and protected distal sampling should be used to look for community, nosocomial, usual and opportunistic pathogens. Special staining techniques and culture, serology, antigen detection, PCR and immunofluorescence are carried out to look for *Legionella*, atypical intracellular bacteria (*Mycoplasma*, *Rickettsia*, *Chlamydia*), viruses (adeno-, rhino-, herpes-, influenza-, cytomegalovirus), *Pneumocystis*, *Aspergillus*, *Mycobacterium tuberculosis* or atypical mycobacteria. The treatments received by the patient should also be reviewed systematically, particularly as some treatments administered during DILD may cause pulmonary toxicity (methotrexate, cyclophosphamide, antibiotics, etc.). Sometimes it is not possible to identify the cause of respiratory decompensation.

The possible causes of respiratory decompensation should be investigated thoroughly before concluding that it due to an exacerbation of DILD that could correspond to terminal progression of pulmonary fibrosis. In a patient receiving spontaneous ventilation, pulmonary specimens should be obtained by an experienced team weighing up the benefit/risk ratio. Non-invasive ventilation (NIV) may be useful to support bronchial fibroscopy with BAL. Finally, when investigations are negative, a lung biopsy should be discussed with an experienced centre and the previous pneumological diagnosis questioned. A lung biopsy will modify the therapeutic management in more than one-half of cases.

Previously Unknown Diffuse Interstitial Lung Disease

The patient is admitted with ARF without any previously identified lung disease. As explained above, investigations should be performed to look for a decompensating factor (heart failure, pulmonary embolus, pneumothorax). The diagnostic strategy is focused on looking for the aetiology of the "de novo" lung disease (Fig. 3).

Anamnesis (importance of questioning the proxies) should clarify how the disease became established, possible prodromes, medical history (in particular cardiac, renal, pulmonary, endocrine, neurological, osteo-articular, dermatological), previous lung infection, acute respiratory distress syndrome (ARDS) and more generally, invasive ventilation, cancer, recent and previous treatments (radiotherapy, methotrexate, amiodarone, cytotoxics, gold salts, carbamazepine, phenytoin, nitrofurantoin, antibiotics, NSAIDs), environmental and professional risk factors (carbon, silica, beryllium, asbestos, tobacco, cocaine, wood industry, pesticides, agricultural environment, contact with birds). Data from previous thoracic imaging are valuable. An analysis of clinical signs system by system permits the investigation of pulmonary symptoms (pleurisy, adenopathy, crepitations, squeaking) and extra-pulmonary signs (adenopathy, articular, cutaneous, renal, neurological and gastrointestinal attacks) that are evocative of connective tissue disease, vasculitis or granulomatosis.

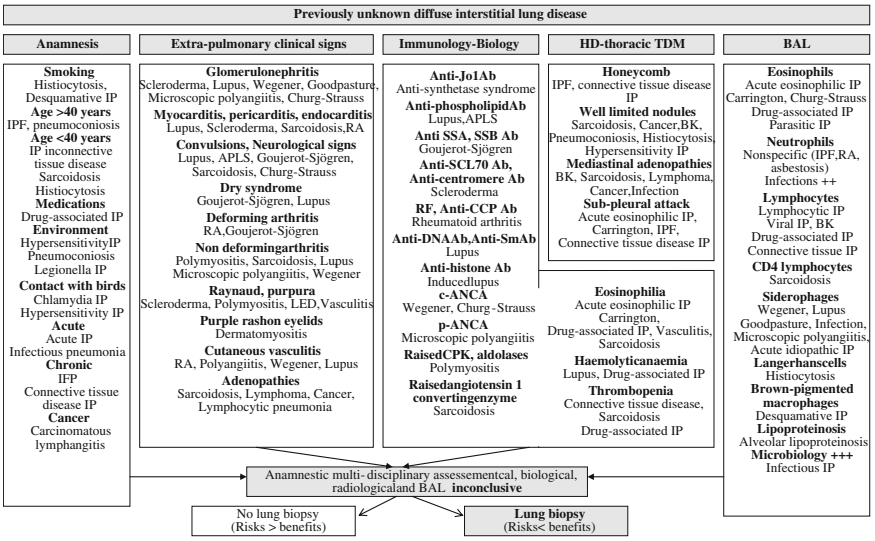

Fig. 3 Main diagnostic orientations as a function of clinical, radiological, biological and BAL results in a patient with previously unknown diffuse interstitial lung disease (DILD)

Biological investigations are orientated by these anamnestic and clinical data. It is useful to measure: creatinine clearance, proteinuria, haematuria, full blood count (eosinophils), CPK, aldolases, serum precipitins, rheumatoid factor, anti-nuclear antibodies (Ab), anti-native DNA Ab, anti-neutrophil cytoplasmic Ab, cryoglobulinaemia, thyroid assessment, angiotensin-converting enzyme. Other auto-antibodies may be requested depending on the disease suspected (cf. Table 2, Fig. 3).

Thoracic TDM is useful because may reveal features that are evocative of certain diseases (IPF, histiocytosis, lymphangioleiomyomatosis) and may sometimes be enough to make the diagnosis (Table 1). It can also be used to determine the best site for BAL (and lung biopsy if necessary).

Bronchial fibroscopy with BAL is essential when looking for an infectious cause. Special staining and culture techniques, serology, antigen detection, PCR and immunofluorescence are used to look for *Legionella*, intracellular bacteria (*Mycoplasma*, *Rickettsia*, *Chlamydia*), viruses (adeno-, rhino-, herpes-, influenza-, cytomegalovirus), *Pneumocystis*, *Aspergillus*, *Mycobacterium tuberculosis* or atypical mycobacteria. BAL cytology can contribute to the diagnosis (presence of neoplastic cells for carcinomatous lymphangitis, siderophages for associated intraalveolar haemorrhage, eosinophils for eosinophilic pneumonia, Churg-Strauss syndrome, CD4 lymphocytosis for sarcoidosis, Langerhans cells for histiocytosis, alveolar lipoproteinosis). Sometimes clinical data (adenopathy, mucocutaneous lesions, dry syndrome, muscular or gastrointestinal attack) will direct the histological diagnosis via biopsy of lymph nodes, skin, muscles, digestive tissue or salivary glands (cf. chapter "Systemic diseases"). Lung cancer or carcinomatous lymphangitis are more rarely the cause of respiratory decompensation. A positive

diagnosis is often obtained by bronchial fibroscopy, BAL cytology, high definition (HD)-angio-TDM and, sometimes, lung biopsy). If these investigations are negative, in particular BAL, a lung biopsy should be discussed with a multidisciplinary team and an experienced centre. In 15–25 % of cases, transbronchial biopsies are associated with pneumothorax and haemorrhagic complications in mechanically ventilated patients. They contribute to the diagnosis in only 50 % of cases, but remain useful for the detection of granulomatosis, sarcoidosis, eosinophilic pneumonia or neoplasia. Surgical lung biopsy (open thorax or thoracoscopy) contributes to the diagnosis in 65–100 % of cases and leads to a modification of treatment in 65–85 % of cases. Pneumothorax and pleuropulmonary fistula are the most frequent complications (10–40 % of cases). Lung biopsy may be guided by data from HD-thoracic TDM.

Therapeutic Management

Ethical Problems

Two types of case should be distinguished on admission to the ICU: (i) the DILD is inaugural without any previously identified lung disease (e.g. DILD in connective tissue disease, infectious DILD, drug-associated, idiopathic acute eosinophilic pneumonia, acute interstitial lung disease); or (ii) the DILD has been identified previously, but without severe chronic respiratory failure (CRF) and with a relatively favourable prognosis (e.g. DILD in connective tissue disease, granulomatosis, PINS, respiratory bronchiolitis with DILD), or the DILD has been identified previously with severe CRF with a poor short- or medium-term prognosis (all cases of terminal stage pulmonary fibrosis). In the case of CRF with IPF, median survival from IPF is 3 years after diagnosis and 10-year mortality is approximately 100 % [4, 5].

In the first case, admission to the ICU does not pose an ethical problem. In the second case, multidisciplinary discussions (pneumologist, treating clinician, intern, intensivist) on the possibilities of recovery should take place because there are no specific treatments that can significantly increase survival and mortality in the ICU is >85 % [5]. The precise therapeutic objectives (admission to ICU, intubation, tracheotomy, catecholamines, extrarenal dialysis) should be clearly discussed with the patient or his/her next of kin. These decisions are recorded in the medical file. If it is decided not to admit the patient to the ICU, palliative care should be proposed. In the context of an emergency admission due to vital distress, if these ethical problems cannot be approach “cold”, the prognostic factors and wishes of the patient should be discussed quickly (confident, family) so that active treatments can be limited and/or discontinued [4, 5]. However, in the case of ARF with a reversible cause during postoperative follow-up in a patient with pulmonary fibrosis, the prognosis is generally more favourable (40–95 % short-term survival) [4].

Mechanical Ventilation

NIV is associated with a high rate of failure (>80 %). It may be proposed but its efficacy should be assessed within a few hours (clinical, blood gases). More than 85 % of patients require invasive ventilation. A strategy of protective ventilation comparable to that in ARDS with acceptable tolerance of hypercapnia is recommended (plateau pressure $\leq$ 30 cm H_2O, running volume of 6 mL/kg predicted weight). The mortality of mechanically ventilated patients with IPF is around 90 % [4–7].

Haemodynamics and Pulmonary Arterial Hypertension

Evaluation of the cardiogenic component is essential during ARF in DILD. Investigations for PAH are carried out by right-sided catheterisation or by ECG. Inhaled nitric oxide and other pulmonary vasodilatory treatments can then be discussed (epoprostenol, bosentan, sildenafil). However, in the case of ARF in pulmonary fibrosis, no study has confirmed the benefit of these treatments [3, 5, 6]. Anticoagulant treatment (or its continuation) is indicated particularly in the presence of PAH, pro-coagulant connective tissue disease and, for some medical teams, in all fibroses [3, 6]. However, the value of starting anticoagulant treatment should be discussed in line with the benefit/risk to the patient.

Anti-Infective Treatments

Faced with the possibility of infectious pneumonia complicating pulmonary fibrosis or responsible for DILD, broad-spectrum antibiotics covering intracellular and opportunistic pathogens are often started after taking microbiological specimens (BAL). Investigations for *Pneumocystis* should be carried out systematically and the disease treated. Treatment should be reassessed systematically as soon as the microbiological results are available and as a function of the evolution of the patient after 48–72 h.

Corticoid and Immunosuppressive Treatment

When DILD has been diagnosed previously (e.g. IPF, fibrosis associated with connective tissue disease, granulomatosis), the patient is often already receiving treatment with corticoids. After elimination of a infectious cause, boluses of corticoids (poorly codified in the literature, 1–15 mg/kg for 1–3 days) are frequently prescribed, particularly because withdrawal of corticotherapy is sometimes

associated with exacerbation. Some teams also add cyclophosphamide. However, these treatments have not yet been validated when the patient is hospitalised in the ICU. In the case of IPF, a recent "international evidence-based guideline" was published not recommending corticotherapy, colchicine, cyclosporine A and corticoid + immunomodulator combinations: interferon-γ, bosentan and etanercept [6]. For some patients with IPF, the combination acetylcysteine + azathioprine + prednisone, acetylcysteine alone and prifenidone are recommended [6]. The prognostic impact in the ICU is often modest and a significant benefit in terms of survival has not been demonstrated when fibrosis is established [3, 4, 6]. DILD associated with pneumocystosis is treated with corticotherapy (1 mg/kg) in association with anti-*Pneumocystis* treatment. Eosinophilic pneumonia, cryptogenic organising pneumonia, DILD in connective tissue disease and systemic granulomatosis, and histiocytosis usually respond favourably to corticotherapy.

Lung Transplantation and Extracorporeal Respiratory Assistance

Lung transplantation concerns patients with previously diagnosed lung disease and placed on a waiting list. A multidisciplinary discussion (pneumologist, intern, intensivist, thoracic surgeon, anaesthetist) is necessary in order to rule out lung transplantation, which usually takes place in the context of a national priority termed "a lung super emergency" whose prognosis is poor. Sometimes, lung transplantation may be discussed after ARF when withdrawal of mechanical ventilation is impossible. Extracorporeal respiratory assistance is an exceptional therapeutic option which should only be used in patients waiting for a lung transplant ("bridge to lung transplantation") or in those with curable fibrosing DILD while waiting for the effects of specific treatment (e.g. infectious DILD with severe ARDS, idiopathic acute eosinophilic pneumonia).

References

1. Talmadge KE (2008) Interstitial lung diseases. In: Fauci AS, Braunwald E, Kasper DL et al (eds) Harrison's principles of internal medicine, 17th edn. McGraw Hill, New York
2. Cottin V, Thivolet-Béjui F, Cordier J-F (2006) Pneumopathies interstitielles diffuses idiopathiques. EMC (Elsevier SAS, Paris) Pneumologie 6-039-K-70
3. Afshar K, Sharma OP (2008) Interstitial lung disease: trials and tribulations. Curr Opin Pulm Med 14:427–433
4. Mallick S (2008) Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit. Respir Med 102:1355–1359
5. Fumeaux T, Rothmeier C, Jolliet P (2003) Les fibroses pulmonaires en réanimation. Réanimation 12:37–45

6. Raghu G, Collard HR, Egan JJ et al (2011) ATS/ERS/JRS/ALAT committee on idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183:788–824
7. Güngör G, Tatar D, Saltürk C et al (2012) Why do patients with interstitial lung diseases fail in the ICU?: A two-center cohort study. Respir Care Aug 16 [Epub ahead of print]

Part V
Nervous System

Amyotrophic Lateral Sclerosis

Stéphane Yannis Donati, Didier Demory and Jean-Michel Arnal

Key Points

- Patient with ALS are at risk of ICU admission mainly because of respiratory failure
- Diagnosis is mainly clinical together with electromyographic study
- A comprehensive management combine ventilation support, secretion management and nutritional support.

Introduction

Amyotrophic Lateral Sclerosis (ALS), also known as motor neurone disease or Lou Gehrig's disease, is a progressive degeneration of voluntary motor neurons of the cortex, brain stem and spinal cord. ALS is the most common motor neuron disease. The French neurologist Jean-Martin Charcot (1825–1893) first described the disease in 1865. In France, the prevalence is currently 5 to 7/100,000 people and the incidence is 1 to 2/100,000 people/year. There has been a 50 % increase in the incidence worldwide in the last 50 years. In France there is a multidisciplinary, coordinated and standardized approach to care for ALS patients and 18 regional ALS expert centers have been created since 2004. The average age of patients is 55 years, and the disease affects men more often than women (1.5 men for 1 woman), however this trend appears to decrease progressively, especially for patients over 70 years old. Five to ten percent of cases are hereditary, with autosomal dominant transmission and the disease appears about 10 years earlier in

S. Y. Donati · D. Demory · J.-M. Arnal (✉)
Service de Réanimation Polyvalente, Hôpital Sainte-Musse, 54, Rue Henri Sainte-Claire-Deville, 83000 Toulon, France
e-mail: jean-michel@arnal.org

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_11,

familial cases as opposed to non-familial cases. Recent data on the physiopathology of ALS have highlighted the mutation of a gene that codes for superoxide dismutase copper/zinc or SOD1, a key enzyme in oxidative metabolism. The mutated SOD1 is responsible for the appearance of abnormal physiopathological activity that is toxic to peripheral and central motor neurons.

Multiple hypotheses, such problems metabolizing calcium or apoptosis, have been proposed to explain the mechanisms that affect the motor neurons. Multiple risk factors have been highlighted, however indisputable proof has not been established for each of the following risk factors: living in a rural environment, intense daily activity, frequent trauma, chronic exposure to lead or other heavy metals, work in the plastic industry, chronic tobacco use, chronic alcoholism, frequent electric shocks, and close contact with domestic animals (especially dogs). It was found that some chemical weapons similar to pesticides have been cited as risk factors for United-States veterans returning from the first golf war in the 1990s. In general, a high prevalence has been observed amongst US army veterans regardless of the operating environment, possibly because of the risk factors previously listed. Environmental and genetic risk factors have been evoked since the description of a particularly high incidence of ALS in two regions in the world (the Kii peninsula in Japan and the American island of Guam in the Pacific). In these regions the ALS is most often associated with patients suffering from other degenerative diseases (Parkinson's disease, Alzheimer's disease).

Initial Signs and Symptoms in Intensive Care

Patients with ALS can be admitted to intensive care units (ICU) for different reasons: reasons independent of a known ALS, complications from a known ALS (especially respiratory complications), acute respiratory distress or difficult weaning from ventilation which leads to an ALS diagnosis. If the patient must be admitted into ICU for a reason independent of ALS, the evolutionary stage must be taken into consideration for ethical reasons and in order to help decide on the level of therapeutic engagement. If invasive ventilation is required, it must be known that there is a risk that weaning from ventilation may be difficult or impossible without use of a non-invasive ventilation after wards or a tracheotomy may be necessary.

In some cases an acute respiratory distress often complicates the evolution of an ALS and can lead to admission into ICU. This risk is unfortunately often unknown by the patient and the patient's friends and family. Causes of acute respiratory distress are; food inhalation because of swallowing disorder, the silent progression of inhalation pneumonia caused by repeated inhalations of salivary secretions, an acute decompensation provoked by a determined etiological factor or the terminal evolution of a respiratory failure that has become chronic. Some rare forms of ALS that initially affect respiratory muscles or bulbar forms could be the origin of an acute respiratory distress that requires admission into ICU.

If the disease has been unknown or neglected beforehand it may be detected and diagnosed because of emergency hospitalization. The medical history collected primarily from questioning the close friends and family and the patient's general practitioner can sometimes evoke the diagnosis of a neuromuscular pathology (physical asthenia, weakness when walking, frequent cramps, signs of a bulbar onset) and sometimes of a chronic alveolar hypoventilation (progressive aggravation of dyspnea, trouble sleeping, daytime sleepiness, morning headaches…). The clinical neurological exam, which is difficult to conduct on a patient in ICU, may lead to this diagnosis. In other cases the diagnosis is made when there are difficulties during the weaning from mechanical ventilation.

Clinical Signs

The onset is often insidious and progressive with misleading symptoms that can lead to diagnostic errors [1]. The average delay between the first appearance of signs and diagnosis is 12 months. However some signs found through questioning the patient (or of friends and family if the patient is in the ICU) can immediately evoke the diagnosis: motor deficit of one or multiple limbs, muscular fasciculation (twitching), difficulties walking, stiffness, cramps, repeated sprains. In most cases, ALS first affects upper limbs asymmetrically and begins distally and progresses proximally. Onset beginning with inferior limbs is less frequent. Bulbar onset generally occurs later but early onset can occur (and even start the disease in 20 to 35 % of cases) in some forms that particularly affect women over 55 years old. In these cases there are problems with phonation then deglutition (swallowing).

The clinical exam will try to detect affected peripheral motor neurons at the spinal stage that will be observed through weakness and a motor deficiency in limbs, an amyotrophy (early signs that can precede motor deficiency), fasciculation (for amyotrophic muscles but also for muscles that appear to be healthy) and hypertonia. During the bulbar stage, when the lower motor neurons are affected there can be problems with deglutition, dysphonia, dysarthria, lingual amyotrophy with fasciculations, paralysis of the soft palate, and salivary stasis. The examination demonstrates the relationship between the signs and the affected upper motor neuron, which are unique to this disease. There is presence of tendon reflexes that are maintained or exaggerated in an amyotrophic area, spastic hypertonia and pseudobulbar signs (spastic laughing or crying, exaggeration of nausea and masseter reflexes, frequent yawning, chin clonus, automatic-voluntary dissociation of the soft palate). When the upper motor neuron is affected in the case of ALS there are unique characteristics, for example in half of all cases Babinski's sign and Hoffmann's sign are not present and abdominal cutaneous reflexes are often maintained. The absence of sensitivity disorders, oculomotor damage, sphincter disorders, dysautonomia and cognitive problems are signs that can lead to an ALS diagnosis. In ICUs other clinical signs can evoke a neuromuscular pathology: limitation of coughing, problems with deglutition during the deflation of the balloon on the intubation tube

during a ventilation weaning test or when first trying oral feeding, difficulties or impossibility to wean from mechanic ventilation, a short expiratory time constant (respiratory system compliance multiplied by the airway resistance, which is measured by certain ventilators). All of these signs should cause the caregiver to consider non-invasive ventilation (NIV) as transition from invasive ventilation or a tracheotomy, which is often permanent.

Para-clinical Exams

Electrodiagnostic Studies

While ALS is primarily a clinical diagnosis, electromyography and nerve conduction studies are a standard component in the evaluation of the disease. Electrodiagnostic studies are most helpful when clinical evidence supporting the diagnosis of ALS is limited. Electrodiagnostic studies should be performed by an experienced neurologist because they are technically difficult to perform, complex to interpret and uncomfortable for an ICU patient.

Electromyography measures muscle activity at rest and during contraction by direct insertion of an electrode in the muscle. It combines features of acute denervation (fibrillation and positive sharp waves), chronic denervation and reinnervation (large amplitude, long duration, complex motor unit action potentials). The electromyographic abnormalities noted in muscles of patients with ALS are not pathognomonic for the disease but may be a sign of ALSwhen similar abnormalities are observed in many muscles of proximal and distal limbs.

Sensory and motor nerve conduction studies are most often normal though compound motor action potential amplitudes may be reduced in severely atrophic and denervated muscles. Motor conduction block should be absent which would rule out the diagnosis of multifocal motor neuropathy. Repetitive nerve stimulation is usually normal which rules out the differential diagnosis of myasthenia gravis and Lambert-Eaton myasthenic syndrome but it may be abnormal in cases of ongoing denervation and reinnervation, leading to diagnostic confusion.

Single fiber electromyography is used to evaluate neuromuscular junction function and fiber density. Transcranial magnetic stimulation remains an experimental technique that assesses the integrity of the upper motor pathway. It can be helpful to rule out the diagnosis of cervical radiculomyelopathy.

Neuroimaging

Magnetic resonance imaging (MRI) should be performed in all segments rostral to the clinical findings, including the brain, cervical spine, and thoracic spine (when legs are affected) in order to rule out differential diagnoses. Conventional MRI is

usually normal in ALS, although increased signal in the corticospinal tracts on T2-weighted and FLAIR images and hypointensity of the motor cortex on T2-weighted images has been reported.

Laboratory Testing

Cerebrospinal fluid examination is normal in ALS. However, it should be performed if there is a clinical suspicion for Lyme disease, HIV infection, chronic inflammatory demyelinating polyneuropathy, or systemic malignancy.

A moderate increase in creatinine kinase may be observed as a result of denervation.

Muscle biopsy is not a routine part of the diagnostic evaluation but may be performed if myopathy is suspected.

Genetic testing is not a routine part of the diagnosis, unless a familial ALS is suspected.

Neuromuscular ultrasound may detect fasciculation, although its true utility in the diagnosis of ALS is questioned.

Differential Diagnosis

Cerebral Damage

Focalized neurological deficits, alteration of consciousness and cranial nerve damage are arguments in favor of a cerebral pathology diagnosis. The diagnosis can be made with help of cerebral imagery (CT scan or MRI), which can identify ischemic lesions, cerebral hemorrhages or central pontine myelinolysis.

Spinal Cord Damage

When faced with a generalized hypotonia, it is difficult to differentiate between spinal cord damage and ALS. The presence of a level of sensitivity, of Babinski's sign, of loss of anal reflex and control of sphincters, or of a hypotonia that is more prominent in the upper limbs rather than lower limbs, can help orient the diagnosis towards spinal cord damage [2]. An MRI of the spinal cord can be used for confirmation.

Neuromuscular Diseases

Damage to the cells of the anterior horn, the neuromuscular junction and muscles leads to motor deficiencies only whereas peripheral nervous system damage associates motor and sensitivity deficiencies. Fasciculation should evoke an ALS or a poliomyelitis due to West Nile virus. Paresthesia, sensitivity deficiencies and symmetric distal motor deficiencies should evoke peripheral nervous system damage, specifically critical illness polyneuropathy. A dysautonomia evokes Guillian-Barre syndrome. Ptosis and difficulty to close eyes suggests myasthenia or a prolonged curarisation. Definitive diagnosis should be done with electroneuromyography (ENMG) (electrodiagnostic testing) with nerve conduction study and muscular biopsy is sometimes necessary.

The two clinical entities most often found in ICU patients are critical illness polyneuropathy and myopathy. Critical illness polyneuropathy arises after sepsis, a burn, or a trauma complicated with a multivisceral failure and leads to a generalized sensorimotor deficiency that prolongs the length of time for ventilation weaning. Motor deficiencies can be partial or complete with a reduction or complete loss of reflexes. Cranial nerves are generally preserved. Sensitivity deficiencies are inconstant. Positive diagnosis is done with ENMG.

Critical illness myopathy is associated with the use of large doses of corticoids and neuromuscular blockers. Patients present a diffuse and symmetric weakness with reduction of reflexes and without sensitivity deficiencies. Facial muscles are often affected. The positive diagnosis is done with ENMG and muscular biopsy, which should only be proposed if other forms of myopathies are suspected [3].

Treatment of Severe Forms

The goal of the therapies and follow up is to accompany the patient and the patient's family during the evolution of the disease in order to bring comfort and optimal support. Because of the nature of this disease, a multidisciplinary collaboration is needed and in France this is coordinated by ALS regional reference centers [4]. Care should be handled with an individualized and holistic approach. The different caregivers must be coordinated and must share information.

Medicinal Therapy

Riluzole, which blocks voltage-dependent sodium and thus reduces the presynaptic liberation of glutamate, is the only drug that is registredspecifically for the treatment of ALS [5]. If administered early, it prolongs the median survival to two or three months in the absence of tracheotomy [5]. Rizuolehas not been shown to be

effective in the treatment ofmotor functions, respiratory functions, fasciculation, muscular force or motor symptoms. It has not been shown to be beneficial in advanced stages of ALS. The use of alpha-tocopherol (vitamin E) associated with riluzole has been shown, with a weak significance, to slow the transition from initial to advanced stages of ALS. Despite the weak level of proof, the associated use is recommended [5].

In the last 15 years, over 70 drugs have been tested on animals, only 30 have resulted in more elaborate studies and all results have been negative. Currently there are two promising axes to be explored: stem cells and therapies that act on oxidative stress and that target non-neuronal cells adjacent to motor neurons (astrocytes and microglia) or skeletal muscle [5].

Non-medicinal Therapy

Because of the rapidly progressive evolution of ALS towards a reduction then loss of autonomy and because of the limited effectiveness of medicinal therapy, care relies on symptomatic treatments and should take into account the will of the patient and the patient's family. Treatment therefore is regularly evaluated and adapted. Treatment includes physical therapy, adapting the patient's environment, help with communication and psychological care. Multidisciplinary treatment is now highly codified and adopted in ALS reference centers. Intensivists may intervene in order to address respiratory and nutritional needs.

Respiratory Needs

ALS affects all muscular groups involved in breathing: upper respiratory tract muscles (affected deglutition and cough), expiratory muscles (ineffective cough), and inspiratory muscles (restrictive respiratory insufficiency). All patients have a high risk of respiratory complications, which is a common cause of death in this population [4].

Problems with deglutition and cough:

Problems with deglutition and cough are closely linked to the malfunctioning muscles in the upper respiratory tract, to bulbar forms and in cases with ineffective coughs. Physical therapy for deglutition, tracheotomy and gastrostomy should be considered early in the care process. Coughing, which is dependent on expiratory muscles, is necessary in order to avoid the accumulation of bronchial secretions. It is best to start a bronchial drainage ifcough peak expiratory flow (PEF) is below 270 l/mn. This consists of a cough that is manually assisted (possibly preceded by a mechanic insufflation) by abdominal or thoracic maneuvers during a cough effort. Insufflation-exsufflation methods are generally effective and reserved for severe cases [4, 6]. For bulbar forms and in the case of ineffective cough tracheotomy should be rapidly considered.

Ventilation failure:

The progressive damage to inspiratory muscles will result inevitably in the appearance of a hypercapnia. It is medically and ethically important to anticipate and plan for this respiratory failure. NIV then invasive ventilation should be put in place via a tracheotomy. Nocturnal alveolar hypoventilation often appears before diurnal symptoms (drowsiness, fatigue, morning headaches, unexplained cognitive deterioration) and includes a well-codified symptomatology (fragmented sleep, snoring, sleep apnea, waking suddenly with a sensation of suffocation). Oxymetry or better yet polygraphy or polysomnography can be conducted in order to get a better understanding of the situation [6]. The existence of signs of diurnal alveolar hypoventilation, a PaCO2 above 45 mm Hg, a vital capacity below 50 % of predicted value and a maximal inspiratory pressure under 60 % of the predicted value are indication to start mechanical ventilation [6]. NIV must be used first except in cases of severe bulbar forms. NIV improves survival [6], sleep and comfort for the patient despite the progression of the physical handicap, which cannot be modified with ventilation [4, 6]. Bronchial drainage can and should be performed. It should be put in place by an experienced team. Its early use and effectiveness on symptoms should not mask the issue of the future of the patient and future choices: a discussion about the possibility of a tracheotomy should not be put off. If there is a failure of or intolerance to NIV or if bronchial blocking is resistant to drainage techniques (more frequent in bulbar forms), tracheotomy should be proposed and discussed [6]. Tracheotomy is an invasive procedure that can cause associated problems and it immediately limits verbal expression. It allows for endotracheal aspiration, protection of the upper respiratory tract and provides ventilation for the patient. This can increase the median survival but does not slow the evolution of the disease [4, 6].

Nutrition Supply

There are many malnutrition etiologies during ALS: dysphagia, weakness in extremities, difficulties with mastication, and hypermetabolism caused by an increase in energy spent during rest [4, 7]. Malnutrition and weight loss are factors that lead to abnormally high death rates [7]. There are no specific indications for parenteral nutrition by peripheral or central veins. Therapeutic approach rapidly requires enteral nutrition. Enteral nutrition can be administered via nasogastric tube or gastrostomy and it should be kept in mind that gastrostomy is more adapted for prolonged nutrition. There are no objective criteria to decide the best time to start, however under nutrition is a factor in a poor prognosis and therefore enteral nutrition should be anticipated. Clinical elements should be taken into consideration: insufficiency of input, difficulty eating, prolonging the time for a meal, repeated choking and weight loss [4, 7].

Ethical Questions

The median survival after diagnosis is about three to 5 years [4]. In this context, information provided by a multidisciplinary team allows the family to establish important decisions about various therapeutic techniques (NIV, tracheotomy, gastrostomy). This decision making process should be applied during different stages of the disease as decisions may be revised as the disease evolves. These elements must be recorded in a medical file that must be available to the different caregivers and those involved in decision-making. In case of an emergency, the situation must be clear and anticipated. In this case the patient's wishes must be respected regarding the continuation, initiation or decision not to use mechanical ventilation. However the situation may be very confusing and some decisions may require time. It is a medical responsibility to make the decision and assume the consequences and to organize the application of the decisions. For example it is possible to start an NIV associated with bronchial clearing in order to gain valuable time to deliberate with colleagues. Intubation can be a solution, especially in the case of acute intercurrent complications that are potentially reversible. The discontinuation of the use of mechanical ventilation must eventually beconsidered in line with the local guidelines of the law [4].

References

1. Shook SJ, Pioro EP (2009) Racing against the clock: recognizing, differentiating, diagnosing, and referring the Amyotrophic Lateral Sclerosis patient. Ann Neurol 65(suppl):S10–S16. doi:10.1002/ana.21545
2. Dhand UK (2006) Clinical approach to the weak patient in the intensive care unit. Respir Care 51(9):1024–1041
3. Gorson KC (2005) Approach to neuromuscular disorders in the intensive care unit. Neurocrit Care 03:195–212
4. Kierman M, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC (2011) Amyotrophic lateral sclerosis. Lancet 377:942–955. doi:10.1016/S0140-6736(10)61156-7
5. Musaro A (2012) Understanding ALS: new therapeutic approaches. FEBS J 1–8 doi:10.1111/febs.12087
6. Benditt O, Boitano L (2008) Respiratory treatment of Amyotrophic Lateral Sclerosis. Phys Med Rehabil Clin N Am 19:559–572. doi:10.1016/j.pmr.2008.02.007
7. Rosenfeld J, Ellis A (2008) Nutrition and dietary supplements in motor neuron disease. Phys Med Rehabil Clin N Am 19:573–589. doi:10.1016/j.pmr.2008.03.001

Parkinson's Disease in Intensive Care Unit

Lionel Velly, Delphine Boumaza and Nicolas Bruder

Key Points

Parkinson's disease is the second most frequent neurodegenerative disease. It is due to the degeneration of pigmented cells in the dopaminergic system of the substantia nigra. Parkinson's disease is one of the rare neurodegenerative disease for which there exists a treatment. Levodopa stays the cornerstone of the medication. An interruption in levodopa or administration of dopamine antagonists can be responsible for a neuroleptic malignant syndrome-like. Dysautonomia is frequent, especially orthostatic hypotension. Aspiration pneumonia is one of the most frequent causes of death in these patients. Drugs interactions with Parkinson's medications are numerous and need to be known by physicians. Severe akinesia can benefit from a treatment with apomorphine. Opioids agents should be used with caution for patients with Parkinson's disease due to the risk of muscular rigidity and its complications.

Introduction

Idiopathic Parkinson's disease is after Alzheimer's disease the second most frequent neurodegenerative disease. Its prevalence in Europe is estimated at 1.6 % of the population over 65 years old in Europe. Frequency reaches 3.5 % of the population over 80 years [1]. This "shaking palsy" has been first described by James Parkinson in 1817. The cardinal symptoms are bradykinesia, extrapyramidal rigidity, rest tremor mainly asymmetrical and postural and gait disorders. Parkinson's disease is associated with the progressive emergence of a handicap, an impaired quality of life and an increased mortality.

L. Velly (✉) · D. Boumaza · N. Bruder
Department of Anesthesiology, CHU Timone Adultes, Aix Marseille University,
264 rue st Pierre, Marseille 13005, France
e-mail: lionel.velly@ap-hm.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_12,

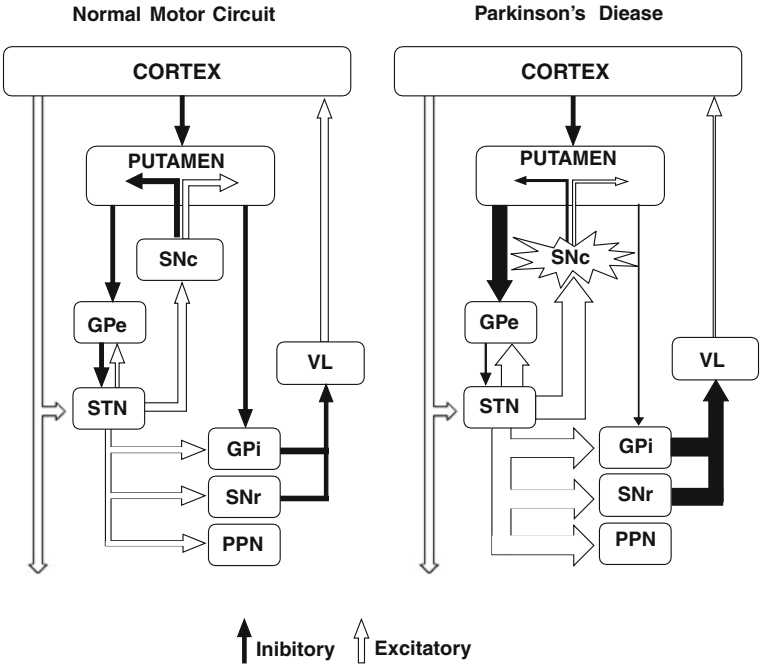

Fig. 1 Schematic representation of the classic model of the basal ganglia, illustrating the direct and indirect pathways connecting the striatum and the globus pallidus, and the modulatory effects of dopaminergic neurons on each of these systems. Excitatory fibres are shown in *black* and inhibitory fibres in *white*. The model predicts that neuronal firing in the STN and GPi are increased in the parkinsonian state, leading to excessive inhibition of brainstem and thalamocortical neurons with the development of parkinsonian motor features. In contrast, the model proposes that dyskinesia is related to decreased firing in the STN and GPi, with reduced inhibition of thalamic and cortical motor regions. *SNc* substantia nigra pars compacta; *GPe* external globus pallidus; *STN* subthalamic nucleus; *VL* ventralis lateralis; *Gpi* internal globus pallidus; *SNr* substantia nigra pars reticularis; *PPN* pedunculopontine nucleus; *DA* dopamine. Adapted from Obeso et al.

Physiopathology

Physiopathology of Parkinson's disease is complex, even though considerable progress has been done after discovering numerous genes involved in rare forms of the disease [2]. The correlation between clinical symptoms and the degeneration of pigmented cells in the substantia nigra dopaminergic system was not recognized until 1983. Briefly, dopaminergic insufficiency in the basal ganglia is responsible for a hyperactivity of the cholinergic neurons of the substantia nigra explaining the rigidity and a hypoactivity of the pallidum explaining the akinesia and the tremor (Fig. 1). Many cerebral structures are affected during the course of the disease. Olfactory process and locus coeruleus are affected early, leading to the initial occurrence of olfactory troubles and sleeping disorders (night agitation and

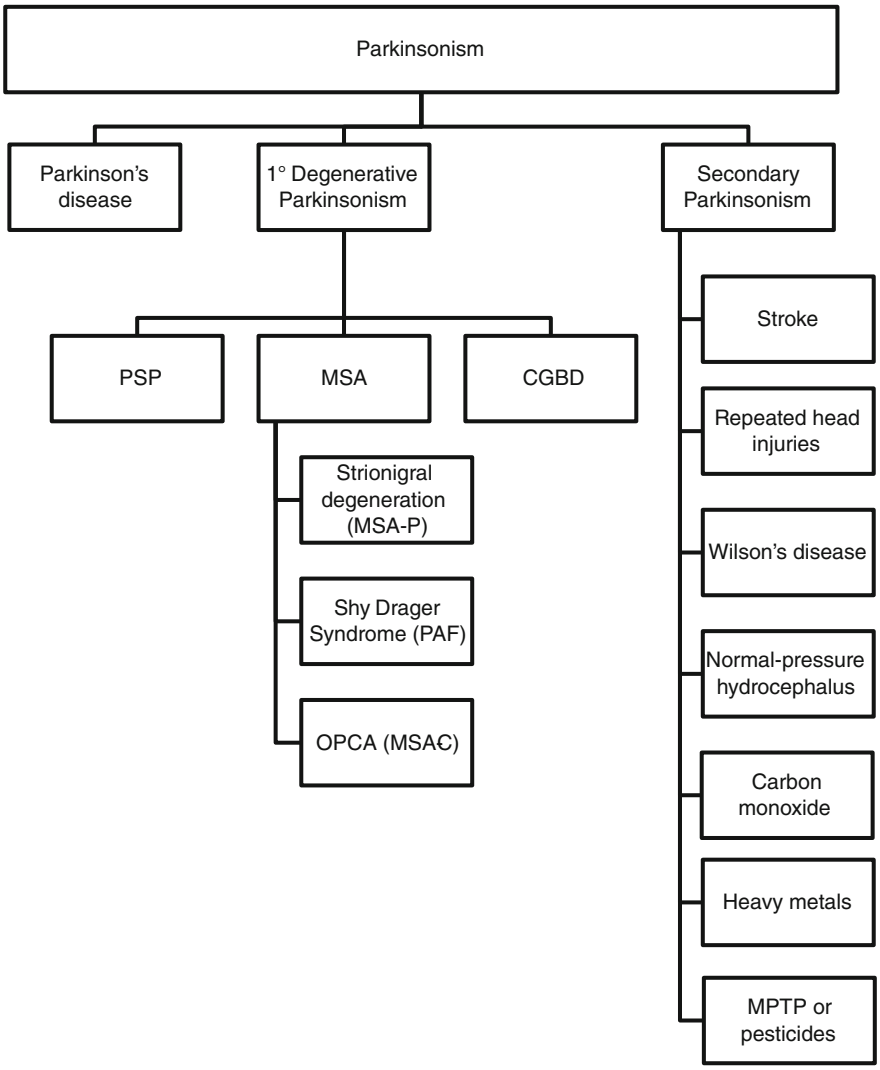

Fig. 2 Differential diagnosis of Parkinson's disease. *MSA-P* Multiple System Atrophy-Parkinsonian; *MSA-C* Multiple System Atrophy-Parkinsonian cerebellar; *PSP* Progressive Supranuclear Palsy; *CGBD* Cortical Basal Ganglionic Degeneration; *PAF* Pure Autonomic Failure; *OPCA* Olivopontocerebellar Atrophy

nightmares). Later on, structures involved in motor regulation such as the substantia nigra, located in the upper part of the brainstem, are involved and lead to motor disorders, characteristic of Parkinson's disease. Lastly, after many decades of evolution, cortical structures can be affected.

Parkinsonism, it is a generic name which includes clinical situations similar to Parkinson's disease (Fig. 2), which can have multiples causes such as arterial

sclerosis (strokes affecting the basal ganglia), repeated head injuries, enzymatic deficiency like Wilson's disease (differential diagnosis to evoke in young patients with familial history), normal-pressure hydrocephalus or following an intoxication with carbon monoxide, heavy metals, MPTP or pesticides,… [3]. It can also occur in the course of diffuse degenerative disease of the central nervous system, such as Lewy-bodies dementia (Parkinsonism appears then in old patients, rapidly associated with cognitive disorders, attention troubles, sleeping disorders and visual hallucinations), progressive supranuclear palsy or Steel Richardson's disease, corticobasal ganglionic degeneration or multiple-system atrophy also known as Shy-Drager syndrome (extrapyramidal signs associated with pyramidal signs, dysautonomia and cerebellar ataxia). These atypical patients have classically a poor response to treatment with Levodopa (L-Dopa: 3,4-dihydroxy-l-phenylanine), in terms of hypertonia and tremor. Furthermore, they suffer from hallucinations and dementia from the early stage of the disease. When a Parkinsonism or a Parkinson's disease is suspected in ICU, the advice of a neurologist is precious. The neurologist can help the diagnosis of an exacerbation of Parkinson's disease and help the prescription of L-Dopa. Parkinsonism can also be induced by administration of classical neuroleptics (butyrophenones, phenothiazines), atypical neuroleptics (amisulpride, risperdone, clozapine, quetiapine,…), but also hidden neuroleptics (metoclopramide) and the use of certain herbs such as kava. In this case, Parkinsonism is reversible with withdrawal of the treatment. When neuroleptics must be maintained, physicians should use preferably atypical neuroleptics such as clozapine or quetiapine, which are less suppliers of Parkinsonism.

Main Elements in the Treatment of Parkinson's Disease

Parkinson's disease is one of the rare neurodegenerative disease for which it exists a treatment. The aim is to reach a balance in striatum activity by increasing the cerebral dopaminergic capacities and/or decreasing the cholinergic activity. There are a lot of research leads regarding Parkinson's disease therapy but L-Dopa stays the cornerstone of the treatment [4].

Medical Treatment

L-Dopa and Adjuvant Therapy

L-Dopa stays since 30 years the most effective anti-Parkinson therapy. L-Dopa is the precursor of dopamine; it crosses the blood–brain barrier and helps to restore balance of the neurotransmitters between dopamine and acetylcholine (Table 1). L-Dopa is always combined with peripheral inhibitor of dopa-decarboxylase, benzerazide (co-beneldopa; Madopar®, Modopar®) or carbidopa (co-careldopa;

Sinemet® Caramet®), which inhibits the peripheral destruction of L-Dopa without crossing the blood–brain barrier. This combination decreases the adverse effects (e.g. nausea, hypotension) and increases cerebral bioavailability of dopamine. The aim of these inhibitors is to avoid the transformation of L-Dopa in dopamine in the digestive tract.

Efficacy of L-Dopa is superior to dopamine agonists. By contrast, it is now well established that L-Dopa has to be introduced later on in the course of the disease, especially in young patients, in order to delay the occurrence of dyskinesia that could be impressive and very disabling. These dyskinesias are writhing movements of various voluntary movements (opening and closing eyes, grimace, tongue movement, head rotation, shoulder lifting, winding of an arm or a leg, etc.). Mechanisms of occurrence of dyskinesia and motor fluctuations are complex and imperfectly understood but they are related to pulsatile administration of L-Dopa, severity of dopaminergic loss, absence of dopamine storage ability and changes of the glutaminergic system. In advanced PD, in order to maintain stable plasma levels, a suspension of micronized levodopa (20 mg/ml) and carbidopa (5 mg/ml) in a methylcellulose gel (Duodopa®) can be infused using a pump via an intestinal catheter placed inside a percutaneous endoscopic gastrostomy tube.

Tolerance of L-Dopa is far better than other Parkinson's medications. There are almost no contraindications, except for myocardial infarction in the acute phase, due to an increased risk of acute dysrhythmias. Confusion and hallucination can occur under treatment with L-Dopa, but rarely compare to these same adverse effects with anticholinergic drugs or dopamine agonists. Administration of L-Dopa with other enzymatic inhibitors allows improving tolerance. Those are the inhibitor of monoamine oxidase B (MAO-B) and inhibitor of catechol-O-methyltransferase (COMT). Selegiline is a relatively selective inhibitor of MAO-B with few effects on MAO-A. COMT is the other main destruction path of L-Dopa in periphery and less importantly in the synapse. COMT inhibition allows delivering a larger amount of L-Dopa, 30 % on average. Entacapone (COMTan® or co-careldopa plus entacapone: Stalevo®) and tolcapone (Tasmar®) are the COMT inhibitors currently commercialized in Europe. They act only in association with L-Dopa. Owing to hepatic side effects, tolcapone should only be used in case of non-response to entacapone.

Dopamine Agonists

The lessening of response and the motor side effects of dopatherapy in the course of the disease has led to the research of other therapeutics to improve dopaminergic transmission by stimulating directly post synaptic dopaminergic receptors in the striatum. Many dopamine agonists have then been discovered either derivate from ergot (bromocriptine, lisuride, pergolide) or synthetic drugs (piribedil, ropinirole, rotigotine). Except from apomorphine, all dopamine agonists have a lower power than L-Dopa, but their half-life and their duration of action are significantly longer and can reach hours. It allows a long-lasting and more stable

Table 1 Main anti-Parkinson Therapy

Levodopa + peripheral inhibitor of dopa-decarboxylase	Inhibitor of COMT	Inhibitor of MAO-B	Dopamine agonists	Anticholinergic agents	Antiglutamatergic agent
L-Dopa + benzerazide	Entacapone	Selegiline	*Derived from ergot*	Trihexyphenidyl	Amantadine
L-Dopa + carbidopa	Tolcapone		Bromocriptine	Tropatepine	
L-Dopa + carbidopa + entacapone			Lisuride	Biperiden	
			Pergolide		
			Synthetic drugs		
			Piribedil		
			Ropinirole		
			Rotigotine		

L-Dopa 3,4-dihydroxy-l-phenylanine; *MAO-B* L-monoamine oxidase B; *COMT* catechol-O-methyltransferase

stimulation of the postsynaptic dopaminergic receptors. Their efficiency as a monotherapy in the early stage of the disease has clearly been demonstrated in various studies. These studies have revealed a diminished incidence of motor complications, particularly the dyskinesia under dopamine agonists compared with L-Dopa alone. But as the disease evolves, association of dopamine agonists and L-Dopa seems superior to L-Dopa alone. When motor fluctuations and dyskinesia occur, the main interest of dopamine agonists is to reduce severity and duration of the "off period". All Dopamine agonists have more or less the same side effects such as nausea, abdominal pain, orthostatic hypotension, dizziness or somnolence. Lower limbs swelling occur with agonists, but more frequently with ergot-derivative drugs. Pulmonary and retroperitoneal fibrosis, although rare, have also been described with ergot-derivative drugs and seems related to a class-effect. Recently, cardiac valvular side effects have been reported with long-term pergolide treatment, probably also due to a class-effect [5]. This problem is thought to be due to pergolide's action at the 5-HT_{2B} serotonin receptors of cardiac myocytes, causing proliferative valve disease by the same mechanism as ergotamine. Switching treatment among agonists involves an estimation of dose equivalence and is done by replacing the agonist with the other one day from another (Table 2). A new transdermal dopamine agonist (rotigotine) is available. However, it seems less efficient than ropinirole and its indication remains to evaluate.

Other Medical Treatments

Amantadine initially prescribed as an antiviral agent has shown interesting anti-Parkinson effects and particularly a significant anti-dyskinesia effect.

Anticholinergic agents (trihexyphenidyl, tropatepine, biperiden) have been historically the first treatments available in Parkinson's disease. Numerous anticholinergic drugs exist and are mainly efficient on tremor, but out over many abdominal, ocular, sphincterian or neuropsychological side effects. Their use is therefore limited and restricted to young patients.

Surgical Treatment

This type of procedure is limited to patients with advanced Parkinson's disease, with frequent blockages, tremor, bradykinesia, rigidity and walking disorders or to patients with severe side-effects of medical treatment. Surgical ablation procedures such as thalamotomy (indicated in severe tremor) or pallidotomy (indicated in disabling rigidity) have been proved efficient but are irreversible. They are nowadays less and less performed. Subcortical stimulation using implanted electrodes has progressively replaced these ablation procedures [6]. Cerebral stimulation has been described for the first time in 1987 in the treatment of Parkinson's disease. Its aim is to trigger a functional inhibition by high frequency stimulation. At first, the

Table 2 Dopamine agonists

Drugs	Trade names	Ergot derivated drugs	Half life (hours)	Dose equivalent to 100 mg of L-Dopa (mg)	Dosing range (mg/day)
Apomorphine (30 mg/30 ml)	*Apokyn, lxense, Spontane, Uprima, Apokinon*	No	0.3–0.5	–	1–10 mg/injection 1–8 injections/day
Ropinirole (0.25; 0.5; 1; 2 and 5 mg)	*Requip, Ropark, Adartrel*	No	3–6	5–6	6–24
Piribedil (20 and 50 mg)	*Pronoran, Trivastal Retard, Trastal, Trivastan*	No	21	50–60	50–250
Pramipexole (0.18 and 0.7 mg)	*Mirapex, Mirapexin, Sifrol*	No	8–12	0.7	1.5–4.5
Bromocriptine (2.5; 5 and 10 mg)	*Parlodel, Cycloset, Bromo-Kin*	Yes	3–8	10	5–40
Pergolide (0.25; 0.25 and 1 mg)	*Permax, Celance*	Yes	16–21	1	0.5–5
Lisuride (0.2 and 0.5 mg)	*Dopergin, Proclacam, Revanil, Arolac*	Yes	1–7	0.6	0.5–5

intermediary ventral nucleus was the target of the stimulation. Now, the stimulation aims the subthalamic nucleus. Cerebral stimulation reduces efficiently for 2–5 years the motor fluctuations and dyskinesia in idiopathic Parkinson's disease. In most centers, after expert assessment by a neurologist seasoned in pharmacological treatment of Parkinson's disease, a pluridisciplinary team selects patients eligible for surgery. The ideal patient in this indication is the one who is severely impaired during the "off period" and in the meantime totally independent during "on period" without significant cognitive disorders. The most accurate prognostic test should be the remaining of a response to L-Dopa therapy. Principal complications related to the surgical technique are seizures (10 %), intra-cerebral hemorrhage (8 %; its incidence increases with per-operative high blood pressure) and temporary post-operative confusion (10 %). This type of procedures generally requires a post-operative care in ICU.

Management of Parkinson's Disease Patients in ICU

Fortunately, Parkinson's disease patients are often admitted to ICU with a pre-established diagnosis of the disease. ICU is not an appropriate place to diagnose *de novo* Parkinson's disease or distinguish the different etiologies of Parkinsonism. Many factors can interfere with neurological assessment (sedation, mechanical ventilation) and make the clinical examination incomplete. The main error that should not be done in the management of these patients is to stop, even for a few hours the dopaminergic therapy. An interruption of this treatment can have dramatic consequences. Some specificities have also to be known in Parkinson's disease patients. Besides the fact that it occurs in an aging population, the major risks are related to the respiratory impairment, favored by swallowing disorders and dysautonomia. It is also important to precise by interviewing family the level of handicap of the patient in daily-living activities.

Specificities Due to the Medical History

Respiratory Failure

The occurrence of respiratory impairment in the course of the Parkinson's disease has been observed since the first description of the disease in 1817 and pulmonary complications, especially aspiration pneumonia are the most frequent cause of death in those patients [7]. These alterations of the respiratory function are more frequent when a dysautonomia is associated to the Parkinsonism. Dysphagia appears from the early stage of the disease [2] and is due to asynchrony between swallowing and respiration and also to an important diminution of efficiency of the cough reflex [8]. Finally a hyper-sialorrhea is frequently present in those patients,

as well as an extended opening on the high esophagus sphincter and a slowing of the gastro-intestinal transit time favoring regurgitations. In any case, these troubles should be systematically investigated, particularly by screening severity criteria: cough during meals or during swallowing, recurrent pneumonias, time for the meal over 1 h, loss of weight. Warning signs should also be collected: tremor of the tongue, blockage of the alimentary bolus in the aerodigestive tract, hypersalivation and salivary incontinence, masseter hypertonia, fractioned swallowing, oral and nasal refluxes, dysphagia, and heartburn. When the reason for admission in ICU is related to pneumonia, an ENT endoscopic screening should be performed. When obvious food aspiration is observed, the indication of tracheotomy should be discussed with neurologist and ENT specialists.

During the course of Parkinson's disease, lung function tests are frequently altered [9]. An obstructive syndrome, responsible for a post-operative respiratory weakness is present in one-third of the patients. The obstructive syndrome can also be associated to a restrictive syndrome. This can be easily understood by the coexistence of rigidity and akinesia of respiratory muscles associated with laryngeal hypertonia, responsible for an inspiratory or expiratory obstruction of the upper airway. This rigidity of the chest wall is particularly important in ICU because it can compromise mechanical ventilation and the withdrawal from ventilator support. After extubation thoracic rigidity leads to hypoventilation, an inefficient cough, atelectasis and an increased risk of aspiration pneumonia. It is then advisable to limit as much as possible the "off periods". Similarly, after extubation, laryngeal akinesia can lead to laryngospasm and acute respiratory failure. L-Dopa or dopamine agonists intake have also a remarkable effect on airway obstruction. These patients have also an increased frequency of sleep apnea. Seldom, severe central apneas, dysrhythmic respiration or a Cheyne-Stokes pattern and central hypoventilation were described during severe Parkinson's syndrome with dysautonomia. Prolonged treatment with ergot-derivated drugs (bromocriptine, lisuride, pergolide) has been associated with pulmonary fibrosis [10].

Autonomic Disorders

They are frequent in Parkinson's disease and are related to a neurodegenerative process which causes a dysfunction of the *locus coeruleus* norepinephrine system and of the dorsal nucleus of the vagus nerve [11]. Dysautonomia is responsible for gastro-intestinal troubles (dyspepsia, hyper-sialorrhea, slowing of the bowel movement with constipation), urinary retention, tachycardia and cardiac arrhythmias. Dysautonomia is associated in more than 70–80 % of case with circulatory disorders. The most frequent trouble is orthostatic hypotension, present in more than 70 % of Parkinson's disease patients, which can be worsened by dopamine agonists. In addition to dysautonomia, the patients hold concurrently several risk factors for hypotension: old age, undernutrition, dehydration, and particular sensitivity to anesthetic agents. Intravenous administration of dopamine as a

vasopressor drug is not recommended in order to control Parkinsonism in ICU. Intravenous dopamine cannot reach the brain and can lead to many cardiovascular side effects such a tachycardia and arrhythmias. Anesthetics agents used for sedation should be titrated according to the clinical effectiveness and not according to defined dosages. These patients can also have thermoregulation troubles with increased sensitivity to hypothermia.

Practical Approach Concerning Anti-Parkinson Therapy in ICU

The principal aim during the stay in ICU is not to stop the dopaminergic treatment, particularly L-Dopa. The half-life of L-Dopa is very short (<3 h) and its interruption, even for a short time period can have important repercussion on muscular rigidity. It is frequent that an interruption of L-Dopa leads to akinesia, swallowing disorders, leading respiratory complications or worsening of a pre-existing respiratory condition. Moreover, an interruption of L-Dopa can also be responsible for an equivalent of malignant neuroleptic syndrome. It combines fever, rigidity, altered consciousness, rhabdomyolysis, sometimes complicated with acute renal failure and coagulation disorders [12]. Treatment with L-Dopa will be maintained at the same dosage than previously, taking care to ensure that the patient did not take more drugs in self-medication than prescribed. Because L-Dopa is absorbed in the jejunum, the difficulty is not to maintain dopa-therapy but rather to administrate it effectively. It is not always easy in those hemodynamically unstable patients to reach a therapeutic concentration range. Yet, at an advanced stage of the disease, motor fluctuations are very sensible to minimal changes in the rhythm of administration or the dose of L-Dopa, even at the protein contain of the food intake. A large intake in protein should decrease the absorption of Sinemet. Protein in the meal is broken down in the intestine into amino acids that must travel across the intestinal wall to get into the blood. Levodopa also must transit the intestine using exactly the same carrier system as the amino acids. In ICU, an administration through a gastric tube, sometimes through a post-pyloric tube in case of gastroparesia, is often the only option. Many galenical formulations exist: standard, sustained-release or dispersible for drinkable solution (rapid action). The standard form of Sinemet®, unlike the sustained form and certain capsule, can be used without significant modification of its pharmacokinetic pattern by muddling and administration through gastric tube. The dispersible form of levodopa can be very useful since it has a much faster and more constant onset of action than the standard preparation. However it has to be given every 2–4 h due to its short half-life. In countries where an intravenous form of L-dopa is available, intravenous administration is convenient and effective for perioperative management. In any case, neurologist advice is essential to adjust the treatment. Administration of vitamin B6 (pyridoxine) should be avoided. Vitamin B6 is a coenzyme of

peripheral L-Dopa decarboxylase, favoring the inactivation of L-Dopa and decreasing its efficacy. When prolonged fasting is necessary (e.g. gastric surgery), administration of Parkinson's medications becomes a real challenge. Subcutaneous injection of apomorphine or transdermal administration of rotigotine (Neupro®) may be an option. The dose of apomorphine to treat akinesia is 2 mg intravenously or subcutaneously every 10–15 min until regression of the symptoms. An important side effect is nausea and vomiting, even more when the patient has never been treated with apomorphine. The approach is less consensual for other treatments. It is probably advisable to stop progressively anticholinergic agents because they increase the risk of delirium. The pursuit of ergot-derivative dopamine agonists should be cautious in case of prescription of catecholamine and strictly proscribed when a prescription of macrolides (erythromycin, josamycine) is needed. There is a potential risk of "*ergotism*", responsible for necrosis of extremities by severe vasoconstriction. Substitution by a synthetic dopamine agonist may be considered after neurologist advice. Monoamine oxydase (MAO) inhibitors type A have been associated with major hemodynamic changes, especially in association with sympathomimetic agents. MAO inhibitors used in the treatment of Parkinson's disease (selegiline) have a selective action on cerebral MAO-B with low affinity on peripheral MAO-A. This explains the possibility to use indirect sympathomimetic agents such as ephedrine, with selegiline. A severe interaction persists though between selegiline and pethidine. The co-prescription of selegiline and opioids is restricted. Usually, selegiline may be interrupted with few adverse effects.

Medication Worsening Parkinsonism

Parkinson's disease patients and neurodegenerative Parkinsonism are particularly susceptible to anti-dopamine agents such as neuroleptics (phenothiazine, butyrophenone) or certain anti-emetics (metoclopramide, promethiazine). Very low doses of these drugs can give rise to severe hypertonia, akinesia and a neuroleptic-like malignant syndrome. If administration of an anti-psychotic agent is necessary, newer agents should be preferred (clozapine or quetiapine) with systematic and repeated screening for worsening of a Parkinson's symptoms or fever. Concerning anti-emetics, it is preferable to use setrons.

Practical Approach Concerning Anaesthetic Agents

Some specificities have to be known by physicians in sedation agent management [13, 14]. Concerning hypnotic agents, little evidence is currently available in literature about Benzodiazepines. It seems that just as the elderly patients, Parkinson's disease patients have an increased susceptibility to this class of drugs.

No complication such as hypertonia or rigidity has been reported with benzodiazepines. Concerning Thiopental, several cases have been reported with worsening of the Parkinson's syndrome following its use. The evidence of a causal link has not been established but its administration should be cautious. In animals, thiopental diminished the dopaminergic release in the striatum. Propofol can be used but with reduced dosage due to the higher susceptibility of Parkinson's disease patients [15]. However dyskinesia with propofol have been described, particularly after interruption of L-Dopa therapy. In patients receiving L-Dopa, co-administration of ketamine can be responsible for an exacerbated sympathetic response. Low doses (0.1–0.5 mg kg^{-1}) treatment has been reported without significant adverse effects. Opioid use should also be cautious in Parkinson's disease patients. There are several cases of muscular rigidity reported in literature following the use of fentanyl. Opioid agents in general induct a muscular rigidity by presynaptic inhibition of dopamine release. Cases of acute dystonia have also been described with alfentanil. Titration of narcotics is difficult because the classical signs of pain (tachycardia, hypertension) can be masked by dysautonomia. Moreover, behavioral pain scales can also be misinterpreted in cases of akinesia. Use of morphine in Parkinson's disease allows, at low doses, a diminution of dyskinesia while high doses can lead to akinesia. There are no reported cases of non-depolarizing neuromuscular blocking drugs worsening the symptoms of Parkinson disease.

Other Preventive Measures

Parkinson's disease patients are more at risk of post-operative complications that are often, diagnosed late in those patients. The diminution of spontaneous movements of the body and limbs due to rigidity and akinesia exposes these patients to an increased risk of deep vein thrombosis, pulmonary embolism, bedsores and peripheral neuropathy by compression. As for the other cases of immobility, anticipation and prescription of prophylactic measures are essential. It is recommended to resort to early mobilization out of bed, intermittent pneumatic compression of the lower limbs and a prescription of a preventive dose of heparin (low molecular weight or unfractionated heparin).

References

1. de Rijk MC et al (1997) Prevalence of Parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study. European community concerted action on the epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry 62(1):10–15
2. Olanow CW, Stern MB, Sethi K (2009) The scientific and clinical basis for the treatment of Parkinson disease. Neurology 72(21 Suppl 4):S1–S136
3. Lees AJ, Hardy J, Revesz T (2009) Parkinson's disease. Lancet 373(9680):2055–2066

4. Poewe W (2009) Treatments for Parkinson disease—past achievements and current clinical needs. Neurology 72(7 Suppl):S65–S73
5. Dupuy D et al (2008) Valvular heart disease in patients with Parkinson's disease treated with pergolide. Course following treatment modifications. J Neurol 255(7):1045–1048
6. Benabid AL et al (2009) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 8(1):67–81
7. Aboussouan LS (2005) Respiratory disorders in neurologic diseases. Clevel Clin J Med 72(6):511–520
8. Ebihara S et al (2003) Impaired efficacy of cough in patients with Parkinson disease. Chest 124(3):1009–1015
9. Shill H, Stacy M (2002) Respiratory complications of Parkinson's disease. Semin Respir Crit care Med 23(3):261–265
10. Tintner R et al (2005) Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for Parkinson disease. Arch Neurol 62(8):1290–1295
11. Micieli G et al (2003) Autonomic dysfunction in Parkinson's disease. Neurol Sci 24(Suppl 1):S32–S34
12. Takubo H et al (2003) A collaborative study on the malignant syndrome in Parkinson's disease and related disorders. Parkinsonism Relat Disord 9(Suppl 1):S31–S41
13. Kalenka A, Schwarz A (2009) Anaesthesia and Parkinson's disease: How to manage with new therapies? Curr Opin Anaesthesiol 22(3):419–424
14. Nicholson G, Pereira AC, Hall GM (2002) Parkinson's disease and anaesthesia. Br J Anaesth 89(6):904–916
15. Fabregas N et al (2002) Modeling of the sedative and airway obstruction effects of propofol in patients with Parkinson disease undergoing stereotactic surgery. Anesthesiology 97(6):1378–1386

Part VI
Internal Medicine Diseases

Management of Autoimmune Systemic Diseases in the Intensive Care Unit

L. Chiche, G. Thomas, C. Guervilly, F. Bernard, J. Allardet-Servent and Jean-Robert Harlé

Key Points

- Specific clinical (syndromic associations) or biological signs should lead the intensivist to suspect an autoimmune systemic disease.
- Several biological (i.e., ANCA autoantibodies) investigations can be rapidly performed in the ICU to help the diagnosis.
- Early detection and management of infections that may occur simultaneously with the flare-up of the systemic autoimmune disease is a priority. An exhaustive workup including, if necessary, invasive investigations

L. Chiche (✉) · G. Thomas · J.-R. Harlé
Département de Médecine Interne, Centre de Compétence PACA Ouest pour la Prise en Charge des Maladies Autoimmunes Systémiques, CHU de la Conception, Marseille, France
e-mail: laurent.chiche@ap-hm.fr

G. Thomas
e-mail: guillemette.thomas@ap-hm.fr

J.-R. Harlé
e-mail: jean-robert.harle@ap-hm.fr

L. Chiche · G. Thomas · C. Guervilly
Intensive Care Unit, Acute Respiratory Distress and Severe Infections, North Hospital, URMITE UMR-CNRS, Aix Marseille Université, Marseille, France
e-mail: christophe.guervilly@ap-hm.fr

F. Bernard
Département de Médecine Interne, CHU Nord, Marseille, France
e-mail: fanny.bernard@ap-hm.fr

J. Allardet-Servent
Département de Réanimation, Hôpital Ambroise-Paré, Marseille, France
e-mail: j.allardetservent@ch-ambroisepare.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_13,

(i.e., pulmonary biopsy) should be proposed before the introduction of immunosuppressive therapies.
- Corticosteroids and sometimes IVIG are the preferred initial options, especially when concomitant infection is suspected or uncontrolled.
- Referent centers should be asked for validation of the therapeutic options, especially when some drugs are used off-label for these severe patients.

Introduction

The term 'systemic disease' (SD) refers to a 'systemic' autoimmune disease, in contrast to autoimmune diseases targeting a specific organ such as diabetes or thyroiditis. SDs can be mainly separated into two types: connective tissue diseases and systemic vasculitis [4]. This distinction is supported by different physiopathological mechanisms, clinical expression, prognosis and management. Patients presenting with a SD may be admitted to an intensive care unit (ICU) at different stages in the evolution of their disease. First, they may present during a severe inaugural flare-up of the SD where the intensivist should know how to evoke the diagnosis. More frequently, the patient is seen during a flare of an already diagnosed SD; in this case, the challenges are on the one hand to define when the patient should be transferred to the ICU and, on the other, to adapt specific treatments to the setting of ICU. At this stage, it is sometimes difficult to distinguish an infectious complication from a flare of the SD. Indeed, due to exposure to immunosuppressive treatments, these patients are at particularly high risk of developing opportunistic and/or severe infections. Finally, considering that even the most severe organ dysfunction can be reversed in some of these autoimmune conditions, the intensivist may need to use maximal supportive treatments. These different situations will be discussed sequentially while attempting to provide practical ideas for intensivists who may face these patients.

Diagnosis of a Systemic Disease in the Intensive Care Unit

"To learn how to diagnose a SD, it is necessary to have learnt how to evoke one". These diseases, often called "orphans", are not as rare as many people in the medical community might think (e.g. the prevalence of systemic lupus erythematosus is 30/100,000). Intensivists may take care of these patients when the SD has not yet been identified. Indeed, some patients may present with an initial acute flare-up of the SD, while others may present with an atypical form of the SD, causing a delay in diagnosis until more severe complications develop.

How do we evoke a diagnosis of a SD in a patient admitted to IC? As multi-organ failure is an everyday event in IC patients, only some clinical and biological signs are relevant to alert the intensivist (Table 1). Some syndromic associations should also lead to the suspicion of a SD.

Many SD can present with diffuse-alveolar hemorrhage, either isolated or as part of a pneumo-renal syndrome (Table 2).

Investigations for anti-polynuclear neutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane antibodies (GMB) should be requested urgently and the results obtained within 24 h.

The association of muscle symptoms with a rapidly progressive infiltrative pneumopathy (in a few weeks) should lead to investigations for a polymyositis or a dermatomyositis. Autoimmune myositis may be associated with a neoplastic disease that must be diagnosed as soon as possible, since the staging of the cancer may limit the use of invasive and prolonged supportive resources needed in the most severe cases.

The association of severe asthma with extrapulmonary manifestations (polyneuritis, cutaneous vascularity, and sinusitis) may suggest Churg-Strauss syndrome.

Finally, some less specific manifestations are frequently observed during SD: arthritis, cytopenia (autoimmune or mechanical in the context of a thrombotic microangiopathy), acute renal failure with or without signs of glomerulopathy (nephritis or nephritic syndrome), central nervous system (multiple strokes, meningo-encephalitis) or peripheral nervous system involvement.

Arterial and venous thromboses are found in vasculitis and in anti-phospholipid syndrome (APS). The intensivist should recognise the fulminant form of APS, referred to as "catastrophic" APS (or CAPS), which has been identified relatively recently. This very acute form is responsible for multiple arterial and venous thromboses occurring over a very short period of time (less than one week), associated with multiple organ failure. The prognosis of CAPS is extremely poor and the mortality rate is around 50 % [1]. The triggering factor is often infectious in nature, but can also be traumatic, neoplastic or linked to the recent withdrawal of long-term anti-coagulants. Systemic lupus is the autoimmune disease most frequently associated with APS and CAPS. CAPS is responsible for multi organ injuries involving the: kidneys (80 %), lungs (65 %), central nervous system (55 %), heart (50 %) and skin (50 %). The adrenal glands and gastrointestinal tract can also be the site of thromboses. Biologically, signs of TMA (mechanical haemolytic anaemia with schizocytosis) and disseminated intravascular coagulation are frequently observed during CAPS. Increased levels of lactate dehydrogenase (LDH) correspond both to the extent of tissue infarction and the intensity of haemolysis. Thrombopenia, sometimes profound, should not delay the introduction of curative anticoagulation with unfractionated heparin. Other therapeutics consist of high dose corticotherapy, plasma exchanges, immunosuppressants and/or intravenous immunoglobulins (IVIG).

Finally, some elements of anamnesis (often determined by questioning the patient's relatives) may orientate or support the diagnosis: history of autoimmunity,

Table 1 Clinico-biological signs of systemic diseases in the intensive care unit and corresponding diagnostic tests

Systemic disease	Clinical signs	Biological signs	Biological diagnostic tests
Systemic lupus erythematosus	Butterfly erythema (vespertilio) Alopecia Oral ulceration	Low CRP Complement consumption Autoimmune cytopenias TMA	ANA Anti-DNA antibodies Anti-Sm antibodies
Systemic sclerosis	Sclerodactylia Raynaud's syndrome Telangiectases	TMA	ANA Anti-centromere or Scl70
Autoimmune myositis (PM/DM)	Purple rash over the upper eyelids Gottron sign Muscular weakness	Raised CPK	ANA Anti-jo1…
APS/CAPS	Livedo Multiple arterial or venous thromboses	Prolonged APTT TMA	Lupus Anticoagulant and/or anti-cardiolipin and anti-B_2GpI antibodies
Adult onset Still's disease	Transient skin eruption on the trunk Pharyngitis	Raised ferritin (glycosylated fraction <20 %) hemophagocytic syndrome	
Behçet's disease	Pseudo-folliculitis, Bipolar aphtha Uveitis Arterial or venous thromboses		Pathergy test HLA B5
Churg-Strauss syndrome	Severe cortico-dependent asthma	Significant eosinophilia (>1,500)	p-ANCA
Wegener syndrome	Sinusitis, otitis Nasal deformation—saddle nose		c-ANCA
Micropolyangitis	Pneumo-renal syndrome		p-ANCA
Cryoglobulinemia	Purpura Raynaud's syndrome	C4 consumption High CRP + low SR	Cryoprecipitate HVC serology
Periarteritis nodosa	Livedo racemosa Ulcers No pulmonary involvement		No ANCA HBV serology

C4 complement fraction 4; *CRP* C-reactive protein; *ANA* anti-nuclear antibodies; *PM* polymyositis; *DM* dermatomyositis; *Gottron* purple eruption on the webs of the fingers sparing the joints; *APS* anti-phospholipid syndrome; *CAPS* catastrophic APS; *TMA* thrombotic microangiopathy; *pathergy test* hypersensitivity at 48 h to puncture points revealed by an intradermal reaction with saline; *ANCA* anti-polynuclear neutrophil cytoplasmic antibodies; *HBV and HVC* hepatitis virus B and C; *SR* sedimentation rate

Table 2 Aetiologies of diffuse-alveolar hemorrhage and/or pneumo-renal syndrome

Systemic lupus erythematosus
Micropolyangitis
Churg-Strauss syndrome (eosinophilic granulomatosis with polyangeitis)
Wegener syndrome (granulomatosis with polyangeitis)
Goodpasture syndrome
APS
Cryoglobulinemia
Rheumatoid purpura
Thrombotic microangiopathy
Sarcoidosis
SD with renal failure causing cardiogenic pulmonary oedema
Pulmonary infections complicating SD responsible for acute renal failure

recent initiation of oestroprogestative contraception or recent pregnancy (lupus), history of repeated miscarriages or thromboses (APS). Epidemiologically, these patients are usually young, with a female predominance for autoimmune connective tissue diseases. The next step is diagnostic confirmation of the SD. This depends on blood tests and histological documentation.

For connective tissue diseases, the key investigation is the demonstration of anti-nuclear antibodies (ANA) whose absence makes the diagnosis unlikely. In contrast, their presence has only low specificity (ANA are frequently positive under several medications) and requires investigations for anti-DNA antibodies (lupus) and anti-ECT (or ENA) antibodies: Sm (lupus), SSA and SSB, RNP, Scl70 and centromere (scleroderma), Jo1 and other myositis-specific autoantibodies.

The detection of anti-cardiolipin antibodies and circulating lupus anticoagulant (the latter being interpreted in the absence of heparin) are necessary biological criteria to confirm the diagnosis of APS (ideally one of the two on two occasions, 12 weeks apart).

In systemic lupus, the presence of hypocomplementaemia (CH50, C3 and C4) is additional evidence which can be obtained rapidly. In the case of renal involvement, a kidney biopsy is necessary to confirm the diagnosis of lupus nephritis and to determine its prognosis. These biopsies are often difficult to obtain because it is necessary to position the patient in strict ventral decubitus with control of respiration. In the context of ICU patients, kidney biopsies can be guided by echography or tomodensitometry or in the case haemostasis/coagulation abnormalities, transjugular biopsy is an alternative, although the quantity of renal material obtained is often smaller. Morbidity of this procedure in the ICU context seems to be acceptable with high diagnostic and therapeutic contributions.

In myositis, magnetic resonance imaging (MRI) can guide a muscle biopsy, carried out in the quadriceps or the deltoid.

For vasculitis, positivity of anti-polynuclear neutrophil cytoplasmic antibodies (ANCA) facilitates the diagnosis. Immunofluorescence (IF) reveals either perinuclear (p-ANCA) or cytoplasmic (c-ANCA) fluorescence. The antigenic target is then specified by ELISA: proteinase 3 (PR3) for c-ANCA and myeloperoxidase

(MPO) for p-ANCA. The absence of ANCA does not eliminate the diagnosis of vasculitis, especially for micropolyangitis (MPA) or Churg-Strauss (CS) syndrome where p-ANCA are present in approximately 70 and 40 % of cases, respectively. Positivity for c-ANCA is quite specific for granulomatosis with polyangeitis (formerly Wegener's disease) and may allow postponement of a risky biopsy (e.g. renal). Conversely, it is not unusual to observe false-positive ANCA (often discordant IF and ELISA) in an infectious or toxic context (endocarditis, cocaine). Biopsy of the temporal artery is a minimally invasive procedure, usually performed to confirm the diagnosis of giant cell arteritis, but which sometimes enables the diagnosis of necrosing vasculitis. An electromyogram can confirm peripheral neurological involvement and/or guide a possible neuro-muscular biopsy. These two examinations rule out the differential diagnosis of a critical illness polyneuropathy. Finally, the detection of cryoglobulinaemia is a lengthy process (>1 week) and presents many technical difficulties which lead to the repetition of this test if there is a strong suspicion (3 consecutive days). Low levels of C4 (with normal levels of C3) and positivity for rheumatoid factor are indirect clues in favour of a cryoglobulinemic vasculitis (CV) and are easier to obtain. Finally, the aetiological assessment of CV should include the search for certain viruses (HIV, HBV, HCV, parvovirus B19) because the treatment can be radically different.

Overall, the clinical picture of a SD usually includes the involvement of several organs (Fig. 1) for which the usual aetiological investigations are negative. In addition to investigations for rarer infectious agents or neoplasia, it is necessary, faced with this clinical picture, to know how to evoke and diagnose an autoimmune SD. First-line biological assessment rapidly strengthens the suspicion. The SD is then confirmed histologically.

Management of a Severe Flare of a Systemic Disease in the Intensive Care Unit

The intensivist who has to manage a patient with an already diagnosed and treated SD, irrespective of the organs involved, should ask only one question: "Is it a flare-up of the SD or a concurrent complication (infectious, iatrogenic)"? Diagnosis is complicated by the frequent presence during a SD of a fever, a biological inflammatory syndrome with a clear increase in CRP (except in the case of lupus where an elevation in serum CRP is only observed in cases of seritis or infectious complications) and unavoidable delays in obtaining the results of blood cultures and immunological investigations. Assessment of the procalcitonin level (PCT) may seem useful to differentiate some infections (particularly bacterial) from SD flares (where PCT is normally negative). However, this PCT-based approach is limited both by false-negatives ("localized" bacterial infections with negative plasma PCT) and false-positives (increase in PCT in hemophagocytic

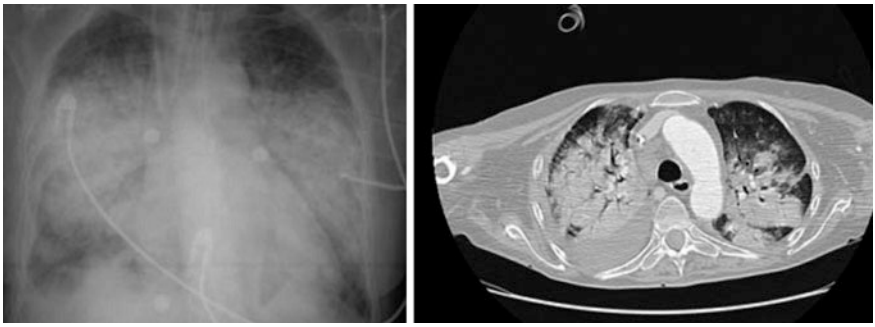

Fig. 1 Systemic disease visualised by thoracic radiography (*left*) and a thoracic scan (*right*)

lymphohistiocytosis syndrome and/or Still's disease) [2]. Furthermore, it is not uncommon to observe the simultaneous occurrence of a SD flare and a concurrent infection. Indeed, one of the possible factors triggering the flare of an autoimmune disease can be an infection. Conversely, a flare-up of the disease could transiently lead toward increased immunosuppression and favour the occurrence of an opportunistic infection. The infections encountered are extremely varied and depend on the disease, the intensity and the nature of the immunosuppressive treatments used. The risk of developing opportunistic infections is not well correlated with the extent of lymphopenia, and pneumocystis prophylaxis is often proposed in patients who receive treatment with cyclophosphamide, irrespective of the results of their TCD4+ lymphocyte count. In the case of respiratory manifestations, the differential diagnosis depends on obtaining broncho-alveolar lavage (BAL) with cytological analysis of alveolar fluid (investigations for intra-alveolar haemorrhage with Perls staining; polynucleosis points to an infectious process or a predominance of lymphocytes may indicate a flare-up of the disease). The microbiological analysis of BAL should be extensive (BK culture and PCR, *Pneumocystis jirovecii* PCR, CMV PCR, HSV culture and PCR, galactomannan *Aspergillus* level, panbacterial 16S PCR, etc.) and associated with serological investigations (aspergillus galactomannan, pp65 antigenaemia and quantitative CMV PCR, serology for atypical germs).

In the case of an unfavourable respiratory evolution, BAL performed for sucsipion of an opportunistic infection should be repeated ideally after stopping all anti-infective treatments for 48–72 h. When several repeated BAL remain negative, or when the respiratory parameters deteriorate (decrease in lung compliance may suggest a process of fibrotic scarring), or when no diagnosis is established, an open lung biopsy should be performed rapidly by a surgeon at the patient's bedside. The risk of complications is low (<5 %) and the benefits in terms of diagnostic and therapeutic impact are important [5]. It may give information that is not obtained from other specimens, often of a nature to radically change the therapeutic management such as the addition of antiviral treatment when cells exhibiting the characteristic cytopathogen effect of herpes viruses are observed. Corticotherapy

should be started when interstitial or endo-alveolar fibrosis is observed. The recent aspect of fibrosis can also predict the response to corticotherapy. Finally, histologic studies can, in some cases, confirm the diagnosis of a SD. When lung biopsy is contra-indicated, suspicion of post-aggressive lung fibrosis may be approached in the future by high levels of procollagen 3 either in blood or in BAL samples.

The "best timing" for deciding when to transfer a patient to the ICU is difficult to codify. These patients are usually heavily immunosuppressed by the disease itself and particularly by the treatments for the SD. A rapid unfavourable evolution is often observed, leading to transfer to an ICU when organ failure is already present. In that situation, there is no place for sequential treatments and the mechanically-ventilated patient receives both broad-spectrum anti-infective treatment and salvage corticotherapy. In some cases, it may therefore appear more judicious to admit the patient to the ICU before respiratory deterioration and to carry out an early BAL without waiting for failure of first or second-line anti-infective treatments. Fiberoptic bronchoscopy under noninvasive ventilation with mild sedation can be safely performed in the ICU even in severe hypoxemic patients.

Conventional ventilation (with orotracheal intubation) is responsible for over-mortality due to infections and barotrauma, notably in Wegener's disease where spontaneous pneumothorax has been reported.

Once the diagnosis of a flare-up of SD has been established, the question of the prognosis and treatment arises. The prognosis in IC is not evaluated using specific scores (e.g. Five Factor Score for vasculitis), but relies on the scores developed by intensivists (e.g. SAPS II, SOFA scores). Nevertheless, it is important to determine the severity of the flare-up using paraclinical and histological tools. It is not unusual that, for technical reasons (mechanical ventilation, haemostasis, etc.), some biopsies are delayed or even cancelled as the benefit-risk ratio of these investigations is unfavourable. The most manageable treatment remains intravenous corticotherapy (methylprednisolone) usually administered in the form of a bolus (500–1000 mg), for 1–3 consecutive days, and followed by corticotherapy at 1–2 mg/kg in more severe cases. Corticotherapy is often well tolerated (when infusions are not shorter than 30 min). However, rapid initiation of immunosuppressive treatment is required in more severe forms of SD (notably, lupus and vasculitis). The treatment of choice is cyclophosphamide (endoxan) used at a dose of 0.5–0.7 mg/m^2 according to protocols dependant on the SD as well as age and/or renal function. Endoxan is readministered every 2–4 weeks with monitoring of blood counts and prevention of organ toxicity by hyperhydration and/or Mesna (Uromitexan®). Due to the high frequency of anaphylactic reactions reported with Mesna in autoimmune conditions and its non-superiority compared to hyperhydration alone, it appears prudent to reserve this drug for patients in whom hyperhydration is problematic due to a high risk of fluid overload. In the case of suspected or proven infection concomitant to the flare-up, there are few alternatives. The use of monthly IGIV in the case of systemic vasculitis appears to be a good transient solution before resuming, as soon as possible, classical immunosuppressive therapy [3]. Rituximab (a monoclonal anti-CD20 inducing the

selective depletion of B-lymphocytes) may be another alternative in these "high risk" infectious situations. Recent data for the induction of SD remission (especially during ANCA vasculitis) are encouraging, but the infectious risk of this biotherapy may be underestimated. It is important to discuss the initiation of such treatments with centres of expertise and/or reference for these SD. Finally, "older" therapies merit the attention of the intensivist. Enzyme-conversion inhibitors are the drugs of choice to manage sclerodermic renal crises, which affect the prognosis of patients. Of note, corticotherapy greater than 15 mg/day is not advised in sclerodermic patients because this treatment could favour the development of renal crises. Plasma exchanges used in cases of thrombotic microangiopathy (lupus and/or APS) also appear to be interesting for the treatment of Goodpasture syndrome (notably intra-alveolar hemorrhages) and improve the renal prognosis of vasculitis with severe renal failure (>500 μmol/L). It should be noted that if, for infectious reasons, the usual corticoid treatment of the patient is interrupted on admission, the intensivist should prevent the development of acute adrenal failure by administering 100–200 mg of hydrocortisone/day until the resumption of corticosteroids.

It should also be noted that the detection of pregnancy by measuring βHCG levels is essential in SD like lupus (triggering factor) and for which detection will affect the choice of treatment (only corticoids, azathioprine, cyclosporine, antimalarials and IVIG are theoretically allowed during pregnancy).

Institution of Supportive Treatments in Intensive Care

Except for scleroderma and forms of autoimmune myositis associated with aggressive pulmonary fibrosis (and/or underlying neoplasia), SD are diseases in which the damage to the organs is usually reversible. From an organ perspective, early initiation of immunosuppressive treatment is crucial to avoid long-term sequelae and loss of function following repeated flare-ups. Patients affected by SD are usually "young" and the fact that most inflammatory lesions are reversible in these patients justifies maximum investment in terms of supportive treatments initiated by the intensivist while waiting for remission. Even in scleroderma or other SD with irreversible pulmonary fibrosis, lung transplantation remains an option because the one-year survival rates are comparable to those of transplanted non-sclerodermic patients There may be a long delay after registration on a non-priority transplantation list and it may be peppered with episodes of nosocomial infection in ventilated patients (bacterial and/or viral).

Acute respiratory failure is the most frequent type of organ failure. Diffuse alveolar hemorrhage (DAH) is responsible for hypoxaemia via a shunt effect. The presence of hypercapnia is the sign of respiratory muscles exhaustion or the existence of a dead-space effect related to micro-thrombi within the pulmonary circulation. Hypoxaemia and/or hypercapnia should lead to a first trial of NIV. Apart a hemostatic effect of positive pressure by NIV, an improvement of oxygenation is expected in DAH whereas it is very inconstant in pulmonary

fibrosis or interstitial infectious disease. It is therefore the evolution of the patient after 1–2 h of NIV that determines continuation of respiratory assistance. If NIV is not well tolerated the use of high flow humidified oxygen therapy way be an alternative. If polypnoea or hypoxaemia persist, the decision to use invasive mechanical ventilation should be made without delay. This will enable BAL to be obtained under good conditions and will reduce oxygen consumption linked to respiratory muscle work. Finally, injuries of the pulmonary parenchyma often lead to worsening or *de novo* pulmonary hypertension.

Aggravation of preexisting pulmonary arterial hypertension (PAH) may lead to refractory hypoxaemia or right ventricular failure, which is particularly prejudicial in this context. The development of acute dilation of the right ventricle leads to acute renal failure and worsens the prognosis of the patient (related mortality of 50 %). Monitoring of pulmonary arterial pressure (PAP) and right ventricular (RV) function is therefore essential in this situation. The pulmonary arterial catheter (PAC) is still the reference tool. However a non invasive and prompt evaluations of PAP and RV function can be easily performed by Trans Thoracic Echocardiography or better in case of mechanical ventilation by Trans Oesophageal Echocardiography. From a therapeutic perspective, the existence of threatening PAH justifies the use of vasodilator treatments. The effect of these drugs is recommended under PAC monitoring. Inhaled nitric oxide (NO) leads to stimulation of GMPc in the smooth muscle cells of the pulmonary capillaries and ensures selective vasodilation in the ventilated areas. If a decrease is observed, the dose of NO should be reduced progressively in order to obtain the minimum dose necessary. If NO is stopped suddenly, there could be a rebound effect. Other classes of drugs are available but only in a galenic oral form. Sildenafil (Revatio®) is a selective inhibitor of phosphodiesterase V. It causes pulmonary vasodilation but also peripheral vasodilation responsible for hypotension 15–30 min after administration. It can be administered via a gastric probe in the ICU at a dose of 20 mg, three times a day. This can be considered as a treatment for the acute phase of PAH but it is not recommended for ARDS. In contrast, Bosentan (Tracleer®), whose mode of action is selective antagonism of the receptors for endothelin-1, is considered more as long-term treatment (delay in action of 4–6 weeks). Stopping this latter drug may be associated with pulmonary hypertensive rebound. It is logical therefore to continue Tracleer® via a gastric probe at the full dose (125 mg twice/day). The administration of prostacyclin (Iloprost®) intravenously or as an aerosol is expensive but offers an alternative solution. Intravenous form of some of the oral drugs mentioned above might be soon available.

Finally, in the case of right ventricular failure that is refractory to vasodilators and to inotropes (dobutamine) and/or refractory hypoxaemia, Extracorporeal Corporeal Membrane Oxygenation (ECMO) may be justified. For a predominantly pulmonary attack (hypoxaemia-hypercapnia), veno-venous ECMO with a centrifugal pump is indicated. Venous-arterial ECMO is indicated when left ventricular failure is associated. RV failure alone secondary to hypoxemia-hypercapnia is not a contra-indication for VV ECMO since after correction of hypoxemia-hypercapnia, pulmonary arterial pressure should drastically decrease. In this situation, ECMO is

only a temporary replacement technique while waiting for either remission from the flare-up after a bolus of an immunosuppressive drug or a bridge to lung or heart–lung transplant. Control of anticoagulation will be particularly difficult due to the quasi-constant thrombopenia and frequent thrombopathy. For this reason, veno-venous assistance is preferable because it does not require anticoagulation at a curative dose. In all cases, the decision to initiate ECMO should be discussed collectively taking into account a number of factors such as the patient's age, number of failing organs, level of platelets and the therapeutic perspectives. When the patient is already on a transplant waiting list, the situation may be revised and the status of the patient changed to a "super-emergency", always in consultation with a specialised multi-disciplinary team. Of course, the early transfer of these patients to a reference centre capable of carrying out an emergency lung transplant is desirable. Furthermore, ECMO can be performed before out of hospital transfer with a specialized mobile team.

Conclusion

In conclusion, dialogue should be encouraged between specialists in autoimmune SD (internists, nephrologists, etc.) and the intensivists who manage SD patients during the most dangerous periods in their disease. The intensivist should know how to evoke a diagnosis of SD. When the diagnosis is already established, the role of the intensivist is to ensure the temporary replacement of vital functions while waiting for the effects of immunomodulatory treatments. The intensivist should be particularly vigilant in the detection and management of infections that are often atypical, severe and may occur simultaneously with the flare-up of the SD. Finally, the intensivist is the central spokesperson among the different specialists in these diseases. In this context, discussions with referent centres should take place daily. An integrative diagnostic and therapeutic approach is proposed to guide the intensivist in this management (Fig. 2).

Three successive steps can be distinguished (which can be performed at the same time) with diagnostic (positive and differential) and therapeutic (specific and symptomatic) goals. The first step is principally diagnostic: investigations for auto-antibodies should be requested urgently (telephone call to the immunologist) and after 24–48 h, particularly if auto-antibodies are negative, an extrapulmonary biopsy should be discussed. At this step, procalcitonin (PCT) and bronchoalveolar lavage (BAL) cytology may help. At 48–72 h, the microbiological results of BAL (bacterial and viral culture, PCR) will allow adaptation of anti-infective treatment initiated at admission due to the severity of the illness. At the end of this first week, if the diagnosis of SD is not established, a lung biopsy should be discussed. When a diagnosis of SD has been made specific immunosuppressive treatment with cyclophosphamide should be initiated in the absence of an uncontrolled infection. While waiting for improvement, symptomatic measures (NO) may enable the patient to get over the hypoxaemic peak. In the case of an unfavourable evolution,

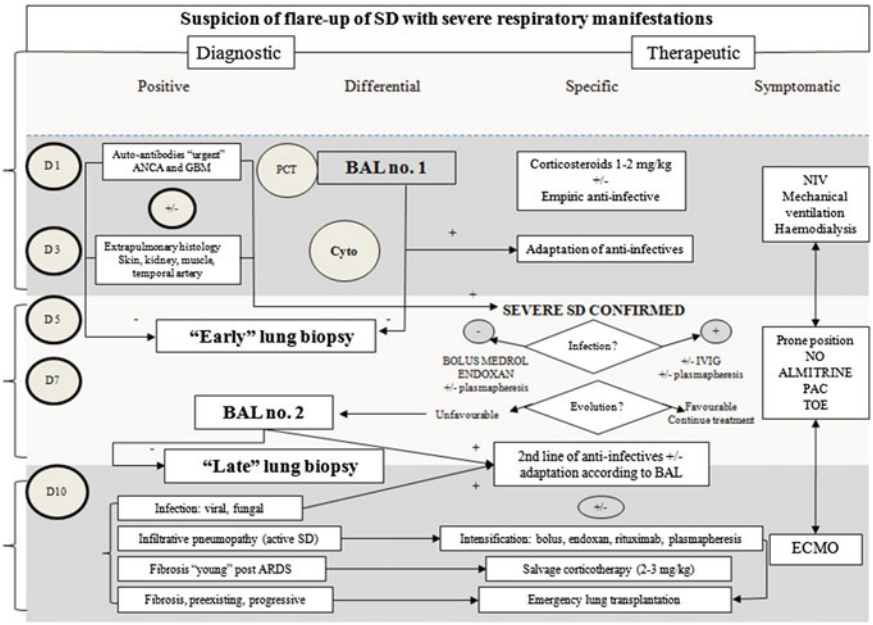

Fig. 2 Management of a probable systemic disease (SD) with severe respiratory manifestations

a final "salvage" step should be undertaken in which treatment will be at best "guided" (BAL and/or lung biospy). While waiting for the results of these investigations and/or the effect of the new therapies initiated, ECMO may be justified in the case of expected reversibility and/or a foreseeable lung transplant.

References

1. Cervera R, Font J, Gómez-Puerta JA et al (2005) Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 64:1205–1209
2. Hausfater P (2007) Procalcitonin measurement in adult clinical practice. Rev Med Interne 28:296–305
3. Martinez V, Cohen P, Pagnoux C et al (2008) Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a mul-ticenter, prospective, open-label study of twenty-two patients. Arthritis Rheum 58:308–317
4. McGonagle D, McDermott MF (2006) A proposed classification of the immunological diseases. PLoS Med 3:e297
5. Papazian L, Doddoli C, Chetaille B et al (2007) A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. Crit Care Med 35:755–762

Mitochondrial Diseases

Djillali Annane and Diane Friedman

Key Points

- Abnormalities of DNAmit or DNAncl genes encoding for the respiratory chain.
- Clinical features include a broad variety of symptoms and involved multiple organs/tissues—past history of mitochondrial disorders in the family is frequent.
- Multiple tissues should be sampled and when negative testing should be repeated.
- No specific treatment is available.

Introduction

Mitochondrial diseases are among the most common metabolic disorders. These diseases are caused by defect in genes encoding for proteins of the mitochondria respiratory chain, including transport RNA, ribosomal RNA, or transport proteins. Epidemiologic data for mitochondrial diseases are scarce. A recent study suggested mutations in mitochondria DNA occurred in 12.5 per 100,000 in-habitants [1].

D. Annane (✉) · D. Friedman
General Intensive Care Unit, School of Medicine Simone Veil, Raymond Poincaré Hospital (AP-HP), University of Versailles SQY, 104 Boulevard Raymond-Poincaré, 92380 Garches, France
e-mail: djillali.annane@rpc.aphp.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_14,

Genetics

Genetic abnormalities that characterised mitochondrial diseases have major influence on the clinical phenotypes and potential therapeutics.

The mitochondrion is an intracellular element of the cells, and includes in its inner membrane the respiratory chain that produced ATP the essential energetic source for life.

Human cells have hundreds of mitochondria. Each mitochondrion has several copies of mitochondrial DNA (mitDNA). Therefore, a cell can have simultaneously normal mitDNA and mutants [2]. This phenomenon is known as heteroplasmy. During cells' divisions, mutations occurred at random within a single organ, according to the mitotic segregation. The phenotype is proportional to the number of mutants in each tissue. Usually, the disease becomes phenotypically obvious when they are at least 80 % of mutants [2].

Another specific characteristic is that the proteins of the respiratory chain can be encoded by genes either from the mitDNA (13 different genes) or from the nuclear DNA—nclDNA (hundreds of different genes). Abnormalities in mitDNA accounted for by 20 % of mitochondrial diseases. They are of maternal transmission whereas nclDNA abnormalities are of mendelian, autosomic or recessive, X-linked or not. Finally, the mitDNA is more subjected to mutations than the nclDNA, and is less able to repair itself [3]. These genetic specificities explain the huge phenotypic heterogeneity and subsequently diagnostic and therapeutic problems.

Pathophysiology

The respiratory chain that produces ATP is made of 5 enzymatic complexes and 2 mobile electrons: the co-enzyme Q10 (CoQ10) and the cytochrome c [1]. The mitochondrion also plays a catabolic role [4] by oxidizing free fatty acids (Beta-oxydation), carboxylic acids (Krebs cycle) and amines acids. ADP is transformed into ATP via oxidative phosphorylation and oxygen consumption in a series of enzymatic reactions.

(1) *Glycolysis* [3]:
In a first step, glucose is being changed into pyruvate and then into acetylCoA by the pyruvate dehydrogenase (PD). Subsequently, acetylCoA is changed into NADH, utilized to produce ATP. PD is blocked via negative feedback from NADH, acetylCoA, ATP and anaerobic conditions. Then, pyruvate is accumulated and metabolized into lactate and alanine. In case of abnormal glycolysis, a meal containing to much sugar will cause hyperlactatemia and may worsen the clinical symptoms of the mitochondrial disease (Fig. 1).

(2) *Oxydation of free fatty acids* [3]:
Beta-oxydation of free fatty acids occurs during fasting. Fatty acids combined to carnitine result in acylcarnitine, which is metabolized into ACoA and FADH2 that helps producing ATP. In fasting conditions, ACoA is metabolized in betahydroxybutyrate, main energetic source for the brain. By contrast, with food intake, ACoA results in NADH.

Beta-oxydation is inhibited by carnitine deficiency and enhanced by a fatty acid enriched meal or a sustained exercise. Then, during fasting, symptoms may worsen in people with abnormal catabolism of fatty acids (Fig. 2).

(3) *Oxydative phosphorylation* [3]:
Oxydative phosphorylation occurs in the 5 complexes of the respiratory chain. NADH is the substrate for complex I (NADH-CoQreductase), and FADH2 for complex II (succinate-CoQreductase). Complexe III is ubiquinone-cyt c reductase, complex IV is cyt c oxydase, and complex V is ATPase. Electrons transfer from complex I or II to other complexes induces a protons gradient. Complex V produces ATP by coupling ADP transformation to the protons' gradient (Fig. 3).

Diagnosis

(1) Cases *reports from the general intensive care unit at Raymond Poincaré Hospital*:
Mr. DL, 31 years-old, member of the hospital staff, was admitted to the ICU for sepsis. He has no past medical history. His sister had motor disability and died prematurely. His young brother was diagnosed with multiple sclerosis presenting with optic neuropathy, cerebellar syndrome, pyramidal syndrome and erectil disorders. His twin brother was also diagnosed with optic neuropathy. Upon ICU admission, urinary tract infection was identified as the source of sepsis. Further investigations allowed establishing the diagnosis of neurological bladder, hydrocephalus, optic neuropathy, altered evoked somesthesic potentials, increased protein levels in the cerebrospinal fluid, increased levels of pyruvate with normal lactate levels and normal pH. Spine MRI was normal. Over the next decade, the patient needed permanent urine drainage by enterocystoplasty, had serial stroke with major deterioration in cognitive function severe motor disability. He also developed a hypertrophic cardiomyopathy. Muscle biopsy found severe Cox mosaic deficit and combined deficit of the respiratory chain.

A 32 years-old man, ingenior in computer science, with no past medical history was admitted to the ICU. His mother died at the 25 years old from a cardiac origin. His grand mother was diagnosed with myopathy and liver disease. The patient presented with progressive fatigue, dyspnea and muscles cramps. Upon admission, liver transaminases were increased by fivefold from normal values, lactate levels were 8 mmol/L and bicarbonate levels were 14 mmol/l. Electromyography recorded muscles abnormalities. Muscle biopsy found normal respiratory chains

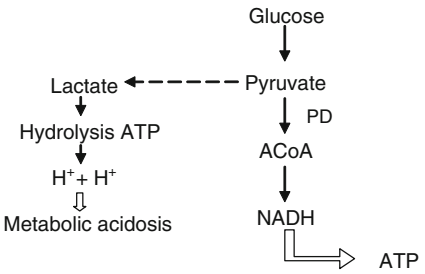

Fig. 1 Glycolysis

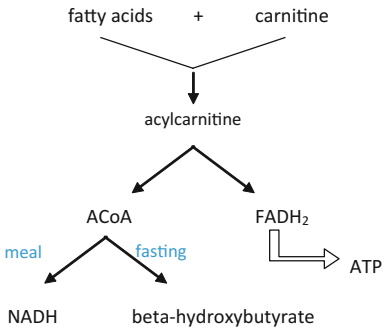

Fig. 2 Oxydation of free fatty acids

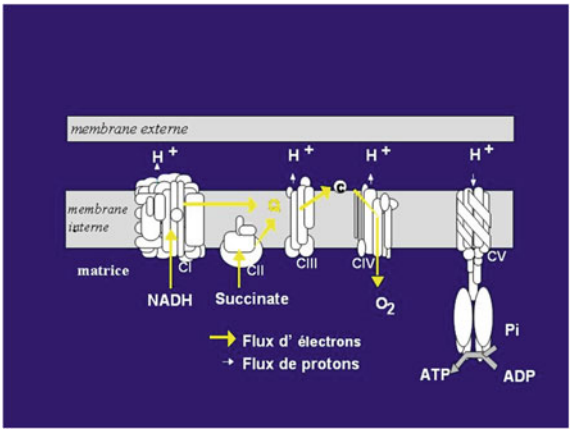

Fig. 3 The mitochondrial respiratory chain

and major lipid vacuolization. Muscle MRI was normal. The chromatography of urines found normal levels for amines acids and carnitine, increased levels for alanine, isoleucine, and decreased levels for citrulline. Initial treatment included L carnitine, bicarbonate and CoQ10. Few weeks later, the patient is re-admitted to the ICU with tetraparesis and severe lactic acidosis (pH: 6,86, pCO2: 1,96 kPa, PO2: 14 kPa, CO2total: 3 mM, lactates: 20 mM), rhabdomyolysis (CPK: 7 N), renal insufficiency and myoglobinuria. EKG recorded a right branch block. The patient presented with acute respiratory failure and was intubated and mechanically

ventilated. Treatment also included renal replacement therapy. The patient clinical status improved and was maintained stable with bicarbonate perfusions. Oxydation of fatty acids was investigated on lymphocytes and was found normal as well as the ratio betahydroxybutyrate/acetoacetate. Resting energetic expenditure was high. Muscle MRI remained normal. The analysis of the respiratory chain revealed a complex IV deficit in muscles, fibroblasts and lymphocytes, and a complex III deficit in hepatocytes. We finally identified a new mutation in leucine RNAt gene.

The genetic specificities of mitochondria can result in a broad variety of clinical phenotypes. Physicians should consider mitochondrial disorders in conditions of multiple organ dysfunction with unclear origin.

(2) *Main Clinical findings* [3]:

- Eyes: ptosis, ophtalmoplegia, optic nerve atrophy, *retinis pigmentosa*, cortical blindness, cataract
- Central nervous system: epilepsy, ataxia, stroke more specifically in occipital and parietal regions, psychosis, dementia, cognitive dysfunction, peripheral neuropathy, migraine
- Heart: obstructive or non obstructive cardiomyopathy, congestive heart failure, conduction blocks
- Muscles: weakness, fatigue, intolerance to exercise
- Skin: dry hair, abnormal pigmentation of exposed skin areas, tricothidystrophy
- Kidney: tubular acidosis, myoglobinury, renal failure
- Thorax: dyspnoea, acute or chronic respiratory failure, hypoventilation, diaphragmatic paralysis, restrictive syndrome, abnormal accessory expiratory muscles; difficulties to wean off mechanical ventilation, prolonged paralysis following curare administration, respiratory failure following minimal use of benzodiazepines or barbiturates, unexplained lactic acidosis, central and obstructive sleep apnoeas, altered response to CO2.
- Digestive tract: non-specific digestive disorders, pancreatic insufficiency
- Ears/Nose/throat: dysphagia, dysphonia, dysarthria, hearing loss
- Endocrine system: diabetes, hypothyroidism, hyperparathyroidism

(3) *Clinical phenotype in relation with age* [5]:

- Neonates: multiple organ failures, hypotonic, coma, myopathy. The disease is commonly autosomic recessive, affecting nuclear DNA.
  - BARTH Syndrome: boys with cardiomyopathy, neutropenia, proximal deficit, dwarfism
  - Toni-Debré-Fanconi Syndrome: proximal tubulopathy
- Young children (1 month—2 years):
  - LEIGH Syndrome: necrotizing encephalomyopathy, brain stem lesions, psychomotor retardation, pyramidal and extra pyramidal syndrome, epilepsy, optic atrophy, respiratory failure
  - ALPERS Syndrome: progressive polydystrophy, liver disease

  - PEARSON Syndrome: anaemia, neutropenia, thrombopenia, pancreatic insufficiency
  - WOLFRAM Syndrome: Diabetes, SIADH, optic atrophy, hearing loss
- Teenager and adults:
  - KEARNS-SAYRE Syndrome: progressive external ophtalmoplegia, *retinis pigmentosa*, ptosis, myopathy, cardiac conduction abnormalities, cerebellar syndrome, diabetes, hypoparathyroidism
  - MNGIE Syndrome: *Myoneurogastrointestinal encephalopathy*: pseudo-occlusions, myopathy, ptosis, ophtalmoplegia, peripheral neuropathy, leuco encephalopathy
  - MELAS Syndrome: *mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes*: vomiting, migraine, dementia, cardiac conduction abnormalities.
  - LHON Syndrome: *Leber hereditary optic neuropathy*: brutal blindness, bilateral optic atrophy, arrhythmia
  - NARP Syndrome: *neutrogenic ataxia retinis pigmentosa*: epilepsy, mental retardation and dementia
  - MERRF Syndrome: *myoclony epilepsy with RRF*: ataxia
  - CoQ10 deficiency: exercise intolerance, axial and proximal weakness, epilepsy, cerebellar syndrome, ataxia, mental retardation, myoglobinury, pyramidal syndrome

Symptoms may usually worsen with heat or cold, drugs (e.g. propofol, ciclosporine, aspirine, cocaïne, catecholamines, theophilline, metformine, valproïc acid, phenobarbital), stress, infections, sport, fasting, alcohol, age (by increasing mutations).

Laboratory investigations

(1) *Blood samples*: increase in lactate levels, in ratio lactate/pyruvate and betahydroxybutyrate/oxaloacetate, in CPK levels, in ketone acids. The levels for the following variables should be obtained: pyruvate, alanine, acylcarnitine, glucose, free fatty acids.
(2) *Cerebrospinal fluid*: increase in protein and lactate levels
(3) *Urine* (*collected over* 24 h): measurement of lactate, pyruvate, glucose, phosphate, amines acids
(4) *Pulmonary function testing*: normal or reduced VEMS, tidal volume, maximum expiratory and inspiratory pressures.
(5) *EMG*: normal or muscular abnormalities
(6) *At exercise*: reduced oxygen comsumption and increased in lactate and inorganic phosphate (Pi) levels
(7) *Muscles and brain MRI Spectroscopy*: in vivo studies, before and after exercise, measurement of phosphocreatine (PCr), ADP and Pi, as a surrogate

of oxydative phosphorylation. In mitochondrial disorders, the main findings include decreased PCr at rest and at stress, and delayed normalization following exercise.

(8) *Muscle biopsy*: can be normal. Common findings included Ragged Red fibers, corresponding to abnormal mitochondria at the periphery of muscles fibers that can be recognized by the trichrome Gomori coloration. One can also observe lipid vacuolization, negative Cox fibers (non reactive in presence of c oxydase). Examination by electron microscopy shows abnormal giant mitochondria with abnormal crystal droplets and para-crystalline inclusions.

(9) *Enzyme activity*: needs fresh muscles fragments to measure the oxygen consumption by each complex. The global activity of complexes can also be measured from frozen samples of muscles, liver, heart.

(10) *Genetic analysis of mitochondrial DNA*: conducted on muscles or leucocytes, uses commonly in situ hybridation technics of part or the whole mitochondrial genome. As leucocytes are subjected to fast cell division and mutants DNA are scarce, genetic analysis can be falsely negative and therefore should be repeated several times on different samples from different tissues.

Decision Tree

See Fig. 4 [3].

Treatment

There is in most cases no specific treatment.

(1) *General advices*:
Patients need to avoid fasting, exposure to cold, drinking alcohol, drugs, parenteral nutrition. Regular aerobic exercise improves the oxidative metabolism and ATP production. Thus, it may improve tolerance to exercise.

(2) *Symptomatic treatments*:
May include: (1) serial transfusions in case of severe anemia, (2) cardiac pacemaker in cases of high degree cardiac conduction abnormalities, (3) heart transplantation, (4) bicarbonate perfusions in cases of severe lactic acidosis with bicarbonates levels <15 mmol/l, (5) anti-epileptic drugs except valproic acid in combination with L carnitine, (6) cochlear implant, (7) renal replacement therapy in case of renal failure and/or severe acidosis.

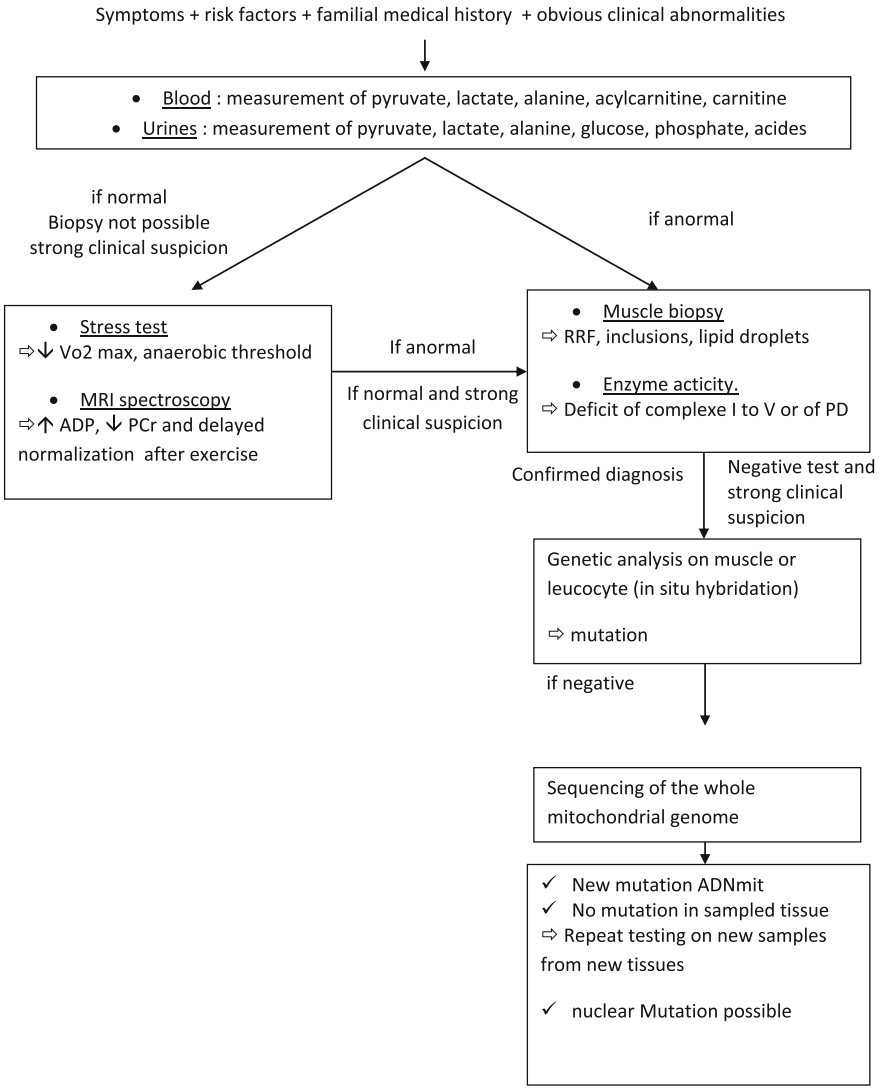

Fig. 4 Decision tree: Symptoms + risk factors + familial medical history + obvious clinical abnormalities

(3) *Specific treatments*:
May include: (1) carnitine, (2) idebenone, a CoQ10 analog, in case of quinone deficit such as in Friedreich ataxia, (3) CoQ and riboflavine may improve cereballar syndrome, (4) dichloroacetate (DCA) inhibits the PD, and reduces lactate production.

(4) *Gene therapy*:
In vitro technics may allow correction of some DNA mutations.

Antenatal diagnosis

Can be proposed when a familial history of mitochondrial disorders is known. The tests are performed at 9–11 AW and on amniocytes on culture at 16 AW. As only 50 % of fibroblasts may express the deficiency, a normal result should not rule out the diagnosis and should prompt repeated analyses.

Lexicon

ACoA: Acetyl coenzyme A. DNAncl: nuclear DNA. DNAmit: mitochondrial DNA. ADP: adenosine diphosphate. ATP: adenosine triphosphate. DCA: dichloroacetate. FADH2: flavine adenine dinucleotide. NADH: nicotinamide adenine dinucleotide. Pi: inorganic phosphate. PCr: phosphocreatine. PD: pyruvate dehydrogenase.

References

1. DiMauro S, Bonilla E (1991) Mitochondrial encephalomyopathie. widespread tissue distribution of a tRNALeu(UUR) mutation in the mitochondrial DNA of a patient with MELAS syndrome. Neurology 41(10):1663–1665
2. Jeanpierre M, Jonveaux P, Lacombe D (2004) Génétique médicale, formelle, chromosomique, moléculaire, clinique. Collège national des enseignants et praticiens de génétique médicale Ed Masson, Paris, pp:184–192
3. Clay AS, Behina M, Brown KK (2001) Mitochondrial disease: a pulmonary and critical care medicine perspective. Chest 120:634–648
4. Rustin P, Chretien D, Gerard B (1996) Biochemical and molecular investigations in respiratory chain deficiencies. Clin Chim Acta 228:35–51
5. Philip N (2002) Les cytopathies mitochondriales. Serveur pédagogique université de médecine de Marseille, Marseille Avril 2002

Part VII
Hematological Diseases

Hemolytic Anemias Resuscitation in Adults

Régis Costello and Violaine Bergoin-Costello

Key Points

- The diagnostic of the origin of the hemolytic anemia is of pivotal importance since treatment greatly varies depending on the etiology.
- Personal and family history are central to the diagnosis of hemolytic anemia due to the existence of congenital origins in some patients.
- Diagnosis of thrombotic thrombopenic purpura has to be performed without any delay since its spontaneous prognosis is very poor but is transformed by plasma exchange.
- Immunotherapy via anti-CD20 monoclonal antibodies is now part of the treatment of auto-immune hemolytic anemia.

Introduction

Hemolytic anemia is a rare disease, the most common form, i.e., autoimmune hemolytic anemia, has an annual incidence of 1–3 per 100,000. Hemolytic anemias are classified as constitutional (either by abnormal erythrocyte membrane or enzyme deficiency) or acquired (either by an immunological mechanism—the most common—or by a non-immunological cause). This classification is of pivotal

R. Costello
Hematology Department, Public Assistance Hospitals of Marseille & Université Aix Marseille, Marseille, France
e-mail: regis.costello@free.fr

V. Bergoin-Costello (✉)
Haemovigilance Service, Centre Hospitalier du Pays d'Aix 1, Avenue des Tamaris, 13100 Aix-en-Provence, France
e-mail: vbergoin@ch-aix.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_15,

interest in the therapeutic approach, which is adapted to each type of etiology. The diagnosis of hemolysis itself obeys the classical criteria; a regenerative anemia, often accompanied by jaundice due to free bilirubin, increased lactic-odéhydrogénase (LDH) and decreased haptoglobin level. These simple diagnostic criteria must still be analyzed accurately; the regenerative nature (increased reticulocytes) and the bilirubin need to be observed some time after the onset of hemolysis. The regenerative nature may disappear in the course of evolution by folate depletion, which blocks erythropoiesis. The distinction between intratissular hemolysis (increased LDH) and intravascular (decreased haptoglobin) is too academic in nature because often the two components are involved. Complications of hemolytic anemia can be distinguished into two components, one related to anemia and one related to the hemolysis *per se*. Complications related to hemolysis by itself are relatively rare; gallstones (in chronic hemolysis), acute renal failure (acute hemolysis) thromboembolic events (more related to immobilization and/or corticosteroid use. One exception is paroxysmal nocturnal hémoglobinuria, with very frequent thrombotic complications. Most of the severity of hemolytic anemia therefore is due to anemia more than to hemolysis.

Hemolytic Anemia with Abnormal Erythrocyte Membrane

The diagnosis of hemolytic anemias is based on a simple and rapid observation of blood smear looking for morphological abnormalities that are used for the classification, hereditary spherocytosis (Minkowski-Chauffard disease), elliptocytosis/poikilocytosis, stomatocytosis/disease permeability to cations [3]. These pathologies result most often chronic hemolysis. However, a sudden worsening the patient can be seen in two circumstances. The first is the sudden exacerbation of hemolysis, which is due to a triggering event such as infection. The treatment of triggering event, and a possible transfusion (based on very low hemoglobin level and bad anemia tolerance) will most often the patient back to his basic hematological status. A complication of chronic hemolysis may complicate the analysis of anemia and requires specific treatment. Indeed some patient can develop a transient erythroblastopenia (Owren-Gasser syndrome) related to infection with parvovirus B19, which may respond favorably to treatment with intravenous gamma globulins.

Hemolytic Anemia Enzyme Deficiency

The enzyme abnormalities leading to hemolysis are numerous and have a lot in common features with regard to clinical manifestations [5]. As an example we discuss the deficit by far the most common, namely glucose-6-phosphate dehydrogenase (G6PD) deficiency. Regarding diagnosis, examination of personal and family

history of the patient is essential. Transmission deficit is related to sex: male subjects are hemizygous and symptomatic while women are often asymptomatic heterozygotes. The interview will seek to determine a precipitating cause; ingestion of beans in the form called "favism" or other oxidative stress including many drugs such as quinolones, sulfonamides and antimalarial compounds. Confirmation of the diagnosis is based on the determination of the deficient enzyme, which has to be done at a distance of hemolytic episode because reticulocytes may have normal levels of the enzyme even in a subject with G63PD deficiency. Hemolysis may be acute after contact with the offending agent. Therapy is based on the transfusion, which is indicated in cases of severe anemia and/or in the absence of reticulocytosis, which prompt to suspect erythroblastopenia or folate deficiency.

The Nocturnal Paroxysmal Hemoglobinuria (NPH)

It is a very special entity that comes from the expansion of a hematopoietic clone containing a mutation of PIG-A gene, required for the synthesis of a lipid moiety, the glycosylphosphatidylinositol (GPI) which can be connected with multiple membrane molecules, some of which (CD55 and CD59) protects red blood cells from destruction by complement fractions [2]. Red blood cells deficient in CD55 and CD59 are very easily destroyed by complement, although the triggering events for hemolytic crises are unclear. Intravascular hemolytic crises can be very brutal and exceed the binding capacity of hemoglobin to haptoglobin, explaining hemoglobinuria. This free hemoglobin is able to bind nitric oxide which tissue depletion manifests by fatigue, abdominal pain, and probably promotes the occurrence of deep vein thrombosis (40 % of cases of NPH) in the two most common sites, i.e. the central nervous system and hepatic veins (Budd-Chiari syndrome). The diagnosis of NPH is based currently on flow cytometric analysis of CD55 and CD59 molecules on cells and cellular elements of the circulating blood. The therapeutic management has evolved recently with the use of eculizumab, a monoclonal antibody directed against the C5 complement fraction. The interest of eculizimab resides in the reduction of the incidence of hemolytic crises and thereby transfusion requirements. Regarding the haemolytic crisis itself, it seems that short-term corticosteroid therapy reduces its duration and severities, but should not be offered for long periods. The addition of androgen (Danazol) also appears to reduce hemolysis, probably by an inhibitory action on the complement cascade. The use of androgens is possible for a short duration, since long-term liver toxicity makes their use undesirable. In NPH, intravascular hemolysis and hemoglobinuria induce a loss of iron. Iron supplementation is therefore recommended in NPH patients, otherwise the patient will not be able to compensate for hemolysis by an increase in reticulocytes. Although iron intake, whatever the route used (oral or intravenous), can also exacerbate hemolysis, its use is recommended by "necessity" in association with corticosteroids and androgens. Finally, based on hemoglobin and clinical tolerance, transfusion of packed red blood cells is possible in NPH. It has been

recommended for a long time to transfuse plasma-depleted packed red cells to avoid complement activation, but this seems in fact not necessary. Finally it is necessary, during any period of hospitalization, to provide an antithrombotic prophylaxis since these patients are at high risk.

Extracorpuscular Non-immunologic Hemolytic Anemia

The aggression of red blood cells by external agents leads to its destruction [1]. A common sign of these diseases is the presence in the blood of shredded red blood cells, called schizocytes. However, these schizocytes are also found in most hemolytic anemias and thus represent a sensitive but nonspecific sign. The causes are many and classified schematically as mechanical (fragmentation), infectious or toxic. Macro-angiopathic etiologies are associated with hemolysis which is often insufficient to cause anemia. We can actually observe hemolysis on vascular or valvular prostheses and more particularly when there is a valvular dysfunction, but also due to cardiopulmonary bypass and or to repeated shocks (karate, percussionists, marathon runner). More clinically relevant is the hemolysis linked to microangiopathic syndromes, mainly through a particular entity, thrombotic thrombocytopenic purpura (TTP) and its child "variant", namely hemolytic uremic syndrome (HUS). This condition is related, at least in part, to a lack of cleavage of polymers of very high molecular weight of von Willebrand factor which leads to the formation of fibrin microthrombi on which red blood cells are fragmented. This lack of cleavage is often due to a deficiency of the metalloprotease responsible for cleaving these polymers, called ADAMTS13, this deficiency being either congenital or due to neutralizing antibody activity. The diagnosis of TTP is based on a diagnostic pentad including thrombocytopenia, fever, renal insufficiency, neurological symptoms and microangiopathic hemolytic anemia (presence of schizocytes and negative Coombs test, excluding an autoimmune hemolytic anemia). Currently, dosage of the deficient enzyme and detection of specific antibodies is part of the diagnostic procedure, but the management should not await these results. TTP is a serious condition with 90 % of deaths if the diagnosis is not made early (central neurological complications leading to coma, myocardial infarction), but rather healed in 90 % of cases with appropriate treatment, i.e. plasmapheresis. Plasmapheresis can remove anti-metalloprotease antibodies (the most common mechanism for TTP) and in all cases provides the missing enzyme. Plasmapheresis should be continued until the hematological and clinical features are not completely normalized. Recently infusions of monoclonal antibody directed against CD20 (Mabthera) have been proposed in particular to prevent TTP recurrences. Although hemolytic anemia is part of the diagnostic pentad of TTP, the severity of the disease is mainly due to microvascular occlusions phenomena. Packed cell transfusions may be proposed depending on hemoglobin level and and clinical tolerance, but platelet transfusions are avoided as it may exacerbate occlusive phenomena.

Autoimmune Hemolytic Anemia (AIHA)

Hemolysis is due to autoantibodies fixed to the surface of red blood that may induce red cell destruction via direct macrophages binding or via complement components [4]. Sometimes red cell lysis can be directly induced by the activation of component terminal fraction (Fig. 1). The AIHA are classified according to intrinsic properties of the antibody bound to the surface of red blood cells, since both the etiology and the therapeutic management are closely linked to this characteristic. When AIHA is suspected, the central diagnosis procedure is the Coombs test. The direct Coombs test reveals the presence of antibodies to the surface of red blood cells, while the indirect Coombs detects the same antibody, not completely fixed on the red blood cells, in serum. Finally, elution-fixation tests are used to determine the specificity of the antibodies to the antigens of blood groups (Fig. 2). Hot antibodies are active at 37 °C, fix complement and are of broad antigenic specificity. Idiopathic in half of the cases, they may be secondary to malignancy, lymphoproliferation, systemic disease or various drugs in the other half of the cases. The so-called cold agglutinins are active below 30 °C, fix complement, and elute easily (which explains that Coombs test is frequently positive only for complement fractions). Cold agglutinin presence can be suggested by the phenomena of spontaneous autoagglutination of red blood cells as soon as they are deposited on the microscope slide, with reversibility if the slide is placed in an oven at 37 °C. The specificity of cold agglutinin is often the I antigen (when secondary to mycoplasma pneumonia infection) or I antigen (after mononucleosis). Finally, the biphasic hemolysin of Donath Landsteiner often follows a viral infection in children. These antibodies are IgM that binds to red blood cells below 15 °C but will cause hemolysis only at 37 °C. Apart from the problems of etiologic diagnosis, these anemias can develop rapidly and can endanger the patient's life by the depth of the anemia. First line treatment for hot antibodies AIHA, in addition to the specific treatment of the underlying disease, is corticosteroid: 1–2 mg/kg/day in most cases. Some authors have reported a higher efficiency of méthyprednisolone bolus (500 mg). After about one month of treatment at full dose, steroids should be reduced gradually over 6 months. If hemolysis do not respond or requires maintenance with excessive levels of corticosteroids, other options should be discussed, and various immunosuppressive or immunomodulatory agents have been proposed; cyclophosphamide, imurel, cyclosporine, intravenous immunoglobulin, plasmapheresis, splenectomy. The use of anti-CD20 monoclonal antibodies (Mabthera) seems of great interest in AIHA, but their action is delayed (several days or weeks). When is it therefore need to quickly increase hemoglobin level, transfusion of packed red blood cells is possible. It is recommended to limit transfusions to a minimum, with small volumes (100 cc twice per day) infused as slowly as possible. The continuous monitoring of blood pressure is required; the occurrence hypotension, back pain or hematuria could reflect an exacerbation of hemolysis and require to immediately stop transfusion. Regarding cold agglutinin disease, corticosteroids are ineffective but MabThera

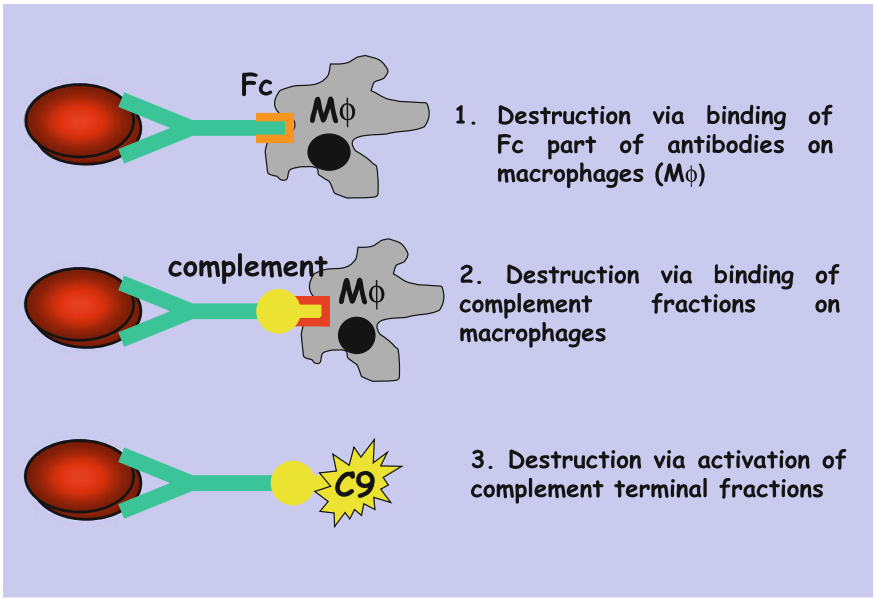

Fig. 1 Mechanisms of AHAI

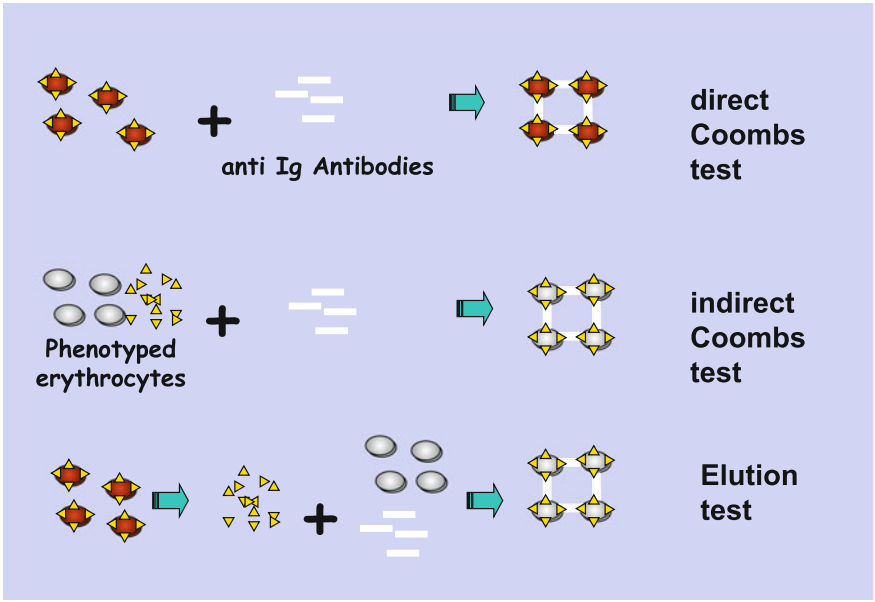

Fig. 2 Antibodies identification in AHAI

may be used. If imperative, the transfusion should use packed red blood cells warmed to 37 °C, the patient should also be kept himself in a warm room, in order to avoid antibody fixation on transfused red blood cells.

Conclusion

Hemolytic anemia often poses a diagnostic problem which will be decisive for the medium-and long-term management of the patient. In the short term, profound anemia can involve the patient's life. Transfusion of packed red blood cells is always possible, even in AIHA with certain precautions. Due to the lack of controlled studies in AIHA, the majority of therapeutic approaches are based on a series of patients analyzed in retrospective or even on isolated case-patients. This argues in favor of the establishment of multicentre studies which will allow to establish evidence-based standard of treatment.

References

1. Bauduer F (2006) Extracorpuscular nonimmunologic hemolysis. EMC (Elsevier, Paris), Haematology, 13-006-D-18
2. Brodsky RA (2008) Advances in the diagnosis and therapy of paroxysmal nocturnal hemoglobinuria. Blood Rev 22(2):65–74
3. Delaunay J (1999) Hemolytic anemias of membrane origin. EMC (Elsevier, Paris), Haematology, 13-006-D-05
4. Michel M (2009) Autoimmune hemolytic anemias. EMC (Elsevier, Paris), Haematology, 13-006-D-20
5. Wajcman H (2006) Glucose-6-phosphate déshydrogénase. EMC (Elsevier, Paris), Haematology, 13-006-D-11

Part VIII
Skin System

Bradykinin-Mediated Angioedema

Bernard Floccard, Jullien Crozon, Brigitte Coppere, Laurence Bouillet and Bernard Allaouchiche

Key Points

- Bradykinin-mediated angioedema are diseases characterised by episodes of subcutaneous or mucosal oedema (extremities, throat, respiratory and digestive tracts), referred to as attacks
- Diagnosis of bradykinin-mediated angioedema must be evoked faced with a patient suffering from transient and recurrent oedema and/or abdominal pain
- All attacks localised over the shoulders (face, neck, throat, respiratory tract) and all abdominal attacks with pain rated >5 on the VAS must be considered severe
- Severe ENT attacks may be life-threatening; in the absence of specific treatment, the mortality rate reaches 25–30 %
- It is not a mastocyte mediator's mediated swelling. Antihistamines are not effective, because bradykinin is the key mediator
- Even in the absence of previous attacks, short-term prophylaxis is necessary as the onset of an attack is unpredictable
- Reference centres should be contacted quickly if they are available.

B. Floccard (✉) · J. Crozon · B. Allaouchiche
Département d'anesthésie réanimation, Centre de Référence des Angiœdèmes à Bradykinine, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France
e-mail: bernard.floccard@chu-lyon.fr

B. Coppere
Service de Médecine Interne, Centre de Référence des Angiœdèmes à Bradykinine, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France

L. Bouillet
Clinique Universitaire de Médecine Interne, Centre National de Référence des Angiœdèmes à Bradykinine, Hôpital Albert Michallon, Grenoble, France

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_16,

Introduction

Bradykinin-mediated angioedema (AE) are diseases characterised by the occurrence of transient and recurrent episodes of subcutaneous or mucosal oedema, referred to as attacks. Depending on the location, these attacks can be severe and potentially life-threatening. Angioedema is a rare genetic or acquired disease, associated with excessive levels of bradykinin and is not a mastocyte mediator's reaction.

International consensus conferences have been published and specific molecules to treat AE have been developed in recent years [1–5].

Angioedema can be classified according to the presence or absence of a C1 inhibitor (C1-INH) deficiency (Fig. 1). Hereditary angioedema (HAE) is an autosomal dominant disease caused by a quantitative (HAE type I) or qualitative (HAE type II) C1-INH deficiency. It is an orphan disease with an estimated prevalence of approximately 1 in 50,000–100,000, without differences in gender or race [6]. Acquired angioedema (AAE) is characterised by an acquired deficiency in C1-INH, with an estimated prevalence between 1:100000 and 1:500000 [7]. Recently, a hereditary variant of AE with normal C1-INH was described and was initially called HAE type III. Drugs induced angioedema has been described with angiotensin converting enzyme (ACE) inhibitors.

A Clinical Syndrome

AE is a clinical syndrome with one mediator and multiples causes.

Clinical Symptoms

The clinical picture is characterised by recurrent episodes of white, soft, deforming, circumscribed and non-pruritic subcutaneous or submucosal oedema affecting the extremities, face, throat (tongue, larynx, and lips), trunk, genitalia or digestive tract that are referred to as attacks [8] (Fig. 2). The oedema develops slowly over a period of up to 36 h and resolves spontaneously within 2–3 days without any residual effects. The clinical signs result from the topography of the oedema, as this can be either isolated or multiple and can affect any part of the body. Swelling affecting the skin is usually painless. About 75 % of patients have attacks localised to the neck, face, tongue or respiratory tract that result in voice alteration, dysphagia or a lump sensation in the throat [9, 10]. About 93 % of patients have abdominal attacks that are associated with oedema of the intestinal wall (i.e., abdominal pain, diarrhoea, vomiting, pseudo-obstructive syndrome, ascites and peritoneal effusion) and can result in unnecessary surgery (14–37 % of patients) [8, 11–13] (Fig. 3).

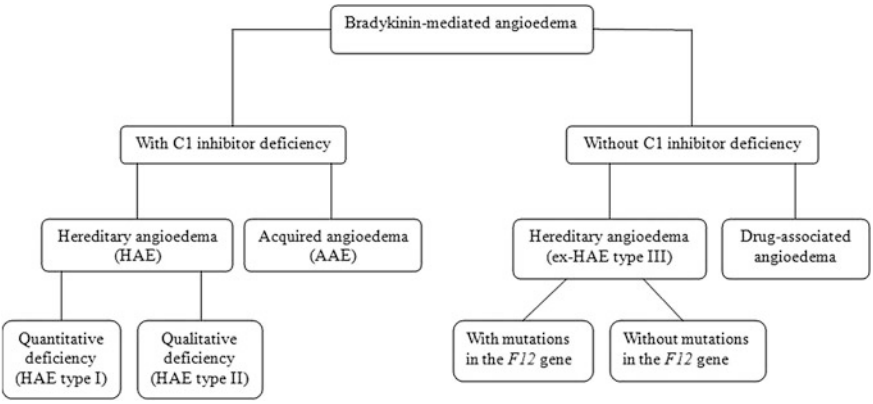

Fig. 1 Pathophysiological classification of bradykinin-mediated angioedema

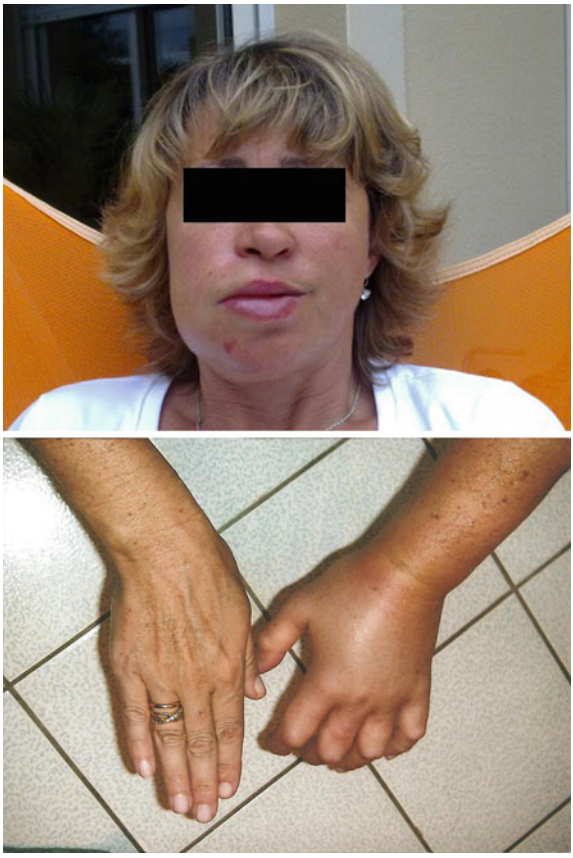

Fig. 2 Swelling in patient with hereditary angioedema. Facial attack and asymmetric swelling of the hand

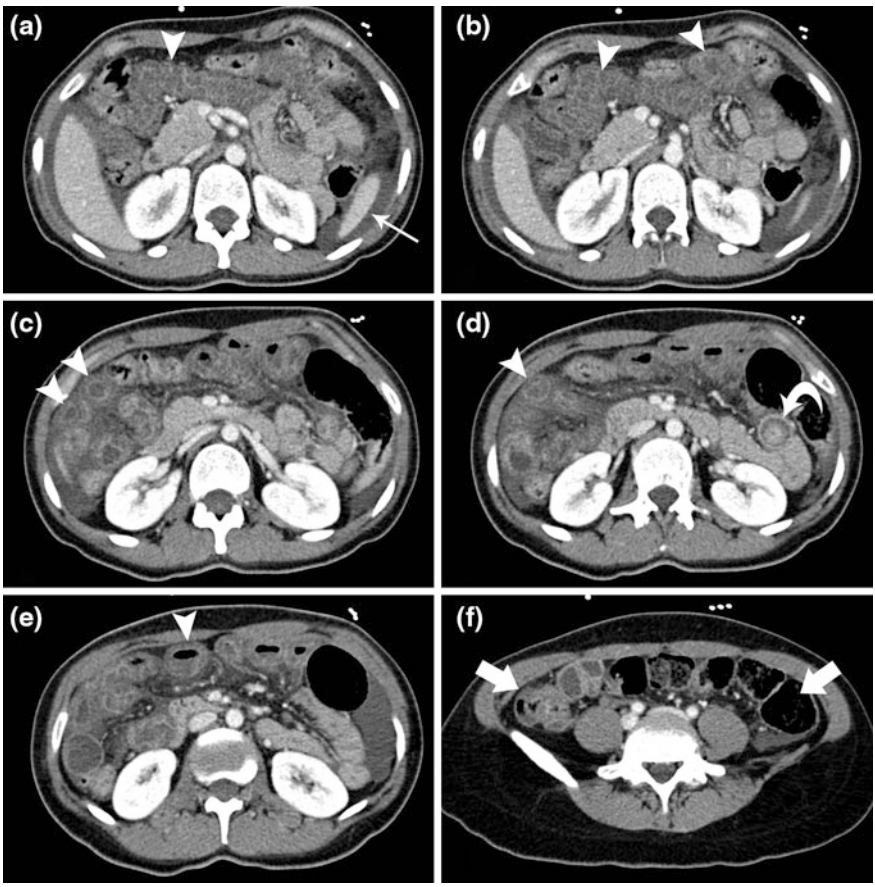

Fig. 3 Contrast-enhanced CT images obtained during the abdominal attack, showing peritoneal fluid (**a** *thin arrow*) and thickening and oedema of the ileum wall (**a**–**e** *arrowheads*). The jejunum was normal (**c**, **d** *arrows*). At the jejuno-ileal junction, a target-like image corresponding to an intussusception was visible (**d** *curve arrow*). The colon was normal (**f** *large arrow*)

The frequency of attacks is extremely variable among patients and even in the same individual at different stages of their life. Patients have attacks every 7–14 days on average, with some patients remaining asymptomatic all their life. A triggering factor can be identified in 50 % of attacks: trauma (even minimal), dental surgery (scaling, tooth extraction), stress (examinations), hormonal changes (contraceptive pills, pregnancy, menstruation), drug treatment (ACE inhibitors), infections (urinary, sinusitis, dental). Tooth extractions without prophylaxis are followed by facial swelling in 21.5 % of patients [14]. There are no clinical differences according to the type of AE.

Severe Attacks

The severity of attacks is variable, according to the localisation of the swelling. Some attacks are life-threatening [8]. In the absence of specific treatment the mortality rate is 25–30 % for ENT localisation [6, 8]. Therefore, all attacks localised over the shoulders must be considered severe, because obstruction of the upper airways is possible (supra-glottic and laryngeal oedema). The mean interval between onset and maximum development of laryngeal oedema is 8.3 h [9]. There are three phases between the onset of fatal laryngeal oedema and asphyxiation: (i) predyspnoea phase (lasting on average 3.7 h); (ii) dyspnoea phase (lasting on average 41 min) and (iii) loss-of-consciousness phase (lasting on average 8.9 min) [15]. Thus, even in the absence of signs of respiratory distress, these attacks should be regarded as severe because their prognosis is unpredictable; death has been found to occur within 20 min or several hours due to laryngeal oedema and acute asphyxiation [9, 10].

Abdominal attacks with pain rated >5 on the visual analogue scale (VAS) are considered severe due to the risk of hypovolaemic shock as a result of plasma leakage [8, 11].

Paraclinical Findings

No paraclinical findings are specific and anomalies disappear within a few days. In case of abdominal attack, ultrasound and abdominal computed tomography scans reveal peritoneal fluid, thickening and oedema of the intestinal wall. Gastroscopy and laryngoscopy show an oedematous and red mucosa.

Laboratory Diagnosis

Laboratory assays are not available in an emergency. They confirm the clinical diagnosis and the type of AE. In case of abnormal results, tests should be repeated at least once to confirm the diagnosis. Testing patients under 1-year of age may not be reliable and the results should be confirmed after the infant has turned one [1, 3].

Numerous diagnostic algorithms are available [1, 3]. Screening is conducted by determining C4 in patient without treatment. C4 is normal between attacks in only 2 % of cases. Quantitative and functional measurements of C1-INH rule out or confirm HAE and its type. C1-INH functional tests should be carried out in experienced laboratories using a chromogenic method. Antigenic levels of C1q are low in AAE (70 %). Genetic testing is not usually necessary to confirm the diagnostic of HAE with C1-INH deficiency. In HAE without C1-INH deficiency, the *F12* gene mutation can be detected in 15 % of patients.

Bradykinin, The Mediator

Bradykinin is the key mediator of angioedema attacks. It is released following activation of a cascade of proteases in the kallikrein-kinin pathway, which is activated by factor XII [6, 8]. Vascular stress activates excessive contact-activated coagulation and leads to the release of large amounts of bradykinin [16]. Bradykinin binds to specific B2 vascular receptors, which then open intercellular junctions and causes an increase in vascular permeability, plasma leakage and oedema [17–19] (Fig. 4). Bradykinin B1 receptors also seem to be involved [20]. Bradykinin is degraded by three enzymes, and their activity is referred to as kininase activity: these consist of ACE, aminopeptidase P and carboxypeptidase. Bradykinin levels can be increased by increases in kininogenase activity (i.e., proteolytic activities of factor XII, plasmin and kallikrein) or by a decrease in kininase activity [17].

Several Causes

Bradykinin-mediated angioedema can be classified according to the presence or absence of a C1-INH deficiency (Fig. 1). C1-INH is the main regulator of the kallikrein-kinin pathway and regulates the activation of kallikrein, plasmin, factors Xa and XIIa, proteins involved in fibrinolysis and the contact phase of coagulation [6, 8, 17, 18].

AE with C1-INH Deficiency

Quantitative (HAE type I) or qualitative (HAE type II) C1-INH deficiency results in an excess of bradykinin [6]. Acquired forms of the disease have also been described and these are thought to be due to increased activity of kininogenase in response to hyper-consumption of C1-INH or a neutralisation of C1-INH by C1 inhibitor antibodies [7]. These forms are often associated with lymphoproliferative disorders or autoimmune diseases that may appear several years after the initial episode.

AE Without C1-INH Deficiency

HAE with normal C1-INH was recently described. The disease is associated with excessive release of bradykinin and can be associated with mutations in the *F12* gene, for 15 % of patients [1, 21]. The disease affects mostly women and can be worsened by contraceptive pills and/or pregnancy.

Drug-induced AE associated with excessive bradykinin release has been reported. The drugs involved the renin-angiotensin system reduce its catabolism and thus increase its activity [22, 23]. Therefore, ACE medications expose patients to a 0.5–1 % risk of angioedema, which can become severe and localise to the face or larynx [24, 25]. Due to the widespread use of ACE inhibitors, this aetiology has dramatically increased over the past 20 years. The association of gliptin and/or mTOR inhibitors with ACE inhibitors increased the risk of AE.

Differential Diagnosis

Histamine-Mediated Angioedema

Clinically, patients present with a rapid onset of swelling, frequently associated with urticaria and pruritis, and sometimes with an anaphylactic reaction. Unlike AE, oedema is enhanced by antihistamines and glucocorticoids. Degranulation of mast cells results in the release of histamine and other proinflammatory mediators. These act to increase vascular permeability.

Abdominal Surgical Emergencies

Response to specific therapy is a therapeutic test to differentiate attacks and surgical emergencies.

Diagnosis in an Emergency

Two emergency situations are possible depending on whether the diagnosis has already been established.

Patient Whose Diagnosis has not been Established

This is the most difficult situation, encountered in emergency departments. The physician must establish a diagnosis and evaluate the severity of AE using a step-by-step approach [6, 18]:

- "Is this an angioedema"? This question must be asked faced with a localised, transient, non-inflammatory and recurrent oedema.

- "Is this histamine-mediated angioedema"? In a bradykinin-mediated angioedema, there is no associated urticaria or itching and the swelling will last for a few days. In particular, treatment with corticosteroids and antihistamines is ineffective.
- "Is this a bradykinin-mediated angioedema"? This angioedema is often associated with abdominal pain. Family history reports similar episodes of oedema or medication use (ACE inhibitors, ARBs).
- "Is it a severe attack"? All attacks localised over the shoulders and all abdominal attacks with pain rated >5 on the VAS must be considered severe.

At this stage, the diagnosis is strictly clinical; no laboratory tests are available for emergency cases.

Patient Whose Diagnosis has Already been Established

The patient should carry a wallet card that explains his/her illness and two doses of a specific treatment [1].

Management and Prophylaxis

Treatment includes support for acute attacks and short-term prophylaxis. Long-term prophylaxis aims to reduce the burden of the disease by reducing the frequency, severity and length of acute attacks. Three classes of drugs: attenuated androgens, antifibrinolytics and CI-INH concentrates are available. Long-term prophylaxis is not discussed here as it is a specialist subject.

Specific Treatments

Currently, several specific treatments are available, but guidelines for treatment have not been established. Results of the phase III clinical studies for these specific treatments cannot be directly compared because different protocols were used. Above all, no studies have compared the effectiveness of all available treatment options [1, 2, 26]. Furthermore, the availability of different treatments and patient access to them differ by country [26]. Updated information is available at: www.haei.org.

Randomised studies have been designed for patients with type I or type II HAE. For the other clinical situations (HAE without C1-INH deficiency, acquired and drug-induced angioedema), only clinical cases have been published documenting the use of C1-INH concentrate or icatibant outside of the authorised indications.

C1-INH Concentrate (Berinert®, from CSL Bering)

C1-INH concentrate is obtained by plasma fractionation after several stages of viral inactivation and pasteurization. Sites of action are presented in Fig. 4.

Various studies have reported the effectiveness of C1-INH concentrate for all types of angioedema [27, 28]. Two early, randomised, double-blind studies using fixed doses in patients with HAE demonstrated symptom relief and 95 % of patients were responsive to treatment within 4 h. A randomised, double-blind, multicentre study compared two doses of C1-INH concentrate to placebo in patients with HAE (IMPACT 1) [29]. In this study, only the 20 U/kg dose led to a more rapid improvement in symptoms. An open follow-up study confirmed these results and demonstrated good long-term effectiveness (IMPACT 2) [30]. No viral transmission has been described using this concentrate and the tolerance of this treatment is good [27, 28]. Rare cases of anaphylaxis have been reported. In AAE, clinical cases have been reported that have occasionally required increased dosages [7].

This drug is available in 500-U vial, the standard dose is 20 U/kg, and it is administered by rapid intravenous injection after reconstitution. The efficacy of this treatment is manifest within 30 min, and the half-life varies with the consumption of the C1-INH (but can be up to 40 h). In the absence of any improvement, it is possible to administer a repeated dose of 500–1,000 U after 2 h. Its shelf life is 30 months at a temperature below 25 °C. Depending on the frequency and severity of the attacks, it may be necessary to provide the patient with an emergency supply at home [1]. This product has been approved for the treatment of attacks in patients with HAE in Europe, the USA and Australia.

Icatibant (Firazyr®, from Shire HGT)

Icatibant is a synthetic antagonist of the bradykinin B2 receptor and blocks oedema formation (Fig. 4). An uncontrolled pilot study demonstrated the efficacy and rapid action of icatibant and found reduced serum concentrations of bradykinin following treatment. Three randomised, double-blind, multicentre studies compared icatibant to either placebo (FAST 1 and FAST 3) or tranexamic acid (FAST 2) in patients with HAE [31]. Symptoms improved faster after icatibant treatment and the duration of the attacks was shorter. In 90 % of cases, a single injection was sufficient. Patient self-administration was also assessed. For HAE without C1-INH deficiency and AAE, and particularly for the drug-induced types, clinical cases have reported improvement following icatibant treatment.

This treatment is available as a pre-filled 3-ml syringe containing 30 mg of icatibant. The dose is 30 mg subcutaneously. The injection can be repeated at 6-h intervals (up to three injections per day). Its bioavailability is excellent, its efficacy is evident within 20-30 min, and its half-life is 2 h. The shelf life is 24 months at room temperature. The side-effects mainly consist of pain at the injection site. There have been no studies in children or pregnant women. Because of its ease of

use and good tolerance, it is recommended that patients have this drug available at home and be trained for self-administrer [1]. This product is approved to treat attacks in patients with HAE and is approved for self-administration in Europe and the USA.

Recombinant C1-INH (Rhucin®/Ruconest™, from Pharming)

Recombinant C1-INH is analogous to human C1-INH and is obtained from the milk of transgenic rabbits. Studies using two different doses have documented the efficacy and safety of recombinant C1-INH in the treatment of acute HAE attacks [32]. Due to its unique glycosylation pattern, its half-life is approximately 3 h.

This drug is available in 2100-U vials, and the dose is 50 mg/kg administered intravenously after reconstitution. Prior to treatment and also either once a year or after 10 uses, the absence of IgE antibodies directed against rabbit epithelium should be confirmed. Type I and II hypersensitivity reactions have been described and the production of neutralising antibodies may occur. This product is not self-administered by patients, and it can only be used in emergency situations for patients who have tested negative for IgE rabbit epithelium antibodies. Recombinant C1-INH is approved to treat attacks in patients with HAE in Europe.

Nanofiltered C1-INH Concentrate (Cinryze®, from ViroPharma, Cetor®, from Sanquin)

Two randomised studies have evaluated the effectiveness of a fixed dose of nanofiltered C1-INH concentrate compared to placebo for the treatment of attacks or as a crossover treatment for prophylaxis [33]. In the first study, the median time for the onset of efficacy was 2 h versus 4 h for placebo, but 70 % of patients required a second injection. In the second study, the numbers of attacks and the level of the severity and duration of the attacks decreased significantly after treatment. There have been no studies comparing different doses, and rare allergic reactions have been described.

The dose for this drug is 1000 U, which is administered by slow intravenous injection after reconstitution for the treatment of attacks or as a prophylaxis.

This product is approved in Europe for the treatment and prophylaxis of HAE in adults and children and in the USA for the prophylaxis of acute HAE attacks.

Ecallantide (Kalbitor®, from Dyax)

Ecallantide is a specific kallikrein recombinant inhibitor (Fig. 4). Several randomised studies have demonstrated its rapid action, efficacy and safety [34]. Anaphylactic reactions and antibody production have been described. The half-life of this treatment is approximately 2 h.

Ecallantide is available in 1-ml vials containing 10 mg of ecallantide and should be kept cool and in the dark. The dose is 30 mg subcutaneously. It is not recommended for self infusion at this time because of a small risk of anaphylaxis. It is approved in the USA but not in Europe.

Treatment of Acute Attack

Corticosteroids and antihistamines are ineffective for the treatment of acute attacks [1, 6].

Severe attacks must be identified because their prognosis is unpredictable and laryngeal oedema or hypovolaemic shock can be life-threatening. All patients experiencing severe attacks should be hospitalised and treated with a specific treatment [1].

Treatment of Severe Attacks

Specific treatment must be initiated as quickly as possible [1, 4, 5].

Phase III studies have recommended the use of C1-INH concentrate, icatibant, recombinant C1-INH, nanofiltered C1-INH or ecallantide for the treatment of severe HAE attacks [1, 4, 5]. No studies concerning the superiority or inferiority of the effectiveness of these molecules exist and guidelines for the selection of theses treatment are not available. Phase IV studies and international consensus conferences are needed. In practice, the choice should be based on the local availability of the treatments and should reflect the national consensus of each country, depending on local customs [1].

Treatment of Laryngeal Oedema

Laryngeal oedema is the main complication responsible for disease severity.

Specific treatments. The effectiveness of C1-INH concentrate, icatibant, nanofiltered C1-INH and ecallantide has been examined for laryngeal oedema in open-phase studies [31, 33–35]. Only recombinant C1-INH was not evaluated for this condition. Symptoms began to improve within approximately 15–30 min and each of these treatments resulted in symptom improvement.

Intubation. Intubation can be very difficult due to the distortion and swelling of the upper airways. This technique should be performed by an experienced physician [1, 6, 18]. To avoid complications, intubation should be considered during the early stages of progressive laryngeal oedema [1, 15]. Intubations using a fiberscope may be affected by the presence of oedema. If this fails, it is necessary to perform a cricothyroidotomy, which can also be difficult or impossible as a result of the oedema. Occasionally, surgical tracheotomy is only remaining option for treatment.

Inhalated epinephrine. Clinical reports have suggested moderate and transient efficacy for inhalated epinephrine, when provided during the early stages of oedema. Due to the pathophysiology of angioedema and the questionable effectiveness of this treatment, the use of aerosolised epinephrine should not delay the initiation of other specific treatments [1, 4].

Other Treatments

Fresh-frozen plasma. The administration of fresh-frozen plasma provides the patient with the C1-INH from the donor. Some clinical case reports have been the only studies to demonstrate the effectiveness of fresh-frozen plasma. This treatment has also been shown to aggravate oedema attacks [1, 4, 6]. Indeed, this product contains contact-activated coagulation proteins, which can produce additional bradykinin and thus worsen the attack. Additionally, the risk of exposure to transmissible diseases (e.g., non-enveloped viruses and prions) is present, as it is with any blood component. Currently, the use of fresh-frozen plasma is strongly discouraged in countries where specific molecular treatment options are available [1, 4].

Analgesics. Although attacks are not usually painful, patients may experience significant pain if the swelling affects points of support, especially in abdominal area, and these conditions may lead to a surgical emergency. Any class of analgesic, antiemetic or antispasmodic may be used for these cases [1, 4, 6].

Fluid therapy. During an abdominal attack, the patient may experience a major collapse, secondary to fluid sequestration in the gastrointestinal tract and abdominal cavity. For these situations, crystalloids and colloids can be used, but dextrans should be excluded [1, 6].

Treatment of Moderate Attacks

Specific treatments. All available treatment options can be used for the treatment of moderate attacks [1, 6]. However, the high price of these treatments leads to the question of their real benefit in terms of public health (i.e., lost work days, social life, quality of life, etc.). For all cases, the aim should be to reduce the morbidity of the disease and to enable patients to live as normally as possible, with the same approach as haemophilia [1, 4]. Health education programs should be developed to empower the patient and patients should be shown how to self-administer C1-INH concentrate and icatibant.

Tranexamic acid. This is an antifibrinolytic agent that controls the formation of plasmin and effectively "saves" C1-INH and limits excessive synthesis of bradykinin (Fig. 4). Two early controlled studies confirmed its effectiveness, but this treatment is more effective when started early. The side effects of this treatment are nausea, faintness and dizziness. It is available in tablets or injectable ampoules, and the dose is 1–2 g/6 h for 48 h [1, 4].

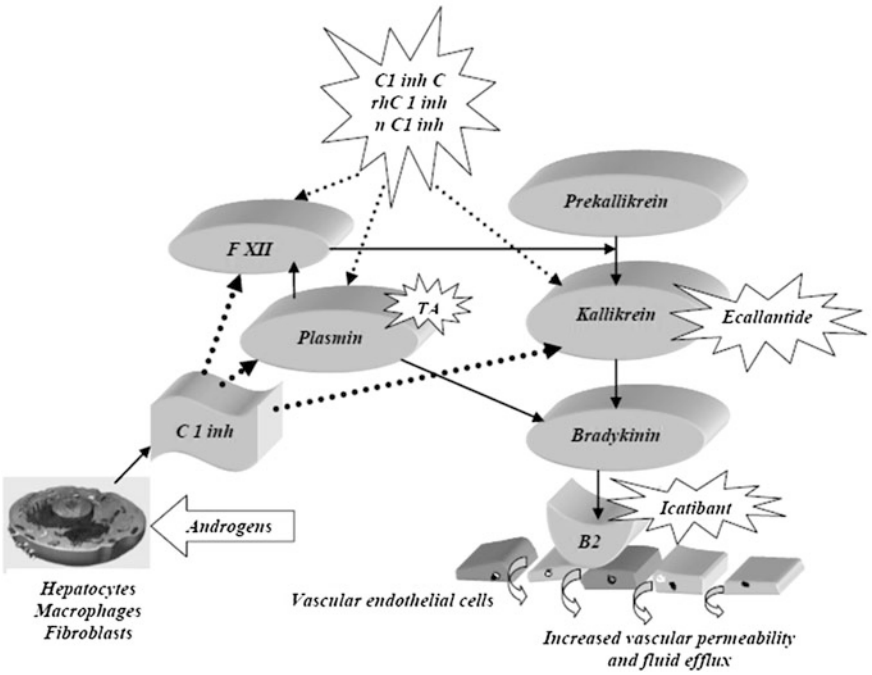

Fig. 4 Pathophysiological model of bradykinin-mediated angioedema and targets of treatments [36]. The *black solid arrows* represent an activation mechanism. The *dotted arrows* represent a mechanism of inhibition. Treatments inhibiting of physiological pathways are represented as *white stars*. Therapeutic agents acting through activation of a physiological pathway are represented by a *white arrow*. *C1 inh* C1 inhibitor physiological, *F XII* factor XII, *C1 inh C* C1 inhibitor concentrate, *rhC1 inh* recombinant C1 inhibitor concentrate, *n C1 inh* nanofiltered C1 inhibitor concentrate, *TA* Tranexamic acid, *B2* endothelial vascular receptor

Short-Term Prophylaxis

The aim of prophylaxis is to avoid attacks in patients who undergo surgical or medical procedures. These procedures include dental surgery, digestive endoscopies and all surgical interventions that require intubation. Prophylaxis should always be used because the possibility of developing an attack is unpredictable [1, 4].

No time available before the procedure. In an emergency or delivery, only C1-INH concentrate and recombinant C1-INH are available. Treatment should be administered 1 h before the procedure and the effect lasts 2–4 days.

With a delay of some days before the procedure. With prophylaxis, protection is never complete. Specific treatment for acute attacks must be available in the operating room [1]. For scheduled procedures, danazol can be administered at a dose of 600 mg/day, 5–7 days before and up to 2–3 days after the procedure (Fig. 4). Tranexamic acid can be used at a dose of 1 g four times a day until 2 days after the procedure.

Conclusion

Angioedema is a disease that any intensive care physician could encounter during an attack. Bradykinin-mediated angioedema should be evoked in cases of transient and recurrent oedema. Severe attacks must be identified. All severe attacks should benefit from early treatment with a specific molecule. Without these treatments, life-threatening situations may arise. The availability of these treatments varies by country, and there is currently no consensus as to the correct choice of a specific treatment.

It is important to encourage the patient to carry two doses of any specific treatment for emergency treatment. Self-administration of the treatment should be the goal.

The rarity of this disease and the characteristics of the specific drugs (i.e., their retention periods, modes of delivery, prices and methods for reimbursement) should encourage hospitals to make strategic choices regarding the creation of an emergency supply of drugs or an institute-wide protocol for the rapid transfer of patients to specialised centres for treatment.

References

1. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B et al (2010) 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol 6(1):24
2. Bowen T (2011) Hereditary angioedema: beyond international consensus—circa December 2010—the Canadian society of allergy and clinical immunology Dr. David McCourtie lecture. Allergy Asthma Clin Immunol 7(1):1
3. Caballero T, Baeza ML, Cabanas R, Campos A, Cimbollek S, Gomez-Traseira C et al (2011) Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part I. Classification, epidemiology, pathophysiology, genetics, clinical symptoms, and diagnosis. J Investig Allergol Clin Immunol 21(5):333–347
4. Caballero T, Baeza ML, Cabanas R, Campos A, Cimbollek S, Gomez-Traseira C et al (2011) Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations. J Investig Allergol Clin Immunol 21(6):422–441
5. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H et al (2011) Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy 67(2):147–157
6. Zuraw BL (2008) Clinical practice. Hereditary angioedema. N Engl J Med 359(10):1027–1036
7. Cicardi M, Zanichelli A (2010) Acquired angioedema. Allergy Asthma Clin Immunol 6(1):14
8. Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L et al (2004) Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 114(3 Suppl):S51–S131
9. Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W (2000) Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clin Proc 75(4):349–354

10. Bork K, Hardt J, Schicketanz KH, Ressel N (2003) Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. Arch Intern Med 163(10):1229–1235
11. Bork K, Staubach P, Eckardt AJ, Hardt J (2006) Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. Am J Gastroenterol 101(3):619–627
12. Nzeako UC (2010) Diagnosis and management of angioedema with abdominal involvement: a gastroenterology perspective. World J Gastroenterol 16(39):4913–4921
13. Guichon C, Floccard B, Coppere B, Hautin E, Bages-Limoges F, Rouviere O et al (2011) One hypovolaemic shock…two kinin pathway abnormalities. Intensive Care Med 37(7):1227–1228
14. Bork K, Hardt J, Staubach-Renz P, Witzke G (2011) Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 112(1):58–64
15. Bork K, Hardt J, Witzke G (2012) Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol 130(3):692–697
16. Maurer M, Bader M, Bas M, Bossi F, Cicardi M, Cugno M, et al (2011) New topics in bradykinin research. Allergy 66(11):1397–1406
17. Davis AE 3rd (2005) The pathophysiology of hereditary angioedema. Clin Immunol 114(1):3–9
18. Bas M, Adams V, Suvorava T, Niehues T, Hoffmann TK, Kojda G (2007) Nonallergic angioedema: role of bradykinin. Allergy 62(8):842–856
19. Kaplan A (2011) Bradykinin and the pathogenesis of hereditary angiodema. WAO J 4:73–75
20. Bossi F, Fischetti F, Regoli D, Durigutto P, Frossi B, Gobeil F Jr et al (2009) Novel pathogenic mechanism and therapeutic approaches to angioedema associated with C1 inhibitor deficiency. J Allergy Clin Immunol 124(6):1303–1310
21. Bouillet L (2010) Hereditary angioedema in women. Allergy Asthma Clin Immunol 6(1):17
22. Brown NJ, Byiers S, Carr D, Maldonado M, Warner BA (2009) Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. Hypertension 54(3):516–523
23. Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P (2010) Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. Clin Exp Allergy 40(1):50–61
24. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE (2008) Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension 51(6):1624–1630
25. Tai S, Mascaro M, Goldstein NA (2010) Angioedema: a review of 367 episodes presenting to three tertiary care hospitals. Ann Otol Rhinol Laryngol 119(12):836–841
26. Morgan BP (2010) Hereditary angioedema-therapies old and new. N Engl J Med 363:581–583
27. De Serres J, Groner A, Lindner J (2003) Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. Transfus Apher Sci 29(3):247–254
28. Longhurst HJ (2005) Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence? Int J Clin Pract 59(5):594–599
29. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K et al (2009) Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 124(4):801–808
30. Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ, et al (2011) C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks—final results of the I.M.P.A.C.T.2 study. Allergy 66(12):1604–1611

31. Cicardi M, Banerji A, Bracho F, Malbran A, Rosenkranz B, Riedl M et al (2010) Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 363(6):532–541
32. Longhurst H (2008) Rhucin, a recombinant C1 inhibitor for the treatment of hereditary angioedema and cerebral ischemia. Curr Opin Investig Drugs 9(3):310–323
33. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J et al (2010) Nanofiltered c1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 363(6):513–522
34. Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M et al (2010) Ecallantide for the treatment of acute attacks in hereditary angioedema. N Engl J Med 363(6):523–531
35. Craig TJ, Wasserman RL, Levy RJ, Bewtra AK, Schneider L, Packer F, et al (2010) Prospective study of rapid relief provided by c1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. J Clin Immunol 126(4):821–827
36. Floccard B, Crozon J, Rimmele T, Vulliez A, Coppere B, Chamouard V, et al (2011) Management of bradykinin-mediated angioedema. Ann F Anesth Reanim 30(7–8):578–588

Toxic Epidermal Necrolysis in Children

Fabrice Michel

Key Points

- The diagnostic of TEN is mainly clinical and must be evoked in case of eruption of maculae with a blister-like centre and prodromic signs as asthenia, conjunctival irritation, oropharyngeal pain or respiratory troubles early after starting a treatment.
- The causative drug should immediately be stopped, and never given again.
- These patients should then be treated as an emergency in a burns or intensive care unit (ICU). The management of children will be optimised by hospitalisation in a paediatric unit.
- Ophtalmological and vaginal lesions should be sought and treated early.
- Systemic corticotherapy and intravenous immunoglobulins are the first treatments to consider but other immunosuppressive treatments could be useful.

Introduction

Toxic epidermal necrolysis (TEN) or Lyell's syndrome was first described by Lyell in 1956. It presents as a painful cutaneous eruption with the formation of bullous lesions and mucosal involvement. Considered as variants of the same pathology, TEN and Stevens-Johnson syndrome (SJS) can be differentiated by the

F. Michel (✉)
Pediatric Anesthesia and Intensive Care Unit, Aix Marseille University,
North Hospital, Marseille, France
e-mail: Fabrice.michel@ap-hm.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_17,

skin surface area affected: <10 % in SJS compared to >30 % in TEN. When 10–30 % of the skin surface is involved, the disease is considered to be an intermediate form, SJS/TEN. The incidence of these toxidermias in the general population is approximately 1.5–2 cases/million/year. While the prognosis of SJS is generally good, TEN has an associated mortality of 20–25 %, often early in the course of the disease. In children, mortality is lower due in part to the absence of comorbidities. However, morbidity is high because >90 % of patients present with sequellae at 1-year. Diagnosis is often late with a mean delay of 3 days after the appearance of the first symptoms, which often suggest a banal viral infection. In the majority of cases, TEN and SJS are caused by an adverse reaction to certain drugs. More than 200 molecules have been incriminated but some are particularly associated with this disease as 50 % of cases are caused by only 10 drugs.

Physiopathology

The physiopathology of TEN remains unclear, but recent studies have led to a better understanding of the different immunological mechanisms involved. In some cases, genetic susceptibility appears to favour the development of the disease.

TEN corresponds to epidermal and epithelial necrolysis due to brutal and widespread apoptosis of keratinocytes. Activated CD8+ T-lymphocytes, which are cytotoxic to keratinocytes, are mainly involved in the development of TEN. They are found in large numbers in the liquid from blisters and in skin biopsies from patients. Their cytotoxicity is mediated by the granzyme B/perforin pathway. Furthermore, keratinocytes carry a membrane receptor Fas, whose ligand FasL is present at the surface of activated T-lymphocytes and NK cells. Keratinocytes also express FasL constitutionally but at a low level and in an inactive form due to its intracellular localisation. During TEN, FasL is overexpressed at the external surface of the membrane leading to Fas-FasL interactions between different keratinocytes leading to widespread apoptosis by activation of the caspase pathway. A soluble form of FasL in the blood also seems to be implicated in the apoptotic phenomenon. Some polymorphisms of FasL may be associated with the development of SJS or TEN [1].

Finally, TNF-α, interferon-γ and many interleukins have been found in cutaneous lesions. These mediators favour the overexpression of FasL, intervene in the expression of membrane adhesion molecules and favour the attraction of lymphocytes. Some metalloproteinases have also been recovered from cutaneous lesions of TEN patients. These calcium-dependent endopeptidases are involved in the regulation of apoptosis.

Genetic susceptibility to TEN may exist. In certain Asian populations, some HLA-B antigens are strongly associated with the development of TEN with a given drug. This has been demonstrated for carbamazepine and allopurinol. The Food and Drug Administration in the USA recommends carrying out HLA typing, with investigations for HLA-B*1502 antigen, before starting treatment with carbamazepine in Asian patients.

Diagnosis

The diagnosis of TEN is mainly clinical. Unfortunately it is often made late, after several days of evolution of the disease, because the initial symptoms are non-specific and may suggest a banal viral infection. Prodromic signs associating asthenia, oropharyngeal pain, dysphagia, conjunctival irritation or respiratory problems appear rapidly after starting the causative drug and are often referred to. In children, before the eruption of maculae with a blister-like centre, it is easy to make an initial diagnosis of varicella in a febrile context. Knowledge of varicella in the patient's medical history should question this diagnosis. The cutaneous lesions initially appear on the trunk and the face and then spread to the extremities. The disease aggravates rapidly with extension of the lesions and epidermal detachment forming flaccid blisters that are easy to pierce, a positive Nikolsky sign, bleeding and involvement of the oral or conjunctival mucosa and sometimes the respiratory and digestive mucosa. This may result in a digestive and/or respiratory picture such as pseudomembranous colitis or acute respiratory distress syndrome which significantly aggravates the prognosis. The patient's general state is altered; there is intense pain and significant anxiety [2].

The definitive diagnosis is established by the anatomopathology of a skin biopsy. This also enables other possible diagnoses to be eliminated, in particular in infants. It confirms necrosis of the full thickness of the epidermis with good conservation of the dermis. Direct immunofluorescence is negative, eliminating possible autoimmune bullous diseases.

A severity score (SCORTEN) has been proposed for adults which should be calculated in the first 24 h after admission. It is based on seven prognostic factors: age, the existence of a haemopathy or cancer, the skin area affected, heart rate, blood urea and bicarbonates and glycaemia. It appears to be well correlated with mortality; however, the score has not been validated in children. The need for mechanical ventilation and the existence of sepsis are not taken into account in the establishment of the initial prognostic score although they have been reported as risk factors for death in adults. Serum lactate dehydrogenase level at the start of disease evolution may also be a marker of severity.

In children, several diseases should be evoked in this context. Burns can present with a similar appearance, but anamnesis and the evolution of the lesions will easily eliminate this diagnosis. Polymorphous erythema may sometimes be bullous, but generally appears in a context that is less dramatic, without a high fever. Impetigo is responsible for very superficial blisters, often located in a specific region. Here, the general state is also unchanged.

Acute staphylococcal epidermolysis (also called "staphylococcal Lyell's syndrome") presents like TEN. It is differentiated by a skin biopsy which shows detachment of the superficial layer of the epidermis in contrast to TEN where the disease affects the full thickness of the epidermis. Acute acquired or congenital epidermolysis should also be evoked.

The drug responsible for TEN should be established rapidly and all treatments should be stopped immediately. The drugs most frequently responsible for TEN in children are: sulphonamides (sulphamethoxazole, sulphadiazine, sulphasalazine), quinine, antiepileptics (phenobarbital, lamotrigine, carbamazepine, phenytoin), non-steroidal anti-inflammatory drugs and salicylates [3]. Rarely used in children, allopurinol is strongly implicated in the development of TEN in adults.

In approximately 5 % of cases, no drug is implicated and the aetiology remains unknown. Infectious causes, in particular *Mycoplasma* infection, are rare and represent approximately 1–2 % of cases.

Management

It is important to make the diagnosis quickly and immediately stop administration of the causative drug. For molecules with a short half-life, early interruption of treatment can decrease the mortality from 26 to 5 %. These patients should then be treated as an emergency in a burns or intensive care unit (ICU). The management of children will be optimised by hospitalisation in a paediatric unit.

The patient should be hospitalised in strict isolation with a high ambient temperature. Initially, intensive care is based on correction of the hydroelectrolytic problems. Fluid intake should be increased in relation to the basal needs and increased proportionally to the body surface affected. Sodium loss is also high and should be compensated. Although increased, there is less sodium and water than in burns due to the fact that there is less inflammation and no vascular involvement. Delay between the appearance of lesions and treatment in the ICU may be responsible for significant dehydration and this should be taken into account in the initial provision. Monitoring of volaemia, which is difficult in small children, may be complicated even more by the cutaneous involvement (catheters impossible to insert, dressings obstructing transthoracic echography). Surveillance of hourly diuresis with the goal of 1 ml/kg/h helps to guide fluid replacement.

Nutritionally, dietary intake should be increased as a function of the body surface area affected. A formula to calculate the calorific requirement in children has been proposed [4]:

$$\begin{aligned} \textit{Calorific requirement} = {} & (\textit{Weight before TEN}\ [kg]\, x\, 24.6) \\ & + (\textit{Body surface area damaged}\ [\%]\, x\, 4.1) + 940\, cal \end{aligned}$$

In adults, enteral feeding is preferable to parenteral nutrition. There are no data in children.

The pain caused by the lesions is often significant. Paracetamol and morphine should be combined. Administration by auto-controlled perfusion or controlled by carers is the solution of choice. Infra-anaesthetic doses of ketamine (0.1–0.2 mg/kg/h) as a continuous perfusion may improve analgesia without provoking a psychodysleptic effect.

Treatment of the cutaneous lesions is an essential part of the management of these patients. However, there is some controversy as to the best approach to take. Some authors advocate wide debridement and covering of the skin with biological dressings, while others propose a more conservative approach leaving the epidermis in place and only covering the lesions where the dermis is exposed. Many types of dressing have been proposed. Dressings containing nanocrystals of silver designed for burns are used by many clinical teams. These have the advantage of avoiding the daily replacement of dressings which could be harmful in the context of extensive bullous detachment. It is important not to use adhesive dressings (catheter site dressings, electrodes, etc.…). These can be protected using loose bandages. Epidermal regeneration takes place in approximately 2–3 weeks.

Anti-infection measures should be intense in these patients. Systematic cutaneous, respiratory and urinary specimens allow surveillance of the bacterial flora. The most frequent pathogens found during sepsis in these patients are *Staphylococcus aureus* first and then *Pseudomonas aeruginosa* much later. Empirical broad-spectrum antibiotics should be avoided as far as possible in all cases and should be adapted as early as possible to the causative microorganism.

The mucous membranes are involved in 90 % of cases of TEN. Ocular lesions are quasi constant and require a rapid ophthalmological consultation to prevent the development of severe conjunctival and corneal lesions [5]. Fifty percent of patients present with ophthalmological sequellae associating dry syndrome, corneal and conjunctival scarring and blindness. Systemic immunosuppressive treatments (corticotherapy, immunoglobulins) have not been shown to be beneficial to these lesions. Corneal grafts may be considered. The use of amniotic membranes appears promising to prevent long-term complications. Examination of the vaginal mucosa should be systematic. Local lubricating and anti-inflammatory treatments may be considered to prevent severe scarring, which is often difficult to treat later.

Immunosuppressive treatment with systemic corticotherapy or intravenous immunoglobulins appeared to be very promising a few years ago but has recently been questioned and its use is controversial. The largest series published to date on 281 patients in France and Germany showed no difference in the prognosis of patients whether they received these treatments or not [6]. On the other hand, corticotherapy appears to be beneficial in SJS. In children, these treatments have also been reported. They appear to be more effective than in adults; however, publications have never included more than 15 patients per study. Their benefit therefore remains uncertain. The complications of these treatments can be serious. In a retrospective study in children, the use of intravenous immunoglobulins was associated with prolonged hospital stay compared to children who received corticoids or no immunosuppressive treatment.

The use of cyclosporine at 3 mg/kg/day has been proposed with satisfactory results in adults. However, these case series are small. In children there are insufficient data to recommend this treatment. An anti-TNF agent has been compared with thalidomide in a prospective, controlled, randomised study. The trial

had to be interrupted due to overmortality in the thalidomide group. The use of anti-TNF has not been reported in children.

Plasmapheresis has been used in adults and in children with severe TEN that has not responded to corticoids or intravenous immunoglobulins. The success rate was 80 %, making plasmapheresis a possible treatment option after failure of more conventional treatments.

In no case should the drug responsible for TEN, when it has been identified, be reintroduced. On the other hand, this does not contraindicate the prescription of molecules of other members of the same family.

TEN and the sometimes disabling sequellae that it engenders may have important psychological consequences. Psychological or even psychiatric follow-up as well as long-term monitoring of patients for sequellae is essential.

Conclusion

TEN is a rare but serious disease, affecting the vital prognosis of children. Treatment should be carried out in paediatric ICU or a paediatric burns centre and should be multidisciplinary. Rapid interruption of drug treatment, hydroelectrolytic replacement, increased dietary intake, analgesia and dressings are the basis of management. Corticotherapy is controversial. Intravenous immunoglobulins and plasmapheresis may have a place in treatment. Other molecules remain to be evaluated. Mucous membrane involvement, in particular in the eyes, should be treated specifically and early. TEN is responsible for sequellae that are often severe. It is advisable to predict these as early as possible as they require long-term monitoring.

References

1. Borchers AT, Lee JL, Naguwa SM et al (2008) Stevens-Johnson syndrome and toxic epidermal necrolysis. Autoimmun Rev 7:598–605
2. Koh M, Tay Y (2009) An update on Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Curr Opin Pediatr 21:505–510
3. Levi N, Bastuji-Garin S, Mockenhaupt M et al (2009) Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. Pediatrics 123:e297–e304
4. Mayes T, Gottschlich M, Khoury J (2008) Energy requirements of pediatric patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Nutr Clin Pract 23:547–550
5. Schneck J, Fagot J, Sekula P et al (2008) Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol 58:33–40
6. Sotozono C, Ueta M, Koizumi N et al (2009) Diagnosis and treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis with ocular complications. Ophthalmology 116:685–690

Part IX
Renal System

The Gitelman and Classical Bartter Syndromes

Guillaume Favre, Jean-Christophe Orban and Carole Ichai

Key Points

- This diagnosis must be evoked systematically in case of symptomatic and profound hypokalemia or hypomagnesemia, associated with an extracellular dehydration.
- The symptomatic treatment is not based on biological findings but on clinical signs.
- The diagnosis is not made in emergency during the intensive care unit hospitalization but later in a stable condition.

Introduction

The classical Bartter (type III) and Gitelman syndromes are congenital tubulopathies that are often diagnosed in adults. Both are autosomal recessive inheritance illnesses leading to a secondary hyperaldosteronism associated with renal hypokalemia and metabolic alkalosis. Phenotypic presentation of Gitelman syndrome is rather a hypomagnesemia and a hypocalciuria, whereas Bartter syndrome is rather a normal magnesemia and a hypercalciuria. Gitelman syndrome is characterized by a mutation that inactivates the gene encoding for the thiazide

G. Favre
Service de Néphrologie, Hôpital Pasteur, CHU de Nice, Nice, France

J.-C. Orban · C. Ichai (✉)
Réanimation Médico-chirurgicale, Faculté de Médecine de Nice, Hôpital Saint-Roch, CHU de Nice, Nice, France
e-mail: ichai@unice.fr

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_18,

diuretic sensible-cotransporter Na–Cl (SCL 12A3). The classical Bartter syndrome is due to a mutation that inactivates the gene encoding for the type B chloride channel (CLCNKB) [1–3]. In this chapter, we will describe the main clinical diagnosis and therapeutic aspects of these syndromes. Clinical presentation can be severe as a consequence of an acute exacerbation of hypokalemia or hypomagnesemia induced by an extracellular dehydration.

Case Report

A 36 years old man without any notable medical history, was hospitalized in emergency for tetraparesia. The history begun 3 days ago by a polyuric-polydipsic syndrome associated with diffuse muscular pain of the four limbs leading to suspect a Guillain-Barre syndrome. Blood samples found a low serum potassium level at 1.5 mmol/L et a U-wave was present on the electrocardiogram (ECG). He was transferred in the intensive care unit. At this moment, the clinical examination confirmed a severe muscle weakness of the lower limbs. Despite an initial intravenous substitution in the emergency room, the patient showed severe electrolytes and acid–base disturbances including a persistent hypokalemia, hypochloremia (97 mmol/L), normonatremia (142 mmol/L), and an extracellular dehydration (protidemia 85 g/L). Serum magnesium, phosphate, calcium levels and blood gases were in normal ranges. However, moderate elevated level of creatinemia and BUN (respectively 142 μmol/L and 13.5 mmol/L) revealed a moderate acute renal failure. Both inappropriate high urinary sodium (75 mmol/L) and urinary potassium (23 mmol/L) levels pointed towards a renal cause of this trouble. A continuous infusion of potassium permitted to increase progressively and to normalize serum potassium level within 24 h. This normalization was concomitantly associated with a clinical improvement as tetraparesia disappeared totally. Considering this profound hypokalemia related to a renal origin, we hypothetize several diagnoses: hidden absorption of thiazidics, Gitelman or a Bartter syndromes. The renal potassium losses in our patient did not support a hypokalemic periodic paralysis. A related-thiazide hypokalemia could not be excluded by a urine measurement that is known to give numerous false positive values. Additional complementary investigations were performed later. They found a secondary hyperaldosteronism (high plasma renin concentration 211 ng/L et high plasma aldosterone concentration 1533 ng/L), hypokalemia with simultaneous potassium renal losses (serum potassium level 2.4 mmol/L, urinary potassium level 172 mmol/day), a metabolic alkalosis without hypomagnesemia and a calcium/creatininemia ratio of 0.23. All of these parameters were in favor of a Gitelman or a Bartter syndrome. The sequence determination of the SCL 12A3 gene revealed a composite heterozygous form with two mutations on the 7 and 23 exons. This confirmed the diagnosis of a Gitelman syndrome. A more precise questioning of the patients confirmed that before this episode, he suffered of excessive sweating when he was working in warm atmospheres. No familial history of hypokalemia was found.

Epidemiology

Because Gitelman and Bartter syndromes are usually diagnosed by chance, it remains difficult to assess their real incidence in a general population (about 1/40000 for the Gitelman syndrome). Consanguinity is not obligatory for the Gitelman syndrome; composite heterozygous forms are frequent with multiple mutations in the SCL 12A3 gene, suggesting that numerous heterozygous subjects exist in a general population [2, 3].

Diagnosis

Severe cases present with tetraparesia or cardiac arrhythmias that result from a rapid worsening of hypokalemia or hypomagnesemia. These symptoms are classically triggered by an extracellular dehydration resulting from intestinal abnormalities (diarrhoea, constipation) or by an excessive sweating (hyperthermia, confined atmospheres). The Gitelman syndrome is rather observed in men and would be due to mutations that inactivate the protein expression [4]. Hemoconcentration with a functional acute kidney injury is frequent. Extracellular dehydration is easily attributed to renal losses because urinary sodium concentration is inappropriately elevated (above 20 mmol/L on a urine sample measurement). Hypokalemia is always associated. Renal potassium losses are defined by an inappropriately elevated urinary potassium level (above 40 mmol/day). When intestinal or cutaneous potassium losses are present, urinary potassium excretion can be low. On the other hand, in case of vomiting, urinary potassium loss is elevated because of the increased filtered alkaline load promoting this phenomenon. If metabolic alkalosis is a typical biological disturbance, it may be masked in case of intestinal bicarbonates losses (diarrhoea), of shock or pre-existent chronic renal insufficiency. Hypocalciuria and renal hypomagnesemia are classical major parameters useful to differentiate the Gitelman and the classical Bartter syndromes. A urinary calcium/creatinine ratio <0.04 or a hypomagnesemia with an inappropriately high urinary magnesium excretion (>1 mmol/day) strongly evoke the diagnosis of the Gitelman syndrome. However, as shown in our case report, these criteria are not absolute and there are similar phenotypes for both syndrome. Parent's consanguinity is not frequent in the Gitelman syndrome. In the past history, some symptoms can be in favor of this diagnosis: moderate extracellular dehydration (dizziness), chronic hypokalemia (cramps, muscle weakness) or hypomagnesemia-related articular chondrocalcinosis [5]. After a clinical stabilisation, the phenotype is confirmed using functional renal tests. These results guide the molecular diagnosis by a sequence determination.

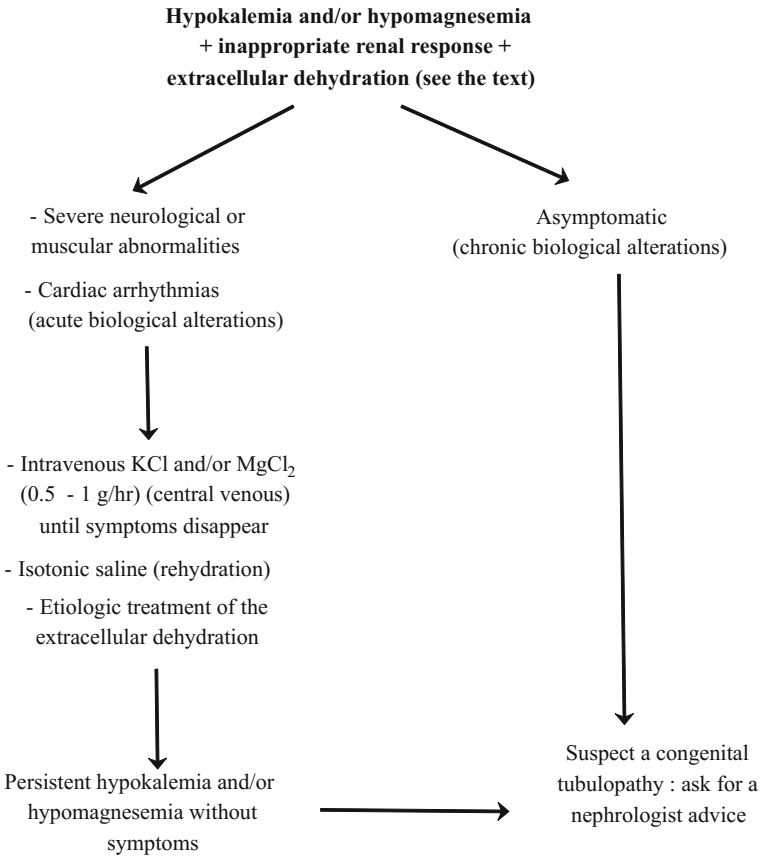

Fig. 1 Practical therapeutic management of the Gitelman and Bartter syndromes

Therapeutic Management

The symptomatic treatment must be rapidly started. An infusion of potassium and magnesium chloride permits to correct cardiac arrhythmias, to restore a normal muscular strength. But this does not normalize serum potassium and magnesium concentrations because of persistent urinary losses. Intravenous supplementation is necessary as long as clinical and electrical signs persist (Fig. 1). An etiologic treatment of the extracellular dehydration is also required. A chronic oral administration of potassium and magnesium seems to be indicated. A treatment with amiloride remains questioned in the Gitelman syndrome.

References

1. Zelikovic I et al (2003) A novel mutation in the chloride channel gene, CLCNKB, as a cause of Gitelman and Bartter syndromes. Kidney Int 63:24–32
2. Simon DB et al (1996) Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na–Cl cotransporter. Nat Genet 12:24–30
3. Simon DB, Lifton RP (1998) Mutations in Na(K)Cl transporters in Gitelman's and Bartter's syndromes. Curr Opin Cell Biol 10:450–454
4. Riveira-Munoz E et al (2007) Transcriptional and functional analyses of SLC12A3 mutations: new clues for the pathogenesis of Gitelman syndrome. J Am Soc Nephrol 18:1271–1283
5. Cruz DN et al (2001) Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. Kidney Int 59:710–717

Part X
Liver System

Uncommon Liver Diseases in ICU

Catherine Paugam-Burtz and Emmanuel Weiss

Key Points

- Acute liver failure is a rare but rapidly progressive critical illness with high mortality.
- Acute liver failure is characterized by the onset of acute coagulopathy and encephalopathy following a severe insult to a previously normal liver.
- Paracetamol overdose and viral hepatitis are the major causes of acute liver failure.
- Early recognition of causes requiring an early specific treatment is crucial at ICU admission.
- Emergency liver transplantation remains frequently the only therapeutic option for acute liver failure and has transformed its prognosis.

C. Paugam-Burtz · E. Weiss
Critical Care and Anesthesiology Department, AP-HP, Hôpital Beaujon, Hôpitaux Universitaires Paris Nord Val de Seine, F-75018 Paris, France

C. Paugam-Burtz (✉) · E. Weiss
Sorbonne Paris Cité, Univ Paris Diderot, F-75018 Paris, France
e-mail: catherine.paugam@bjn.aphp.fr

C. Paugam-Burtz · E. Weiss
INSERM U773, CRB3, F-75018 Paris, France

M. Leone et al. (eds.), *Uncommon Diseases in the ICU*,
DOI: 10.1007/978-3-319-04576-4_19,

Introduction

Patients with chronic liver diseases are prone to develop life-threatening complications that require ICU admission. Most of the time, they present acute decompensation of cirrhosis defined by the onset of one or more major complications such as portal hypertension-related digestive bleeding, sepsis, hepatic encephalopathy and/or acute renal failure. When associated with organ failure(s) and systemic inflammatory response syndrome, acute decompensation is named acute on chronic liver failure and is responsible for a high short-term mortality [1]. Beside these high-prevalence diseases, acute liver diseases, primarily acute liver failure (ALF), are rare, with an incidence less than five cases per million population per year [2]. Acute hepatitis is severe if prothrombin rate is less than 50 % corresponding to an International Normalized Ratio (INR) $\geq$ 1.5. Acute liver failure (ALF, sometimes referred to as fulminant hepatitis) is most commonly defined as the association of coagulopathy (INR $\geq$ 1.5) and encephalopathy (any degree of altered mental status) occurring within 8 weeks of symptom appearance in a patient without pre-existing liver disease or cirrhosis [3]. Only 10 % of patients with acute hepatitis, will develop a severe disease and, among those, less than 1 % an ALF. From a nosological point of view, ALF is nowadays commonly divided into three groups depending on the interval between the development of jaundice and the onset of encephalopathy: hyperacute (<7 days), acute (7–28 days) and subacute (4–12 weeks).

The introduction of emergency liver transplantation (LT) has transformed the prognosis of ALF. Indeed, survival rate rose from 20–25 % before 1984 to 77 % between 2005 and 2008 but remains inferior to planned LT for cirrhosis [4, 5]. ALF accounted for 8 % of indications of LT in Europe during 1999–2009 [6]. Series from specialized centers in the US, continental Europe and the UK consistently showed that 45–51 % of patients admitted for ALF underwent LT [7].

Management of ALF relies initially on etiological diagnosis aiming the recognition of the few causes of ALF that required early specific treatment. Then, while symptomatic treatment of organ failures is performed, natural disease prognosis has to be established to identify patients who will require emergency LT.

Clinical Picture of Acute Liver Failure

Regardless of the etiology, ALF has a common clinical picture that represents the final stage of acute organ failure, different from cirrhosis but specific to one organ, the liver. ALF is responsible for numerous systemic manifestations (Table 1) and sometimes for organ failures that may mimic gram-negative sepsis.

Table 1 Acute liver failure-related systemic manifestations

Organs	Manifestations
Lungs	Acute lung injury Acute respiratory distress syndrome
Heat	Cardiovascular collapse Endothelial dysfunction Frequent subclinical myocardial injury
Digestive tract	Ileus
Hepato-biliary system and pancreas	Portal hypertension Pancreatitis
Metabolism	Adrenal insufficiency High energy expenditure and muscle catabolism
Kidney	Renal injury and failure
Immune system	Systemic inflammatory response Immunoparesis Neutrophil dysfunction
Brain	Hepatic encephalopathy Brain edema Intracranial hypertension

Etiologies

Laboratory testing should be driven by the need of recognition of the few etiologies of ALF that can benefit from early cause-specific treatments to limit the severity of liver injury and potentially prevent progression from isolated hepatic failure to muti-organ failure. Extensive medical history should be collected from patient relatives and physical examination should be carefully performed.

ALF etiologies have been recently reviewed [8]. Paracetamol poisoning and viral hepatitis are the major causes of acute liver failure. It should be noted that paracetamol poisoning has surpassed viral etiology and has become the leading cause of ALF in US and UK (46 and 61 % of cases respectively). Toxic and non-paracetamol drug-induced liver injuries (including idiosyncratic reactions) represent 13 % of ALF cases in the US. In many cases, the etiology of ALF remains unclear despite extensive history taking and laboratory assessment and ALF is indeterminate. Accounting for 14–43 % of cases, these indeterminate forms are finally the second cause of ALF. The rare causes, which altogether account for 10–25 % of ALF cases, are displayed in Table 2. HSV-related hepatitis, a rare cause of ALF (1 % of ICU-admitted ALF), usually affects immunocompromised patients but can also concern immunocompetent individuals such as pregnant women [9]. Typical picture includes abdominal or dorsal pain, fever and chills, vesicular skin lesions and an important elevation of aminotransferases. However, because those signs are often missing, HSV-related hepatitis diagnosis is difficult and prognosis remains poor. Fever (>38.5 °C) and an important rise of aminotransferases are the most frequent symptoms; leucopenia and skin lesions are

Table 2 Etiological laboratory assessment

Etiologies	Biological diagnosis
Frequent causes	
Paracetamol	Serum paracetamol
Virus	HBs antigen, HBc IgM, HAV IgM
Rare causes	
Virus : Hepatitis E, HSV 1 and 2, VZV	HVE IgM, HVE PCR HSV1 and 2 IgM, HSV1 and 2 PCR VZV IgM, VZV PCR
Parvovirus B19	B19 PCR
Dengue fever	Dengue IgM and IgG
Leptospirosis	Microagglutination test
Wilson disease	Cupremia, cupruria, ceruloplasmin, ex ophtalmologic examination (Kayser-Fleischer ring)
Autoimmune hepatitis	Antinuclear antibodies, smooth muscle antibodies (SMA), antibodies to liver and kidney microsomes (anti-LKM)
Hypoxic hepatitis	Major hepatocellular injury (AST $\gg$ ALT)
Reye's syndrome	Moderate hepatocellular injury, normal serum bilirubin
Acute fatty liver of pregnancy	Moderate hepatocellular injury, normal serum bilirubin
HELLP syndrome	Low platelet count, hepatocellular injury, hemolysis, disseminated intravascular coagulation, renal failure
Neoplastic infiltration	Bone marrow infiltration, liver infiltration on biopsy
Heat shock	Hepatocellular injury, rhabdomyolysis, multiple organ failure
Mushroom poisoning	History taking
Acute Budd-Chiari syndrome	Abdominal ultrasound (hepatic vein thrombosis), thrombophilia

frequently lacking. Diagnosis is confirmed by real-time PCR and, to a lesser extent, by viral culture. Serological tests are not useful during the acute phase.

Amanita spp. poisoning is an other rare cause of ALF [10]. The toxicity of Amanita spp. is related to two distinct toxins, both heat resistant. First phase of the disease is characterized by profuse diarrhea-related to phallotoxin that causes alterations of the cellular membrane of enterocytes. During the second phase, amatoxin inhibits protein synthesis at a transcriptional level within hepatocytes and proximal tubular cells thereby inducing massive liver cell necrosis, decrease of coagulation factor and acute kidney injury (frequently aggravated by diarrhea). Global mortality rate of these intoxications is 25 %. An interval between ingestion and the onset of the diarrhea shorter than 8 h, female gender, decrease in prothrombin rate below 10 % (INR $>$ 6) 4 days or more after ingestion and a biphasic evolution of aminotransferases are associated with a fatal outcome.

Treatments

Disease-Specific Treatments

Specific treatments for ALF are scarce and dedicated to a few causes of ALF. All these treatments share a common feature: their administration has to be performed as early as possible in the evolution of the liver injury to provide clinical benefit. N-acetylcysteine (NAC), a glutathione precursor has been shown to reduce liver injury and probably to improve prognosis of paracetamol overdose. Thus, NAC has to be administered as early as possible for all cases of suspected paracetamol-induced ALF. Interestingly, some data suggests that NAC may attenuate cerebral complications and improve transplant-free survival of non-paracetamol induced ALF. Based on these results, NAC treatment is frequently considered for non-paracetamol induced ALF and tends to be extensively used in ALF whether paracetamol-induced or not. In severe autoimmune hepatitis, no benefit of systemic steroids has been shown. There is no specific treatment for acute forms of hepatitis A, B or E. D-penicillamine treatment is not active on fulminant forms of Wilson-disease. In case of suspicion of HSV or in cases of feverish ALF of unknown origin, since results of diagnostic tests might not be readily available, antiviral therapy (acyclovir) should be pre-emptively administered without waiting virological confirmation.

Symptomatic Treatments

The place of artificial liver support in ALF treatment remains controversial. This is particularly true in France where liver grafts from deceased donors can be obtained rapidly. Artificial liver supports have been shown in several small studies to improve biochemical parameters (serum bilirubin and ammonia), hemodynamics (increase in mean arterial pressure and decrease in portal pressure), jaundice and pruritus (clearance of bile acids). In addition, those systems have been shown to reduce levels of substances that are believed to play a pathophysiological role in ALF such as cytokines, vasoactive substances, metabolites of nitric oxid or free radicals [11]. Finally, beneficial effects on hepatic encephalopathy and/or intracranial pressure are sporadically described. However, whether the above-mentioned benefits will translate in a better clinical outcome is still a matter of debate. A recent randomized, controlled trial in France (FULMAR) compared Molecular Adsorbent Recycling System (MARS^{TM}) plus standard medical treatment (SMT) versus SMT alone in patients with ALF fulfilling criteria for LT [12]. Fifty-three patients received MARS treatment and 49 had SMT. Results of this study showed no survival benefit of MARS in ALF. A non-statistically significant trend for improved 6-month survival was recorded in the MARS group in paracetamol-induced ALF. However, a major confounder was the very short listing-to-transplant time in this study (median time of 16.2 h).

Numerous physiopathological mechanisms are involved in ALF-related encephalopathy and cerebral edema. Among them, raised concentrations of circulating neurotoxins, especially ammonia probably play a central role through changes in neurotransmitter synthesis and release and astrocytic metabolism of ammonia into glutamine. The overall result is a change in cerebral function and an astrocytic swelling (related to intracellular glutamine accumulation). Although the frequency of clinically overt cerebral edema has decreased over the past 20 years, such hypertension still account for 20–25 % of deaths [13]. Cerebral blood flow and/or intracranial pressure monitoring in case of ALF-related coma is controversial. Invasive monitoring techniques are associated with both morbidity and mortality, with a study by the ALF group on 332 patients from 24 centers revealing the finding of intracranial hemorrhage in 10.3 % of patients with invasive intracranial monitoring [14]. Furthermore, to date, none of the monitoring techniques showed a benefit in term of survival. The possible role of non invasive techniques such as transcranial doppler remains to be evaluated. In a study of 16 patients with ALF, information obtained from transcranial doppler signal of the middle cerebral artery wave forms were promising [15]. Management of ALF-related intracranial hypertension is similar to that of severe traumatic brain injury: 30° head-up position, control of systemic-related secondary brain injuries, use of osmotic therapy (hypertonic saline or mannitol) in case of cerebral herniation. An ample body of experimental and human data provides a rationale for the use of therapeutic hypothermia (between 32 and 34 °C) to improve the control of intracranial pressure in case of ALF-related intracranial hypertension. However, multicenter randomized controlled trials are still needed to confirm that hypothermia secures the brain and improves survival without causing harm before its incorporation into standard clinical practice.

Liver Transplantation

LT has to be considered when native liver regeneration within a period of time consistent with survival is unlikely. It depends, in part, on the etiology of ALF [8]. Indeed, liver injuries related to paracetamol overdose and viral hepatitis A as well as those following hypoxic hepatitis improve most often spontaneously. Conversely, only 20 % of autoimmune, indeterminate or non-paracetamol drug induced ALF have a spontaneous favorable course. Patients who will not achieve sufficient regeneration need to be identified early in the course of their disease to increase the probability of successful emergency transplantation. However, the ideal means for identification and selection of patients who are likely to benefit emergency LT remains controversial and transplantation decision-making always consists in choosing between two strategies:

- An early decision of transplantation aiming to reduce mortality during waiting-list and perioperative period that might lead to futile LT: a patient who would

otherwise have survived with medical management and who has incorrectly received a graft will be subjected to an unnecessary surgical procedure and life-long immunosuppression both associated with an increased risk of death. Furthermore, a graft that could be used in a more appropriate candidate will be lost.
- A late decision of listing will avoid unnecessary LT but will increase the risk of potentially preventable death during listing and perioperative periods.

To guide this decision, different selection criteria for emergency transplantation have been proposed. Clichy criteria take into account the existence of a coma or confusion associated with factor V concentrations less than 20 % in patients aged less than 30 years or less than 30 % in patients aged more than 30 years [4]. Those criteria are based on old data showing a 90 %-mortality rate among patients meeting these criteria in case of standard medical therapy. According to Kings college criteria, listing should be considered in case of paracetamol-related ALF if arterial pH is less than 7.3 following adequate fluid resuscitation, or comination of encephalopathy grade 3 or more, creatinine 300 μmol/L or more, and INR more than 6.5 [16]. In case of non-paracetamol-related ALF, listing criteria are any grade encephalopathy and INR more than 6.5, or any three of: INR more than 3.5, bilirubin 300 μmol/L or more, age less than ten or more than 40 years, unfavorable cause (drug-induced liver injury, seronegative disease). Recently, a new prognostic model combining coma grade, serum bilirubin, INR, phosphorus and M30 (cytokeratin-18 fragment, a marker of hepatocyte apoptosis and necrosis) has been developed by the Acute Liver Failure Study Group (ALFSG index) [17]. Its ability for predicting need for liver transplantation or death was better than Kings college criteria but M30 tests are not available for routine use. In practice, using these criteria, patients are nationally listed in emergent fashion. A new evaluation of the patient's condition is crucial at the time a donor organ becomes available to ensure that there is no sign of liver function recovery and that the severity of ALF-associated organ failures has not reached the point of no return. The latter is particularly difficult to judge because no formal criteria for assuming the futility of transplantation have been implemented to date.

The European Liver Transplant Registry (ELTR) holds data on 87,963 LT performed in 79,063 patients in 23 European countries over 43 years, and has been used to evaluate outcomes and evolution of LT for ALF [6]. It shows that survival of patients transplanted for ALF between 1988 and 2009 at 1, 3, 5 and 10 years was 74, 70, 68 and 63 %, respectively. The ELTR data also show a constant and progressive improvement in survival over time with an increase in 5 year-survival of 12 % between 1988–1993 and 2004–2009 periods. However, outcomes of emergency transplantation for ALF are consistently lower than those of elective transplantation for cirrhosis. Despite substantial improvement of anesthesia and intensive care, early post transplant mortality of ALF remains high, mainly as a result of sepsis and ALF associated multi-organ failure and cerebral complications such as cerebral herniation.

When ALF etiology suggests an ability of the native liver to regenerate to normal morphology, auxiliary LT is an interesting alternative to conventional

transplantation. With this approach, the right lobe is usually replaced and the native left lobe remains in situ. In carefully selected series, the native liver regenerates within 1–3 years to the degree that immunosuppression can be withdrawn slowly resulting in atrophy of the graft. Paracetamol-induced liver failure and the hyperacute syndromes are much more favorable candidates for this approach than patients with seronegative hepatitis and the subacute syndromes.

Conclusion

Acute liver failure prognosis has been transformed by emergency LT with a one-year survival exceeding 70 %. Management of patients with ALF has to be performed in specialized centers with a multi-disciplinary team associating an hepatologist, an intensivist and a transplant surgeon.

References

1. Moreau R, Jalan R, Gines P et al (2013) Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 144:1426–1437, 1437 e1-9
2. Bower WA, Johns M, Margolis HS, Williams IT, Bell BP (2007) Population-based surveillance for acute liver failure. Am J Gastroenterol 102:2459–2463
3. Trey C, Davidson CS (1970) The management of fulminant hepatic failure. Prog Liver Dis 3:282–298
4. Bernuau J, Goudeau A, Poynard T et al (1986) Multivariate analysis of prognostic factors in fulminant hepatitis B. Hepatology 6:648–651
5. Bernal W, Auzinger G, Dhawan A, Wendon J (2010) Acute liver failure. Lancet 376:190–201
6. Germani G, Theocharidou E, Adam R et al (2012) Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol 57:288–296
7. O'Grady J (2012) Liver transplantation for acute liver failure. Best Pract Res Clin Gastroenterol 26:27–33
8. Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH (2008) Acute liver failure: summary of a workshop. Hepatology 47:1401–1415
9. Ichai P, Samuel D (2009) Liver transplantation for fulminant hepatitis. Gastroenterol Clin Biol 33:51–60
10. Escudie L, Francoz C, Vinel JP et al (2007) Amanita phalloides poisoning: reassessment of prognostic factors and indications for emergency liver transplantation. J Hepatol 46:466–473
11. Nevens F, Laleman W (2012) Artificial liver support devices as treatment option for liver failure. Best Pract Res Clin Gastroenterol 26:17–26
12. Saliba F CC, Durand F et al and the FULMAR study group (2008) Randomized controlled multicenter trial evaluating the efficacy and safety of albumin dialysis with MARS in patients with fulminant and subfulminant hepatic failure. Abstract of the American Association for the Study of Liver Disease (AASLD). Hepatology 48:Abs LB4
13. Bernal W, Hyyrylainen A, Gera A et al (2013) Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol 59:74–80

14. Vaquero J, Fontana RJ, Larson AM et al (2005) Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl 11:1581–1589
15. Aggarwal S, Brooks DM, Kang Y, Linden PK, Patzer JF 2nd (2008) Noninvasive monitoring of cerebral perfusion pressure in patients with acute liver failure using transcranial doppler ultrasonography. Liver Transpl 14:1048–1057
16. O'Grady JG, Alexander GJ, Hayllar KM, Williams R (1989) Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 97:439–445
17. Rutherford A, King LY, Hynan LS et al (2012) Development of an accurate index for predicting outcomes of patients with acute liver failure. Gastroenterology 143:1237–1243