# Consultation Document for Case Definitions

## Adverse Events of Special Interest and Adverse Events Following Immunization during COVID-19 Vaccine Introduction

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# CONTENTS

# ABREVIATIONS AND ACRONYMS

| | |
|---|---|
| AAA | Acute aseptic arthritis |
| AASM | American Academy of Sleep Medicine |
| ABI | Ankle-brachial index |
| ACCESS | Vaccine COVID-19 monitoring readiness |
| ACS | Acute coronary syndrome |
| ADEM | Acute disseminated encephalomyelitis |
| ADQI | Acute Dialysis Quality Initiative |
| AEFI | Adverse events following immunization |
| AESI | Adverse events of special interest |
| AF | Atrial fibrillation |
| AHF | Acute heart failure |
| AHEI | Acute haemorrhagic edema of infancy |
| AKI | Acute kidney injury |
| AKIN | Acute Kidney Injury Network |
| ALF | Acute liver failure |
| ALI | Acute liver injury |
| ALP | Alkaline phosphatase |
| ALT | Alanine transaminase |
| AMI | Acute myocardial infarction |
| AP | Acute pancreatitis |
| ARDS | Acute respiratory distress syndrome |
| BC | Brighton Collaboration |
| BNP | Brain natriuretic peptide |
| BSA | Body surface area |
| CCP | Anticitrullinated peptides antibodies |
| CDC | Centers for Disease Control and Prevention |
| CEPI | Coalition for Epidemic Preparedness Innovations |
| CFR | Coronary flow reserve |
| CFS | Chronic fatigue syndrome |
| CMD | Coronary microvascular dysfunction |
| CMR | Cardiac magnetic resonance |
| COVID-19 | Coronavirus disease 2019 |
| CPAP | Continuous positive airway pressure |
| CRS | Chronic rhinosinusitis |
| CSF | Cerebrospinal fluid |
| CSVV | Cutaneous small vessel vasculitis |
| CV | Cutaneous vasculitis |
| DILI | Drug-induced liver injury |
| DVT | Deep vein thrombosis |
| DWI | Diffusion weighted |
| ECG | Electrocardiogram |
| EDF | Event definition form |
| EM | Erythema multiforme |
| ESKD | End-stage kidney disease |
| FIO2 | Fraction of inspired oxygen |
| FFR | Fractional flow reserve |
| FLAIR | Fluid-attenuated inversion recovery |
| GBS | Guillain-Barré syndrome |
| GFR | Glomerular filtration rate |

| | |
|---|---|
| GGT | Gamma-glutamyl transferase |
| HE | Hepatic encephalopathy |
| HF | Heart failure |
| HFmrEF | Heart failure with mid-range ejection fraction |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| IASL | International Association for the Study of the Liver |
| IASP | International Association for the Study of Pain |
| IgE | immunoglobulin E |
| IMR | Index of coronary muscular resistance |
| INR | International normalized ratio |
| KD | Kawasaki disease |
| KDIGO | Kidney Disease-Improving Global Outcomes |
| LUMP | Solid formation |
| LV | Left ventricular |
| LVEF | Left ventricular ejection fraction |
| MAS | Macrophage activation syndrome |
| MDRD | Modification of diet in renal disease |
| MI | Myocardial infarction |
| MIS-A | Multisystem inflammatory syndrome in adult |
| MIS-C | Multisystem inflammatory syndrome in children |
| MRI | Magnetic resonance imaging |
| MSLT | Mean sleep latency |
| PAO2 | Partial pressure of arterial oxygen |
| PAC | Premature atrial contractions |
| PAD | Peripheral artery disease |
| PCR | Polymerase chain reaction |
| PE | Pulmonary Thromboembolism |
| PEEP | Positive end-expiratory pressure |
| PMN | Polymorphonuclear leukocyte |
| POAD | Peripheral occlusive artery disease |
| PSVT | Paroxysmal supraventricular tachycardia |
| PT | Prothrombin time |
| PVC | Premature ventricular complexes |
| QTc | Corrected QT interval |
| RA | Rheumatoid arthritis |
| RHABDO | Rhabdomyolysis |
| RIFLE | Risk of renal dysfunction, injury to the kidney, failure or loss of kidney function, and end-stage kidney disease |
| RRT | Renal replacement therapy |
| RSV | Respiratory syncytial virus |
| r-VSV | Recombinant vesicular stomatitis virus |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SAT | Subacute thyroiditis |
| Scr | Serum creatinine |
| SOCV | Single organ cutaneous vasculitis |
| SPEAC | Safety Platform for Emergency Vaccines |
| SSS | Sick sinus syndrome |
| TBL | Total bilirubin level |
| TP | Thrombocytopenia |
| TSH | Thyroid-stimulating hormone |
| TTS | Takotsubo syndrome (stress cardiomyopathy) |

| | |
|---|---|
| ULN | Upper limit of normal |
| URI | Upper respiratory infection |
| URTI | Upper respiratory tract infection |
| VAED | Vaccine-associated enhanced disease |
| VTE | Venous thromboembolism |
| WHO | World Health Organization |
| WPW | Wolff-Parkinson-White |

# INTRODUCTION

The COVID-19 pandemic has pressed the scientific community to innovate, develop, and implement new technologies to address the challenges required to prevent and treat the disease. Fortunately, the response has been successful; to date, several vaccines have been produced and many more are in process. These vaccines will be used on large numbers of people in different environments and in different populations.

Development of these vaccines has required creativity and flexibility, employing processes that usually take several years to complete, yet these vaccines have moved from design to production and authorization for use in less than a year. Risks have been taken by manufacturers in initiating production of vaccines while simultaneously conducting the required developmental and authorization work. Clinical studies of the vaccines that have thus far received emergency authorization for use will require close follow-up by multiple stakeholders, including National Regulatory Authorities, immunization programs, health care workers, and civil society, to ensure that use of these vaccines will continue to be as safe and effective in the field as was shown during clinical trials. In these trials, safety data on vaccines was accumulated up to two months after the last volunteer had been recruited and last dose administered.

COVID-19 vaccine safety surveillance will be of the utmost importance and will require collaboration by all stakeholders once a vaccine is introduced. Sharing data and information will be critical and thus criteria and definitions for events and clinical developments need to be standardized as part of the vaccine safety surveillance. Regarding post-vaccination adverse event surveillance, the World Health Organization (WHO) warns that conventional vaccine safety surveillance and pharmacovigilance systems will need to adapt quickly to new surveillance techniques and ensure that post-vaccination safety and exposure information is collected and processed quickly.

The objective of the present consultation document is to list and provide definitions of adverse events of special interest (AESI) and adverse events following immunization (AEFI) for COVID-19 vaccines that can be used as a common language for reporting these events. The importance of standardizing definitions of adverse events and their guidelines is that this will allow for data comparability and will lead to a better understanding of the adverse event.

The basic definitions to be used in the tool, as defined by WHO, are the following (*1*):

> **Adverse event of special interest (AESI):** A pre-identified, predefined, medically significant event that has the potential to be causally associated with a vaccine product, and that needs to be carefully monitored and confirmed by further specific studies (*1*).
>
> The list of such events considered potentially applicable to COVID-19 vaccines includes serious events that:
>
> (a) occurred with other vaccines (such as Guillain-Barré syndrome, acute disseminated encephalomyelitis (ADEM), or anaphylaxis).
>
> (b) are potentially related to new platforms.
>
> (c) are potentially related to adjuvants.
>
> (d) are related to the failure of the immunogenicity of the vaccine; and
>
> (e) are potentially specific to special populations.
>
> The list can potentially include the exacerbation of the disease intensified by the vaccine (if vaccination is related to a more severe subsequent infection with SARS-CoV-2). Other events of special interest may include respiratory, cardiac, acute kidney and liver

damage, neurological disorders, sepsis and septic shock, hypercoagulability, rhabdomyolysis and multisystemic inflammatory syndrome in children (MIS-C). One reason for updating the AESI list is to be prepared to monitor these events pre- and post-introduction and to assess whether case definitions are needed (2).

**Adverse event following immunization (AEFI):** Any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.

**Serious AEFI:** An event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.

For the present document, AEFI and AESI definitions were collected and pooled from different sources prioritizing the Brighton Collaboration publications; and if not available, also including those from WHO, the Emergency Vaccine Safety Platform (SPEAC) and the vACCine COVID-19 monitoring readinESS (ACCESS).

Standardized definitions may facilitate implementation of study protocols as well as contribute to increasing global awareness of harmonized terminologies, educating about their benefits, monitoring their global use, and facilitating access.

The Coalition for Epidemic Preparedness Innovations (CEPI) has an agreement with the Brighton Collaboration, through the Global Health Task Force, to harmonize the safety assessment of vaccines financed by CEPI through SPEAC. As part of its analysis of the COVID-19 landscape, this document reflects information from the SPEAC document that describes the methods and results SPEAC used to develop the list of AESI (2).

Brighton Collaboration publications were accessed and used for the case definition of AESI and guidelines for collection, analysis, and presentation of immunization safety data related to thrombocytopenia, aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM), facial nerve palsy including Bell's palsy, Guillain-Barré syndrome, generalized convulsive seizure, anaphylaxis, single organ cutaneous vasculitis, and vaccine-associated enhanced disease (VAED) as a final version in submission. The Brighton Collaboration publications also mention acute respiratory distress syndrome (ARDS) and multisystem inflammatory syndrome in children and adults (MIS-C/A). At present, however, these remain without a case definition; thus, the case definitions revised from ACCESS were used, as well as for the other AESI, including anosmia, ageusia, meningoencephalitis, narcolepsy, acute aseptic arthritis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis/pericarditis, venous and pulmonary thromboembolism (VTE/PE), hemorrhage, cerebrovascular stroke, limb ischemia, acute kidney injury, chilblain-like lesions, erythema multiforme, and acute liver injury.

# PART A

# Adverse events of special interest (AESI)

The following tables set out AESI, the use of terms by the relevant agencies/organizations, and the source for the case definition used.

## 1. Generalized convulsive

| Brighton Collaboration case definition and SPEAC. Relevant for vaccination in general. | | |
|---|---|---|
| **Category** | Neurologic | |
| **Rationale for inclusion** | Proven association with immunization encompassing several different vaccines and theoretical concern related to viral replication during wild type disease (2). | |
| **About the AESI** | According to Bonhoeffer et al., seizures are "episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness. Descriptions and classifications of seizures are complex and subject to change because the etiology and pathogenesis of most seizures remain to be elucidated. Of primary interest in vaccine safety studies is the diagnosis certainty, whether a seizure was truly present or not, and whether fever was present immediately prior to the onset of a seizure. The certainty about the type of seizure is of secondary importance from the vaccine safety point of view" (3). | |
| **Case definition** | According to the case definition of Bonhoeffer et al:<br>*Level 1 of diagnostic certainty:*<br>• witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.<br>*Level 2 of diagnostic certainty:*<br>• history of unconsciousness AND generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.<br>*Level 3 of diagnostic certainty:*<br>• history of unconsciousness AND other generalized motor manifestations (3). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS, FDA/CDC | |

## 2. Guillain-Barré syndrome (GBS)

| Brighton Collaboration case definition and SPEAC. Relevant for vaccination in general. | |
|---|---|
| **Category** | Neurologic |
| **Rationale for inclusion** | Proven association with immunization encompassing several different vaccines and theoretical concern related to viral replication during wild type disease (2). |
| **About the AESI** | According to Sejvar James et al, "among the various events reported as adverse outcomes following immunizations, neurologic adverse events following immunization (AEFI) are among the most severe and the most difficult to assess. The multifaceted presentation of neurologic illness, the relative lack of familiarity of many clinicians with the approach to and diagnosis of neurologic disease, and the relative scarcity of trained neurologists in many parts of the world make neurologic AEFI some of the most challenging issues in clinical vaccinology" (4). |

| | | |
|---|---|---|
| **Case definition** | According to the case definition of Sejvar James et al:<br>*Level 1 of diagnostic certainty:*<br>• Bilateral AND flaccid weakness of the limbs; AND<br>• Decreased or absent deep tendon reflexes in weak limbs.<br>AND<br>• Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau.<br>AND<br>• Electrophysiologic findings consistent with GBS;<br>AND<br>• Cytoalbuminologic dissociation (i.e., elevation of cerebrospinal fluid (CSF) protein level above laboratory normal value<br>AND<br>• CSF total white cell count <50 cells/µl).<br>AND<br>• Absence of an identified alternative diagnosis for weakness (*4*). | **Complete case definition** |
| **Basal frequency** | The annual incidence of GBS has been estimated at between 0.4 and 4.0 cases per 100,000 population per year, depending upon study methodology and case ascertainment; most well-designed prospective studies in developed countries have suggested an incidence of 1–2 per 100,000 population per year (*4*). | |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS, FDA/CDC | |

## 3. **Acute disseminated encephalomyelitis (ADEM)**

| Brighton Collaboration case definition and SPEAC. Relevant for vaccination in general. | | |
|---|---|---|
| **Category** | Neurologic | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis (*2*). Occurs rarely and has not been proven to be caused by immunization.<br>Known/possible association with: Live viral vaccines including measles (*2*).<br>Despite this, a single ADEM case could completely disrupt an immunization program, which is why it has been identified as an AESI (*5*). | |
| **About the AESI** | According to Sejvar James et al, "among the various events reported as adverse outcomes following immunizations, neurologic adverse events following immunization (AEFI) are among the most severe and the most difficult to assess. The multifaceted presentation of neurologic illness, the relative lack of familiarity of many clinicians with the approach to and diagnosis of neurologic disease, and the relative scarcity of trained neurologists in many parts of the world make neurologic AEFI some of the most challenging issues in clinical vaccinology" (*6*). | |
| **Case definition** | According to the case definition of Sejvar James et al:<br>*Level 1 of diagnostic certainty:*<br>(a) Demonstration of diffuse or multifocal areas of demyelination by histopathology (*6*). | **Complete case definition** |
| **Basal frequency** | Frequency in the general population: Estimates of viral encephalitis rates have ranged from 0.08/100,000 population in national passive surveillance studies to 1–6 cases per 100,000 in hospital-based studies to 7.4 cases per 100,000 in one population-based study (*6*). | |

| | |
|---|---|
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS, FDA/CDC |

## 4. **Anosmia, ageusia**

| SPEAC listed the event as prioritized on May 25, 2020. Relevant for COVID-19. | | |
|---|---|---|
| **Category** | Neurologic | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease (2).<br>These effects are so common with acute COVID-19 infections that they have been proposed for the COVID-19 screening. It is recommended that relatively high priority should be placed on raising awareness about these conditions and determining their background rates, since they are also known to occur with other viral respiratory infections like influenza. This will be especially high priority in settings where there is ongoing community spread of COVID-19 disease (5). | |
| **About the AESI** | According to ACCESS, "Ageusia is the loss of taste functions of the tongue, and Anosmia the loss of the ability to detect one or more smells" (7). | |
| **Case definition** | Definition not available in Brighton Collaboration; presented by ACCESS, which is still under construction.<br>**Anosmia**: absent smell function with two causes for the event: 1) conductive and / or traumatic and 2) sensorineural.<br>**Ageusia**: absent taste function. Staging system to assess whether the patient has ageusia or dysgeusia. A scale ranging from 0, which refers to the absence of taste, to 4, which refers to the total loss of flavor, can be useful in the evaluation (7). | **Complete case definition** |
| **Basal frequency** | Anosmia – 20% of the population (8). | |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS | |

## 5. Meningoencephalitis

| SPEAC listed the event as prioritized on May 25, 2020. Relevant for COVID-19. | | |
|---|---|---|
| **Category** | Neurologic | |
| **Rationale for inclusion** | Proven association with immunization encompassing several different vaccines and theoretical concern related to viral replication during wild type disease (2).<br>Meningoencephalitis is an issue for live attenuated vaccines, especially in immunocompromised individuals. Although currently it seems unlikely that there will be live attenuated COVID-19 vaccines in use, but if they are implemented, meningoencephalitis should be a higher priority in the AESI surveillance than for programs that implement inactivated vaccines (5). | |
| **About the AESI** | According to ACCESS, "encephalitis is defined as inflammation of the parenchyma of the brain. Strictly speaking, it is a pathologic diagnosis, in which the presence of inflammation, edema, and neuronophagia (neuronal cell death) is demonstrated by histopathology" (9). | |
| **Case definition** | ACCESS case definition:<br>*Level 1 of diagnostic certainty:*<br>(a) demonstration of acute inflammation of central nervous system parenchyma (± meninges) by histopathology (9). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS, FDA/CDC | |

## 6. Aseptic meningitis

| Brighton Collaboration case definition and SPEAC. Relevant for specific vaccine platforms for COVID-19 vaccines. | | |
|---|---|---|
| **Category** | Neurologic | |
| **Rationale for inclusion** | Allow standardized assessment and improve comparability of cases of aseptic meningitis (*2*). | |
| **About the AESI** | According to Tapiainen et al., "Aseptic meningitis is commonly defined as a syndrome characterized by acute onset of signs and symptoms of meningeal inflammation, cerebrospinal fluid (CSF) pleocytosis and the absence of microorganisms on Gram stain and/or on routine culture. Aseptic meningitis is frequently caused by viral agents, particularly by enteroviruses. Aseptic meningitis following immunization usually is benign and resolves without sequelae" (*10*). | |
| **Case definition** | According to the case definition of Tapiainen et al.:<br>*Level 1 of diagnostic certainty:*<br>• Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity, or other signs of meningeal irritation; AND<br>• Pleocytosis in CSF determined as:<br>○ >5 leukocytes/mm3 (L) if patient is 2 months of age or older.<br>○ >15 leukocytes/$mm^3$ (L) in infants younger than 2 months.<br>AND<br>• Absence of any microorganism on Gram stain of CSF; AND<br>• Negative routine bacterial culture of CSF in the absence of antibiotic treatment before obtaining the first CSF sample (*10*). | **Complete case definition** |
| **Incidence** | Reported incidences with mumps vaccination have ranged from a frequency of 1:2,041 for the Urabe strain to 1 > 1,800,000 for Jeryl-Lynn. In one further study, the incidence of aseptic meningitis after mass immunization with measles-rubella vaccine (i.e., without a mumps vaccine strain) has been reported to be low with an incidence of 1:867,000 doses (*10*). | |
| **Listed** | Brighton Collaboration/SPEAC, FDA/CDC | |

## 7. Facial nerve palsy

| Brighton Collaboration case definition | |
|---|---|
| **Category** | Neurologic |
| **Rationale for inclusion** | According to Barbara Rath et al., "recognizing the many variables and uncertainties that affect the definition and diagnosis of peripheral facial nerve palsy, including Bell's palsy, it was important to establish useful and practical guidelines to standardize the collection, analysis, and presentation of peripheral facial data, or Bell's palsy, in the context of pre- and post-licensing clinical trials, surveillance and epidemiological studies of vaccine safety" (*11*). |
| **About the AESI** | According to Barbara Rath et al., "facial nerve palsy is classified based on the location of its lesion. Peripheral facial nerve palsy is the partial (i.e., paresis) or complete (i.e., paralysis) loss of function of some or all the structures innervated by the facial nerve (i.e., cranial nerve VII). Facial nerve palsy is also classified by the time course of its development depending on whether acute (minutes to days), subacute (days to weeks), or chronic (longer than weeks)" (*11*). |

| | | |
|---|---|---|
| **Case definition** | According to the case definition of Barbara Rath et al., given the lack of consensus on the term Bell's palsy and the use sometimes synonymous with peripheral facial nerve palsy, Brighton Collaboration collaborators developed an algorithm/decision tree that leads to a common definition of idiopathic facial nerve palsy, systematically excluding the known causes of such paralysis, with a more relevant approach for vaccinologists to identify and confirm true cases of idiopathic paralysis.<br>Peripheral facial nerve palsy: initially, the diagnosis of acute-onset peripheral facial nerve palsy needs to be confirmed. Peripheral facial nerve palsy is defined as a weakness of the facial muscles innervated by cranial nerve VII, which is either complete (paralysis) OR incomplete (paresis). Notes 1 and 2 and may manifest unilaterally OR bilaterally Note 3.<br>*Level 1 of diagnostic certainty:*<br>Manifests with the acute onset decreased ability (paralysis OR paresis) to wrinkle the forehead OR to raise the eyebrows at the affected side (*11*). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC | |

## 8. Narcolepsy

| Brighton Collaboration case definition | | |
|---|---|---|
| **Category** | Autoimmune | |
| **Rationale for inclusion** | "Due to the history of a possible relationship between narcolepsy and the H1N1 vaccine and can be used to monitor the risk-benefit profile of upcoming COVID-19 vaccines." (12). | |
| **About the AESI** | According to Francesca Poli et al., narcolepsy is a sleep disorder primarily characterized by excessive daytime sleepiness and cataplexy – episodes of muscle weakness brought on by emotions (12). | |
| **Case definition** | According to the case definition of Francesca Poli et al.:<br>*Level 1 of diagnostic certainty:*<br>In the presence of:<br>Excessive daytime sleepiness; OR<br>Unambiguous cataplexy,<br>AND<br>CSF hypocretin-1 deficiency (12). | **Complete case definition** |
| **Basal frequency** | 19–56 per 100,000 people in Europe and the USA (*13*). | |
| **Listed** | EMA/ACCESS, FDA/CDC | |

## 9. Enhanced COVID-19 disease following immunization

| Brighton Collaboration case definition and SPEAC. Relevant for COVID-19. | |
|---|---|
| **Category** | Immunologic |
| **Rationale for inclusion** | After using inactivated viral vaccines for measles and respiratory syncytial virus (RSV) severe disease has been documented resulting from infection in individuals primed with non-protective antibodies. Disease enhancement has also been observed with dengue and pandemic influenza (*2*). |

| | | |
|---|---|---|
| **About the AESI** | According to Munoz et al., vaccine-associated enhanced diseases (VAED) are modified presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccination for the same pathogen. Vaccine-associated enhanced respiratory (VAERD) disease refers to a disease with predominant involvement of the lower respiratory tract". The reference remains the same. *(14)* | |
| **Case definition** | According to the case definition of Munoz et al., vaccine-associated enhanced disease (VAED) is characterized by a vaccine that results in increased disease severity if the subject is afterwards infected by the natural virus *(14)*. | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC, FDA/CDC | |

## 10. Multisystem inflammatory syndrome in children (MIS-C)

| SPEAC listed the event as prioritized on May 25, 2020. Relevant to COVID-19. | | |
|---|---|---|
| **Category** | Immunologic | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease (*2*). | |
| **About the AESI** | According to the publication ACCESS, "multisystemic inflammatory syndrome in children, also known as MIS-C, is a syndrome that appears to be a rare complication of COVID-19 in children. When we think that COVID-19 did not affect children, it appears that children who were previously healthy can become seriously ill with COVID-19. The syndrome is like incomplete Kawasaki disease (KD), a febrile childhood disease involving inflammation of the blood vessels that can result in coronary artery aneurysms. Symptoms usually occur 1 to 6 weeks after infection with COVID-19 and may overlap with an acute respiratory presentation of COVID-19" (*15*). | |
| **Case definition** | According to ACCESS, "MIS-C can be present like the criteria used for Kawasaki disease or at least some of them. Besides these symptoms, children can present with evidence of multi-organ failure. The main difference between KD and MIS-C is that classic KD typically affects infants and young children, whereas MIS-C affects mostly older children and adolescents. Children with MIS-C have a median age of 9 years old, which is 2.7 years for those with KD. Gastrointestinal symptoms are often dominant in children with MIS, whereas these symptoms are less prominent in classic KD. This also applies to myocardial dysfunction and shock, which occurs more commonly in MIS-C than in classic KD" (*15*). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC, EMA/ACCESS, FDA/CDC | |

## 11. Anaphylaxis

| Brighton Collaboration case definition and SPEAC. Relevant for vaccination in general. | |
|---|---|
| **Category** | Immunologic |
| **Rationale for inclusion** | Proven association with immunization encompassing several different vaccines, and proven association with immunization encompassing several different vaccines (*2*). |

| | | |
|---|---|---|
| **About the AESI** | According to Jens Ruggeberg et al., "anaphylaxis is an acute hypersensitivity reaction with multiorgan-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, and immunizations. Anaphylaxis is triggered by the binding of allergen to specific immunoglobulin E (IgE)" (*16*). | |
| **Case definition** | According to the case definition of Jens Ruggeberg et al., for all levels of diagnostic certainty anaphylaxis is a clinical syndrome characterized by sudden onset AND rapid progression of signs and symptoms AND involving multiple (≥2) organ systems, as follows.<br>*Level 1 of diagnostic certainty:*<br>• ≥1 major dermatological; AND<br>• ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion (*16*). | **Complete case definition** |
| **Basal frequency** | USA 0.05-2% Europe approx. 3% (*17*). | |
| **Listed** | Brighton Collaboration/SPEAC | |

## 12. Acute aseptic arthritis (AAA)

| | | |
|---|---|---|
| Brighton Collaboration case definition and SPEAC. Relevant for specific vaccine platforms for COVID-19 vaccines. | | |
| **Category** | Immunologic | |
| **Rationale for inclusion** | It has been recognized to be potentially associated with r-VSV platform (*2*). | |
| **About the AESI** | According to Andreas Woerner and the review of collaborators for ACCESS, acute aseptic arthritis (AAA) is a clinical syndrome characterized by the acute onset of signs and symptoms of joint inflammation for a period not exceeding 6 weeks, increased synovial white blood cell count, and absence of microorganisms in Gram stain, routine culture, and/or polymerase chain reaction (PCR) (*18*,*19*). | |
| **Case definition** | According to the case definition of Andreas Woerner et al., and the complement of the review of collaborators for ACCESS, the case definition has been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of AAA can be captured. All levels of diagnostic certainty: one or more of the following clinical signs and symptoms assessed by a health care provider, articular or peri-articular swelling, articular effusion, articular or peri-articular erythema, increased warmth palpable over capsular contour of the joint, restricted range of movement, AND duration of less than 6 weeks until complete resolution of symptoms AND, absence of recent articular trauma Level 1 of diagnostic certainty (*18*,*19*). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC | |

## 13. Acute respiratory distress syndrome (ARDS)

| SPEAC listed the event as prioritized on May 25, 2020. Relevant to COVID-19. | | |
|---|---|---|
| **Category** | Respiratory | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease (*2*). | |
| **About the AESI** | Acute respiratory distress syndrome (ARDS) was defined in 2011 by a panel of experts comprised of the European Society of Intensive Care endorsed by the American Thoracic Society and the Society of Critical Care Medicine, known as the Berlin definition. (*20*) | |
| **Case definition** | According to The Berlin Definition of Acute Respiratory Distress Syndrome: timing – within 1 week of a known clinical insult or new or worsening respiratory symptoms; Chest imaging – bilateral opacities; Origin of edema – respiratory failure explained by effusions; Oxygenation. *(20)* | **Complete case definition** |
| **Incidence** | Estimated incidence and mortality rate in a 5-million-person population base 10-14 cases per 100,000 people (*21*). | |
| **Basal frequency** | 1.5 to nearly 79 cases per 100000 Europe 1.8 to 31 per 100000 Brazil (*22*). | |
| **Listed** | Brighton Collaboration/SPEAC, FDA/CDC | |
| *"Abbreviations: CPAP, continuous positive airway pressure; FIO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure."* | | |

## 14. Acute cardiac injury

| SPEAC: Acute cardiac injury relevant for COVID-19. Myocarditis relevant for specific vaccine platforms for COVID-19. | | |
|---|---|---|
| **Category** | Cardiac | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease. It is known the association with Modified Vaccinia Virus Ankara platform (*2*).<br>Would be of higher priority in settings and populations where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, chronic renal failure) (*5*). | |
| **About the AESI** | According SPEAC the acute cardiac injury including: Microangiopathy, Heart failure (HF) and cardiogenic shock, Stress cardiomyopathy, Coronary artery disease, Arrhythmia, Myocarditis, pericarditis (*2*). | |
| **Case definition** | **According** to ACCESS:<br>**Microangiopathy:** Cardiac microangiopathy leads to microvascular dysfunction which can manifest in different clinical scenarios.<br>**Heart failure:** HF is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue).<br>**Stress cardiomyopathy** has as signs and symptoms: acute chest pain, dyspnoea, syncope, new electrocardiogram (ECG) changes, sudden elevation of cardiac biomarkers, induced by physical stress.<br>**Coronary artery disease:** or ischemic heart disease describes a set of clinical symptoms due to an inadequate blood supply to the myocardium. This pathological process is characterized by | **Complete case definition** |

| | | |
|---|---|---|
| | atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive.<br><br>**Arrhythmia:** A cardiac arrhythmia is an abnormality or perturbation in the normal activation or beating of the heart myocardium.<br><br>**Myocarditis:** Inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immunohistochemical criteria.<br><br>**Pericarditis:** is the inflammation of the pericardium from various origins, such as infection, neoplasm, autoimmune process, injuries, or drug induced (*23*). | |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS, FDA/CDC | |

## 15. Coagulation disorder

| SPEAC listed the event as prioritized on May 25, 2020. Relevant for COVID-19. | | |
|---|---|---|
| **Category** | Hematologic | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease. Should be of higher priority in settings where there are other infections that could present with bleeding, such as dengue. It will be important to have testing in place to establish if any observed coagulation disorders are coincidental to immunization or are caused by immunization (*2*). | |
| **About the AESI** | According to ACCESS, "this event definition form (EDF) is about multiple groups of diseases under the overarching name of coagulation disorder. A coagulation disorder is a problem with blood clotting. This can either be to mush clotting leading to thrombosis, emboli, or stroke, or too little clotting leading to bleeding and again stroke" (*24*). | |
| **Case definition** | ACCESS case definition:<br><br>**Venous thromboembolism (VTE):** Deep vein thrombosis (DVT) refers to the formation of a blood clot in one of the body's large veins.<br><br>**Pulmonary thromboembolism (PE):** When a thrombus, origination most often in the lower limb, breaks loose from the vessel wall it travels freely thru the blood vessel on its way to the heart and lungs until it hits a point where it can no longer pass.<br><br>**Stroke:** Stroke is defined as the acute onset of focal neurological findings in a vascular territory as a result of underlying cerebrovascular disease.<br><br>**Limb ischemia:** This is defined as a quickly developing or sudden decrease in limb perfusion.<br><br>**Hemorrhagic disease:** This part of the coagulation disorders focuses on a lack of blood clotting. The blood is hypo coagulable resulting in bleeding (*24*). | **Complete case definition** |
| **Basal frequency** | 104 to 183 per 100,000 person-years (thromboembolism) (*25*). | |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS, FDA/CDC | |

## 16. Thrombocytopenia (TP)

| Brighton Collaboration case definition and SPEAC. Relevant for vaccination in general. | | |
|---|---|---|
| **Category** | Hematologic | |
| **Rationale for inclusion** | Proven association with immunization encompassing several different vaccines (*2*). | |
| **About the AESI** | According to Robert Wise, "TP is an abnormally low platelet count. Pathogenic mechanisms include insufficient production, abnormal distribution, or excessive destruction of platelets. Excessive destruction can be caused by microangiopathy, hereditary platelet abnormalities, or immunologic mechanisms" (*26*). | |
| **Case definition** | According to the case definition of Robert Wise et al:<br>*Level 1 of diagnostic certainty:*<br>Platelet count less than $150 \times 10^9\ L^{-1}$ AND, confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding (*26*). | **Complete case definition** |
| **Basal frequency** | 14.8 cases per 100,000 per year (*27*). | |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS, FDA/CDC | |

## 17. Acute kidney injury (AKI)

| SPEAC listed the event as prioritized on May 25, 2020. Relevant for COVID-19. | | |
|---|---|---|
| **Category** | Renal | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease (*2*).<br>Would be of higher priority in settings and populations where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, chronic renal failure) (*5*). | |
| **About the AESI** | According to ACCESS, "AKI is not a single disease entity. It is a heterogeneous group of conditions characterized by sudden decrease in glomerular filtration rate (GFR) followed by an increase in serum creatinine concentration or oliguria. It occurs in the setting of acute or chronic illness" (*28*). | |
| **Case definition** | In the ACCESS case definition, "AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that rarely has a sole and distinct pathophysiology" (*28*). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC | |

## 18. Chilblain-like lesions

| SPEAC listed the event as prioritized on May 25, 2020. Relevant for COVID-19. | |
|---|---|
| **Category** | Dermatologic |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease (*2*). |
| **About the AESI** | According to ACCESS, "during the recent COVID-19 pandemic patients with little or no symptoms presented themselves with chilblain-like lesions located on the toes and fingers" (*29*). |

| | | |
|---|---|---|
| **Case definition** | In the ACCESS case definition, "Chilblains, also referred to as perniosis or pernio, is a condition of the skin which manifests as erythematous to violaceous macules, papules, plaques, or nodules in sites of cold exposure and damp environments (idiopathic chilblains)" (29). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS | |

## 19. Single organ cutaneous vasculitis (SOCV)

| | | |
|---|---|---|
| Brighton Collaboration case definition and SPEAC. Relevant to COVID-19. | | |
| **Category** | Dermatologic | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease (2). | |
| **About the AESI** | According to Zanoni et al., "vasculitides are a group of heterogeneous conditions characterized by inflammation of the blood vessel walls, which can occur in any organ system. Cutaneous involvement occurs almost exclusively with vasculitis of small and medium-sized vessels" (30). | |
| **Case definition** | According to the case definition of Zanoni et al., "SOCV is a syndrome characterized by clinical and histological features of small vessel vasculitis of the skin without involvement of other organ systems.<br>(a) 2.1. For all levels of diagnostic certainty<br>Clinical features[2]<br>Hemorrhagic papules<br>OR<br>Urticaria-like lesions[3]<br>OR<br>Purpuric rash involving the face, ears, and extremities AND edema AND low-grade fever (only for AHEI)" (30) | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS | |

## 20. Erythema multiforme (EM)

| | | |
|---|---|---|
| SPEAC listed the event as prioritized on May 25, 2020. Relevant for COVID-19. | | |
| **Category** | Dermatologic | |
| **Rationale for inclusion** | Theoretical concern based on immunopathogenesis and related to viral replication during wild type disease (2). | |
| **About the AESI** | According to the ACCESS, "erythema multiforme was only included in its major form called erythema multiforme major" (31). | |
| **Case definition** | In the ACCESS case definition, "erythema multiforme (EM) is an acute, self-limited disease that is typically associated with hypersensitivity reactions to viruses, as well as drugs. It is characterized by targetoid erythematous lesions with predominant acral localization and can be subdivided into isolated cutaneous and combined mucocutaneous forms" (31). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS | |

## 21. Acute liver injury (ALI)

| SPEAC positions in priority list date May 25, 2020. Relevant for COVID-19. | | |
|---|---|---|
| **Category** | Gastrointestinal | |
| **Rationale for inclusion** | AESI that can be used to monitor the risk-benefit profile of upcoming COVID-19 vaccines (*2*).<br>Would be of higher priority in settings and populations where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, chronic renal failure) (*5*). | |
| **About the AESI** | According to ACCESS, "the disease process is associated with development of a coagulopathy of liver etiology, and clinically apparent altered level of consciousness due to hepatic encephalopathy (HE)" (*32*). | |
| **Case definition** | ACCESS cites the European Association for the Study of the Liver in the case definition for acute liver failure (IHA). "As highly specific and rare syndrome, characterized by an acute abnormality of liver blood tests in an individual without underlying chronic liver disease. The disease process is associated with development of a coagulopathy of liver etiology, and clinically apparent altered level of consciousness due to hepatic encephalopathy (HE)" (*32*). | **Complete case definition** |
| **Basal frequency** | 10 cases per million population in the developed world (*33*). | |
| **Listed** | Brighton Collaboration/SPEAC, WHO, EMA/ACCESS | |

## 22. Subacute thyroiditis (SAT)

| SPEAC listed the event as prioritized on Dec 23, 2020. Relevant for COVID-19. | | |
|---|---|---|
| **Category** | Endocrine | |
| **About the AESI** | The development of SAT during the period following vaccination for viruses is a rarely reported clinical entity (*34*, *35*). | |
| **Case definition** | Preliminary definition approach: It is characterized by a generally self-limiting, usually painful inflammatory lesion of the thyroid gland, most probably of viral origin. SAT begins with a prodrome of generalized myalgias, pharyngitis, low-grade fever, and fatigue. Patients then present with fever and severe neck pain, swelling, or both (*34, 35*). Occurs predominantly as a post-infectious illness with onset several weeks after the acute COVID-19. (*34*, *35*). | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC | |

## 23. Rhabdomyolysis

| SPEAC listed the event as prioritized on Dec 23, 2020. Relevant for COVID-19. | |
|---|---|
| **Category** | Renal |
| **About the AESI** | Rhabdomyolysis is a well-known cause of kidney failure and is commonly associated with drugs, toxins, and infections. Muscle syndrome such as rhabdomyolysis is recognized to not infrequently complicate viral infections, the |

| | | |
|---|---|---|
| | most common associations being with influenza A and B, cytomegalovirus, adenovirus, Coxsackie virus, Herpes virus and Epstein-Barr (*36*). | |
| **Case definition** | Preliminary definition: In rhabdomyolysis, there is breakdown of skeletal muscle cells, resulting in the release of cellular constituents such as electrolytes, myoglobin, and cellular enzymes, including creatine kinase. The consequences thereof can include life-threatening disseminated intravascular coagulation, electrolyte disturbances, and acute kidney injury (*36*).<br><br>One or more symptoms of rhabdo:<br>Muscle cramps, aches, or pains more intense than expected,<br>Dark urine (tea-colored or cola),<br>Weak or tired, inability to complete work tasks or finish an exercise routine,<br>The only way to know if a person has rhabdomyolysis is through a blood test that checks for the presence of a muscle protein, creatine kinase (CK), in the blood.<br>Symptoms can appear at any time after the muscle injury, or even several days after the initial injury. *(37)* | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC | |

## 24. Acute pancreatitis (AP)

| SPEAC listed the event as prioritized on Dec 23, 2020. Relevant for COVID-19. | | |
|---|---|---|
| **Category** | Gastrointestinal | |
| **About the AESI** | Preliminary definition: Acute pancreatitis (AP) is defined as an acute inflammatory disease of the pancreas with variable involvement of peripancreatic tissues and/or remote organ systems (*38*). | |
| **Case definition** | Acute pancreatitis is an inflammation of the pancreas with the activation of pancreatic enzymes within the country, which classically presents pain, vomiting and fatigue. The diagnosis is based on clinical symptoms, a three-fold increase in pancreatic enzymes and radiological evaluation *(38)*. | **Complete case definition** |
| **Listed** | Brighton Collaboration/SPEAC | |

# PART B

# Adverse events following immunization (AEFI)

The following tables list those AEFIs that were identified and notified during the clinical trials of the COVID-19 vaccines and were presented to the National Regulatory Authorities for emergency use authorization.

## 25. Fever following immunization

| Brighton Collaboration case definition. | | | | |
|---|---|---|---|---|
| **Category** | Systemic events | | | |
| **About the AEFI** | According to Marcy et al., fever is "a common clinical complaint in adults and children with a variety of infectious illnesses, as well as a frequently reported adverse event following immunization. Although the level of measured temperature indicative of a "fever" was first defined in 1868, it remains unclear what role fever has as a physiologic reaction to invading substances, how best to measure body temperature and compare measurements from different body sites, and, consequently, how to interpret fever data derived from vaccine safety trials or immunization safety surveillance. However, even with many aspects of the societal, medical, economic, and epidemiologic meanings of fever as an adverse event following immunization (AEFI) still elusive, it is a generally benign—albeit common—clinical sign. By standardizing the definition and means of assessment of fever in vaccine safety studies, thereby permitting comparability of data, we hope to arrive at an improved understanding of its importance as an AEFI" (*39*). | | | |
| **Case definition** | According to Marcy et al., The definition of a case of fever as an adverse event after immunization has 3 levels of assessment:<br><br>• Level 1 of diagnostic certainty<br>Fever is defined as the endogenous elevation of at least one measured body temperature of ≥38 °C.[2,3]<br>Temperature ⩾38 ° C (100.4 ° F), average anywhere using a validated instrument (*39*). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| **(°C)**<br>**(°F)** | 37.9 – 38.4<br>100.1 – 101.1 | 38.5 – 38.9<br>101.2 – 102.0 | 39.0 – 40.0<br>102.1 – 104.0 | >40.0<br>>104.0 |
| | | | | |

## 26. Fatigue

| Brighton Collaboration case definition | |
|---|---|
| **Category** | Systemic events |
| **About the AEFI** | According to Jones et al., "fatiguing illnesses, including chronic fatigue syndrome (CFS), following infection are well-documented. Fatigue and related symptoms following immunization have also been described, and the role of immunization as a causative factor in CFS has been hypothesized. Similar to the post-infection setting, post-immunization fatigue is not likely to be limited to the syndrome |

| | | | | |
|---|---|---|---|---|
| | designated as CFS, as short-lived fatigue states are far more common and transiently disabling" (41). | | | |
| **Case definition** | According to Jones' case definition et al., (41)<br>**Level 1 of diagnostic certainty (persons ≥ 5 years of age)**[a,b]<br>**Level 1a (fatigue state)**<br>• A new symptom[c,d] of fatigue (or a synonym),[e] *that is*<br>• The primary complaint,[f] *and is*<br>• Not relieved by rest,[g] *and*<br>• Interferes with an individual's function.[h] | | | |
| **Event rating scale** (40) | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | Does not interfere with activity | Some interference with activity | Prevents routine daily activity | Emergency visit or hospitalization for severe fatigue |

## 27. Joint pain

| Brighton Collaboration case definition | | | | |
|---|---|---|---|---|
| **Category** | Systemic events | | | |
| **About the AEFI** | According to Catherine Panozzo et al., "arthritis and arthralgia are reported as adverse events following immunization with various vaccines. The current evidence linking vaccination to incident arthritis or worsening arthritis is too heterogeneous and incomplete to infer a causal association" (42). | | | |
| **Case definition** | According to J. Gidudu' case definition et al., it can be any discomfort, pain, or inflammation that occurs in any part of the joint - including cartilage, bone, ligament, tendons, or muscles. Most common, however, joint pain refers to arthritis or arthralgia, which is inflammation or pain that comes from the joint itself (42). | | | |
| **Event rating scale** (40) | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | Does not interfere with activity | Some interference with activity | Prevents routine daily activity | Emergency visit or hospitalization for severe new or worsening joint pain |

## 28. Diarrhea

| Brighton Collaboration case definition | |
|---|---|
| **Category** | Systemic events |
| **About the AEFI** | According to J. Gidudu' et al., "diarrhea, also spelled diarrhoea, is a common medical condition that is characterized by increased frequency of bowel movements and increased liquidity of stool. Although acute diarrhea is typically self-limiting, it can be severe and can lead to profound dehydration, which can lead to abnormally low blood volume, low blood pressure, and damage to the kidneys, heart, liver, brain, and other organs" (43). |
| **Case definition** | According to J. Gidudu' case definition et al., it is defined as an increase of three or more bowel movements (defecation), above normal or baseline, occurring in a period of 24 hours and with liquid consistency stools and at a second level due to an increase in the frequency of bowel movements with a liquid consistency (43). |

| | | | | |
|---|---|---|---|---|
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | 2 to 3 loose stools in 24 hours | 4 to 5 loose stools in 24 hours | 6 or more loose stools in 24 hours | Emergency visit or hospitalization for severe diarrhea |

## 29. Chills

| | | | | |
|---|---|---|---|---|
| **Category** | Systemic events | | | |
| **About the AEFI** | The search for adverse events of rigors and chills has been associated with nausea, neoplasms, headache, infectious disorder, and reaction to medications. Rigors and Chills Adverse Event has been linked to Fibroblast Activation. (*44*). | | | |
| **Case definition** | Cold feeling accompanied by shaking (*44*) | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | Does not interfere with activity | Some interference with activity | Prevents routine daily activity | Emergency visit or hospitalization for severe chills |

## 30. Headache

| | | | | |
|---|---|---|---|---|
| **Category** | Systemic events | | | |
| **About the AEFI** | Headache is pain in any region of the head. Headaches may occur on one or both sides of the head, be isolated to a certain location, radiate across the head from one point, or have a viselike quality. A headache may appear as a sharp pain, a throbbing sensation, or a dull ache. Headaches can develop gradually or suddenly and may last from less than an hour to several days (*45*). | | | |
| **Case definition** | Headache is pain in any region of the head. They can occur on one or both sides of the head, be isolated to a particular location, radiate through the head from one point, or have a sensation of screw pressure. A headache can appear as a sharp pain, a throbbing sensation, or a dull ache. They can last from less than an hour to several days. Can be a primary headache is caused by overactivity of or problems with pain-sensitive structures in the head. (*45*). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | Does not interfere with activity. | Some interference with activity. | Prevents routine daily activity. | Emergency visit or hospitalization for severe headache. |

## 31. Injection site reactions

| Brighton Collaboration case definition | | | | |
|---|---|---|---|---|
| **Category** | Local reactions | | | |
| **About the AEFI** | Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (International Association for the Study of Pain, IASP). Pain is the most frequent local adverse event following immunization (AEFI). It results from the stimulation of nociceptive sensory neurons at the time of vaccine administration or inflammatory process in the damaged tissue afterward (*46*). | | | |
| **Case definition** | **Pain**: is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, that occurs at the site of immunization (*46*).<br>**Cellulitis**: is defined as an acute, infectious, and spreading inflammatory condition of the skin, characterized by inclusion and exclusion criteria attached. It should be noted that cellulitis can be accompanied by fever and / or regional lymphadenopathy, although its presence or absence does not influence the level of certainty of the diagnosis (*47*).<br>**Nodule**: is a solid formation (lump) of more than 2.5 cm in diameter that persists for more than a month, caused by epidermal thickening, inflammatory infiltration of the skin or subcutaneous tissues, or by deposits of substances at the administration site. They are firm and may include increased sensitivity, pain, and itching (*48*).<br>**Induration**: is a palpable, firm, and hardened thickening of soft tissue that must be carefully distinguished from abscesses, nodules, cellulitis, and swelling (*49*).<br>**Abscess**: is a collection of localized soft tissue materials that occurs at the site of administration and is defined as an abscess of infectious etiology that may be accompanied by fever and / or regional lymphadenopathy and sterile abscess (*50*). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | Does not interfere with activity. | Some interference with activity. | Prevents routine daily activity. | Emergency visit or hospitalization for severe pain. |

## 32. Malaise

| **Category** | Systemic events | | | |
|---|---|---|---|---|
| **About the AEFI** | Malaise is a symptom that can occur with almost any health condition. It may start slowly or quickly, depending on the type of disease (*51*). | | | |
| **Case definition** | General feeling of discomfort, illness, or lack of well-being (*51*). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | | | | |

## 33. Muscle pain (myalgia)

| | | | | |
|---|---|---|---|---|
| **Category** | Systemic events | | | |
| **About the AEFI** | Muscle aches and pains are common and can involve more than one muscle. Muscle pain also can involve ligaments, tendons, and fascia. Fascias are the soft tissues that connect muscles, bones, and organs (52). | | | |
| **Case definition** | It is described as muscle pain, pain associated with ligaments, tendons, and soft tissue that connect bones, organs, and muscles (52). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | Does not interfere with activity. | Some interference with activity. | Prevents routine daily activity. | Emergency visit or hospitalization for new severe pain or worsening muscle pain. |

## 34. Nausea/vomiting

| | | | | |
|---|---|---|---|---|
| **Category** | Systemic events | | | |
| **About the AEFI** | Nausea and vomiting are symptoms of many different conditions, including early pregnancy, concussions, and the stomach flu. Happening in both adults and children, there are many ways to relieve nausea. Drinking ice-cold beverages and eating light, bland foods can help (53). | | | |
| **Case definition** | A sick and uncomfor feeling in the stomach that may come with the urge to vomit. It is the emptying of the stomach through the mouth, whether voluntary, forced, or involuntary (53). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | *1-2 times in 24 hours* | *> 2 times in 24 hours* | *Requires IV hydration* | Emergency visit or hospitalization for hypotensive shock. |

## 35. Neutropenia

| | |
|---|---|
| **Category** | Systemic events |
| **About the AEFI** | Neutropenia is a reduction in the blood neutrophil count. If it is severe, the risk and severity of bacterial and fungal infections increases. Focal symptoms of infection may go unnoticed, but there is a fever during most serious infections. Diagnosis is made by leukocyte count with differential formula, but evaluation requires identifying the cause. If fever is present, an infection is presumed, and immediate empirical treatment with broad-spectrum antibiotics is required, especially when neutropenia is severe. Treatment with granulocyte colony stimulating factor is sometimes helpful (54). |

| | | | | |
|---|---|---|---|---|
| **Case definition** | Transient neutropenia is associated with a transient fall in the neutrophil count, and many of the underlying causes are reversible (54). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | | | | |

## 36. Redness

| | | | | |
|---|---|---|---|---|
| **Category** | Local reactions | | | |
| **About the AEFI** | Redness can occur at the injection site, in general, it is a mild and well-tolerated manifestation, lasting 24 to 48 hours (55). | | | |
| **Case definition** | Local inflammatory sign that usually subsides within the first 24 hours following vaccine application (55). | | | |
| **Event rating scale.** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | > 2.0 cm to 5.0 cm (5 to 10 instrument measurement units). | > 5.0 cm to 10.0 cm (11 to 20 instrument measurement units). | 10 cm (≥21 instrument measurement units). | Necrosis or exfoliative dermatitis. |

## 37. Swelling

| | | | | |
|---|---|---|---|---|
| **Category** | Local reactions | | | |
| **About the AEFI** | This reaction is a consequence of the introduction of the needle and the vaccination in muscle tissue (55).<br><br>Swelling at the injection site is the most common Adverse event following immunization (AEFI) and is also an AEFI frequently reported in clinical vaccine trials (56). | | | |
| **Case definition** | Considered a local reaction or close to the administration site and can occur after the application of any vaccine (55).<br><br>According to case definition of Katrin Kohl, is a visible enlargement of an injected limb with or without objective measurement (56). | | | |
| **Event rating scale** *(40)* | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potential life threat (Grade 4)** |
| | > 2.0 cm to 5.0 cm (5 to 10 instrument measurement units). | > 5.0 cm to 10.0 cm (11 to 20 instrument measurement units). | > 10 cm (≥21 instrument measurement units). | Necrosis. |

## 38. Lymphadenopathy

| | |
|---|---|
| **Category** | Local reactions |
| **About the AESI** | Lymphadenopathy or lymphadenitis refers to lymph nodes that are abnormal in size, number, or consistency and is often used synonymously with swollen or enlarged lymph nodes (*57*). |
| **Case definition** | According to the Manual de Vigilancia Epidemiológica de Eventos Adversos pós-vacinação (Ministry of Health, Brazil), is a hypertrophied lymph node larger than 3 cm with no evidence of suppuration (fluctuation and / or fistulation). Suppurated regional lymphadenopathy are hypertrophied axillary lymph nodes, supra or infraclavicular, initially hardened. They can reach more than 3 cm in diameter, followed by the formation of an abscess with central softening that may undergo drainage spontaneous, which can lead to a residual sinus path (fistula) (*58*). |

## 39. Allergic reactions (hypersensitivity)

| | |
|---|---|
| **Category** | Immunologic |
| **About the AESI** | An allergy is a reaction of your immune system to something that does not bother most other people. People who have allergies often are sensitive to more than one thing. Substances that often cause reactions (*59*). |
| **Case definition** | A disorder characterized by an adverse local or general response to exposure to an allergen. A local or general reaction of an organism after contact with a specific allergen to which it has been previously exposed and to which it has been sensitized (*59*). |

## 40. Death

| | |
|---|---|
| **Category** | |
| **About the AESI** | Serious adverse event that can cause risk of death (that is, induce the need for immediate clinical intervention to prevent death) or cause death (*60*). |
| **Case definition** | According to the medico-legal concept, sudden death is the unexpected death that happens in a person considered healthy or considered as such, and due to the way, it occurs, it raises suspicion that it is a violent death. Only in rare and situations can death result from vaccination. The objective of epidemiological surveillance of deaths is, primarily, to rule out coincident and unduly attributed causes to vaccines (60). |

# PART C

# Expanded case definitions

## 1. Generalized convulsive

According to Brighton Collaboration case definition of generalized convulsive seizure as an adverse event following immunization

*Level 1 of diagnostic certainty:*

- witnessed sudden loss of consciousness AND
- generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.

*Level 2 of diagnostic certainty:*

- history of unconsciousness AND
- generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations.

*Level 3 of diagnostic certainty:*

- history of unconsciousness AND
- other generalized motor manifestations.

(go back 1)

---

## 2. Guillain-Barré syndrome

According to Brighton Collaboration case definition:

*Level 1 of diagnostic certainty:*

- Bilateral AND flaccid weakness of the limbs,

AND

- Decreased or absent deep tendon reflexes in weak limbs,

AND

- Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau

AND

- Electrophysiologic findings consistent with GBS

AND

- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/µl),

AND

- Absence of an identified alternative diagnosis for weakness

*Level 2 of diagnostic certainty:*

- Bilateral AND flaccid weakness of the limbs,

AND

- Decreased or absent deep tendon reflexes in weak limbs

AND

- Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau

AND

- CSF total white cell count <50 cells/µl (with or without CSF protein elevation above laboratory normal value),

OR

- IF CSF not collected or results not available, electrophysiologic studies consistent with GBS

AND

- Absence of identified alternative diagnosis for weakness.

*Level 3 of diagnostic certainty:*

- Bilateral AND flaccid weakness of the limbs

AND

- Decreased or absent deep tendon reflexes in weak limbs

AND

- Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau,

AND

- Absence of identified alternative diagnosis for weakness.

**Frequency**: The annual incidence of GBS has been estimated at between 0.4 and 4.0 cases per 100,000 population per year, depending upon study methodology and case ascertainment; most well-designed prospective studies in developed countries have suggested an incidence of 1–2 per 100,000 population per year. In North America and Europe, GBS is more common in adults, and steadily increases with age. Many studies have suggested that men are more likely to be affected than women. Most cases are sporadic and there does not appear to be a seasonal pattern, with some exceptions. Clinically, GBS is characterized by the acute or subacute onset of varying degrees of weakness in limbs or cranial nerve-innervated muscles, associated with hypo- or areflexia, and a characteristic profile in the cerebrospinal fluid (CSF).

These definitions do not apply for children under the 2 years, because their nervous system has not achieved the same level of development as in older children and adults.

**(go back 2)**

## 3. Acute disseminated encephalomyelitis (ADEM)

According to Brighton Collaboration case definition:

*Level 1 of diagnostic certainty:*

(a) Demonstration of diffuse or multifocal areas of demyelination by histopathology.

OR

(b) Focal or multifocal findings referable to the central nervous system, including one or more of the following:

1. Encephalopathy (see case definition for encephalitis for specification of encephalopathy);
2. Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness).
3. Cranial nerve abnormality/abnormalities.
4. Visual field defect/defects.
5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex).
6. Motor weakness (either diffuse or focal; more often focal).
7. Sensory abnormalities (either positive or negative; sensory level).
8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes); or

9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

AND

(c) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2- weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences).

AND
(d) Monophasic pattern to illness (i.e., absence of relapse within a minimum of 3 months of symptomatic nadir).

*Level 2 of diagnostic certainty:*
(a) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
10. Encephalopathy (see case definition for encephalitis for specification of encephalopathy);
11. Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness).
12. Cranial nerve abnormality/abnormalities.
13. Visual field defect/defects.
14. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex);
15. Motor weakness (either diffuse or focal; more often focal);
16. Sensory abnormalities (either positive or negative; sensory level);
17. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes); or
18. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

AND
(b) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2- weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (± gadolinium enhancement on T1 sequences).

AND
(c) Insufficient follow up time achieved to document absence of relapse within a minimum period of 3 months following symptomatic nadir.

*Level 3 of diagnostic certainty:*
(a) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
19. Encephalopathy (see case definition for encephalitis for specification of encephalopathy);
20. Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness);
21. Cranial nerve abnormality/abnormalities.
22. Visual field defect/defects.
23. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex).
24. Motor weakness (either diffuse or focal; more often focal).
25. Sensory abnormalities (either positive or negative; sensory level).
26. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes); or
27. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

*Level 3A of diagnostic certainty:*
• Insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

*Exclusion criteria for all levels of diagnostic certainty:*

- Presence of a clear alternative acute infectious or other diagnosis for illness. Recurrence or relapse of illness at any point following a 3-month period of clinical improvement from symptomatic nadir; or
- If known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.

**Frequency and incidence:** Estimate of viral encephalitis rates have ranged from 0.08/100,000 population in national passive surveillance studies to 1–6 cases per 100,000 in hospital-based studies to 7.4 cases per 100,000 in one population-based study. The incidence of encephalitis has generally been lower than that of aseptic meningitis, and children are at higher risk than adults. Case-fatality rates and incidence of severe neurologic sequelae also vary, dependent upon study methods and underlying etiologic agent. Population-based and hospital-based estimates of neurologic sequelae have ranged from 0.35 to 2.7 per 100,000 cases, with case fatality rates from 1 to 10%. Certain agents are associated with higher case fatality rates; mortality rates of up to 33% have been reported with Herpes simplex encephalitis.

Exclusion criteria for all levels of diagnostic certainty: presence of a clear alternative acute infectious or other diagnosis for illness, recurrence or relapse of illness at any point following a 3-month period of clinical improvement from symptomatic nadir, or If known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.

**(go back 3)**

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## 4. Anosmia, ageusia

According to ACCESS case definition:

*Anosmia*
Anosmia: Absent smell function
Two causes for anosmia:
1) conductive and/or traumatic
2) sensorineural
1) Obstructive nasal diseases, such as chronic rhinosinusitis (CRS), nasal polyposis, allergic rhinitis, and nasal masses, can obstruct nasal airflow to the olfactory cleft.
(excluding) Chronic rhinosinusitis as a cause of diminished smell
There must be a time limit, non-necessarily
Chronic rhinosinusitis after immunization is possible
Approximately 20-30% of patients who experience head trauma develop some degree of olfactory dysfunction, whereas up to 5% experience anosmia.
Exclusion of recent trauma
2) A recent history of upper respiratory infection (URI) is reported by 20-30% of patients with acquired olfactory dysfunction.
Excluding congenital anosmia? Yes
Kallmann syndrome (congenital), which can be distinguished by the presence of hypogonadotropic hypogonadism, must be ruled out in similar cases because the presentation can be similar. Damage to the olfactory bulb can also be seen with many neurodegenerative diseases, such as Alzheimer disease and Parkinson disease.
Exclusion of anosmia as a part of another disease.

Numerous commonly prescribed medications, such as antihypertensive and antihyperlipidemic drugs, are associated with smell disturbance.

Exclusion of anosmia caused using specific medication.

Angiotensin-converting-enzyme inhibitors, diuretics, calcium channel blockers, and statins

*Ageusia*

Ageusia: Absent taste function

Staging system to assess whether the patient has ageusia or dysgeusia. A scale that ranges from 0, which refers to no taste, to 4, which refers to total taste loss, may be useful in evaluation.

Ageusia is the loss of taste functions of the tongue
Anosmia the loss of the ability to detect one or more smells (5)

(go back 4)

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## 5. Meningoencephalitis

According to Brighton Collaboration case definition:

*Level 1 of diagnostic certainty:*

(a) demonstration of acute inflammation of central nervous system parenchyma (± meninges) by histopathology.

*Level 2 of diagnostic certainty:*

(a) encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change lasting >24h).

*AND INCLUDING*

(b) one more of the following:

1. decreased or absent response to environment, as defined by response to loud noise or painful stimuli.
2. decreased or absent eye contact.
3. inconsistent of absent response to external stimuli.
4. decreased arousability; or
5. seizure associated with loss of consciousness.

*OR*

(c) focal or multifocal findings referable to the central nervous system, including one or more of the following:

1. focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness);
2. cranial nerve abnormality/abnormalities.
3. visual field defect/defect(s).
4. presence of primitive reflexes (Babinkski's sign, glabellar reflex, snout/sucking reflex).
5. motor weakness (either diffuse or focal; more often focal).
6. sensory abnormalities (either positive or negative; sensory level).
7. altered deep tendon reflex (hypo- or hyperreflexia, reflex asymmetry).
8. cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

*AND (for both possibilities to reach Level 2)*
(d) two or more of the following indicators of inflammation of the CNS:
1. fever (temperature ≥38 ° C.
2. CSF pleocytosis (>5 WBC/mm3 in children >2 months of age; >15 WBC/mm3 in children <2 months of age).
3. EEG findings consistent with encephalitis; or
4. neuroimaging consistent with encephalitis.

*Level 3 of diagnostic certainty:*
(a) encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality cange lasting <24h).

*AND INCLUDING*

(b) one or more of the following:
1. decreased or absent response to environment, as defined by response to loud noise or painful stimuli.
2. decreased or absent eye contact.
3. inconsistent or absent response to external stimuli.
4. decreased arousability; or
5. seizure associated with loss of consciousness.

OR

(c) focal or multifocal findings referable to the central nervous system, including one or more of the following:
1. focal, cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness).
2. cranial nerve abnormality/abnormalities.
3. visual field defect/defect(s).
4. presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex).
5. motor weakness (either diffuse or focal; more often focal).
6. sensory abnormalities (either positive or negative; sensory level).
7. altered deep tendon reflexes (hyop-or hyperreflexia, reflex asymmetry); or
8. cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

AND (for both possibilities to reach level 3)
(d) one of the following indicators of inflammation of CNS:
1. fever (temperature ≥38 °C).
2. CSF pleocytosis (>5 WBC/mm3 in children >2 months of age; >15 WBC/mm3 in children <2 months of age).
3. EEG findings consistent with encephalitis; or
4. neuroimaging consistent with encephalitis.

*Level 3A of diagnostic certainty:*
(a) insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

*Exclusion criterion for level 2 and 3 of diagnostic certainty:*
(a) other diagnosis for illness present.

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## 6. Aseptic Meningitis

According to Brighton Collaboration case definition:

*Level 1 of diagnostic certainty:*

- Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity, or other signs of meningeal irritation,

AND

- Pleocytosis in CSF determined as:
  - >5 leukocytes/mm3 (L) if patient is 2 months of age or older,
  - >15 leukocytes/mm$^3$ (L) in infants younger than 2 months

AND

- Absence of any microorganism on gram stain of CSF,

AND

- Negative routine bacterial culture of CSF in the absence of antibiotic treatment before obtaining the first CSF sample.

*Level 2 of diagnostic certainty:*

- Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity, or other signs of meningeal irritation,

AND

- Pleocytosis in CSF determined as:
  - >5 leukocytes/mm$^3$ (L) if patient is 2 months of age or older,
  - >15 leukocytes/mm$^3$ (L) in infants younger than 2 months,

AND

- Absence of any microorganism on Gram stain of CSF,

AND

- No bacterial culture of CSF obtained, OR negative culture in the presence of antibiotic treatment before obtaining the first CSF sample.

*Level 3 of diagnostic certainty:*
Not applicable

If the case meets criteria for aseptic meningitis and encephalitis case definition, it should be reported only as encephalitis.

[a] In presumed traumatic lumbar puncture (i.e., erythrocytes in the CSF without other known cause such as head trauma, haemorrhagic stroke, or necrotizing encephalitis), CSF pleocytosis is defined as a >1:1 ratio of observed and predicted leukocytes in CSF.

Predicted CSF leukocytes are calculated by using the formula: predicted CSF leukocytes = CSF erythrocytes × (blood leukocytes/blood erythrocytes). In the absence of data on blood erythrocytes and leukocytes, pleocytosis can be defined as a >1:500 ratio of CSF leukocytes and CSF erythrocytes.

b

Chronological age (birth date).

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## 7. Facial nerve palsy

According to Brighton Collaboration case definition:

Given the lack of consensus about the term Bell's palsy and the sometimes synonymous use with peripheral facial nerve palsy, we do not aim to describe a definition for "Bell's palsy". Instead, we have developed an algorithm/decision tree that ultimately leads to a common definition of idiopathic facial nerve palsy by systematically excluding known causes of such palsies. We have chosen this approach as it is most relevant for vaccinologists to identify and confirm true cases of idiopathic palsies.

(a) 2.1. Peripheral facial nerve palsy

Initially, the diagnosis of acute-onset peripheral facial nerve palsy needs to be confirmed. Peripheral facial nerve palsy is defined as a weakness of the facial muscles innervated by cranial nerve VII, which is either complete (paralysis) OR incomplete (paresis)[Notes 1 and 2] and may manifest unilaterally OR bilaterally [Note 3].

*Level 1 of diagnostic certainty:*
Manifests with the acute onset decreased ability (paralysis OR paresis)

- to wrinkle the forehead

OR

- to raise the eyebrows at the affected side.

*Level 2 of diagnostic certainty:*
*Not applicable*.

*Level 3 of diagnostic certainty:*
*Not applicable*.

(b) 2.2. Idiopathic peripheral facial nerve palsy

*For all levels of diagnostic certainty:*
Idiopathic peripheral facial nerve palsy has an *unknown aetiology*, which

- has a sudden onset [Note 4]

AND

- shows initial rapid progression of symptoms and signs [Note 5]

AND

• shows resolution [Note 6]

*Level 1 of diagnostic certainty:*
Remains unexplained after excluding known causes [Note 7] by

• review of clinical history
AND

• physical examination
AND

• laboratory investigations
AND

• radiological studies

*Level 2 of diagnostic certainty:*
Remains unexplained after excluding known causes [Note 7] by

• review of clinical history
AND

• physical examination
AND

• laboratory investigations

*Level 3 of diagnostic certainty:*
Remains unexplained after excluding known causes [Note 7] by

• review of clinical history
AND

• physical examination

*Notes for the case definition:*
[Note 1] ***Facial Muscle Weakness***: Weakness of facial muscle activity would include decreased movement of the corner of the mouth on the affected side, decreased ability to close the eye on the affected side or decreased movement of the forehead skin on the affected side. In most cases of peripheral facial nerve palsy, the weakness would involve all branches of the facial nerve. In some cases of peripheral facial nerve palsy, there may be obvious involvement of only 1 or 2 branches of the facial nerve. Such cases will meet the case definition, as long as all of the remaining criteria are fulfilled.
[Note 2] ***Decreased Facial Muscles Movement***: Decreased movement of facial muscles in infants and young children and other persons with limited ability to cooperate in an examination (e.g., persons with dementia) may be based on a period of observation for spontaneous or provoked movement of the affected muscles.
[Note 3] ***Unilateral versus bilateral palsy***: Bilateral peripheral facial nerve palsy is an unusual manifestation. All attempts to exclude an alternative cause for the bilateral facial weakness should be attempted in the setting of this clinical entity.
[Note 4] ***Sudden Onset***: This criterion refers to an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition.

Note [5] ***Rapid progression***: This criterion refers to the worsening of disease over a short period of time.
Note [6] ***Resolution occurs***: There is symptom and sign resolution, with or without treatment.
Note [7] ***Multiple causality***: known causes of facial nerve palsy include the diagnosis of an alternative illness (listed below).

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## 8. Narcolepsy

According to Brighton Collaboration case definition:

*Level 1*
In the presence of:
Excessive daytime sleepiness[a] OR
Unambiguous cataplexy[c]
AND
CSF hypocretin-1 deficiency[b]

Level 2
In the presence of:
Excessive daytime sleepiness[a]
AND
Unambiguous cataplexy[c]
AND
MSLT[d] mean sleep latency ≤8 min in adults OR
MSLT[d] mean sleep latency ≤12 min in children and adolescents OR
MSLT[d] SOREMP ≥ 2

Level 3
In the presence of:
Excessive daytime sleepiness[a]
AND
MSLT[d] mean sleep latency ≤8 min in adults OR
MSLT[d] mean sleep latency ≤12 min in children and adolescents
AND
MSLT[d] SOREMP ≥ 2

All levels
AND in the absence of other mimicking disorders, see[e]

[a] Excessive daytime sleepiness
In adults (≥16 years):
- unintended sleep episodes during the day
AND
- present almost daily for at least one month
In children and adolescents (<16 years):
- an increase in daytime sleep episodes
AND
- present almost daily for at least one month

*Note: usually in combination with feelings of subjective sleepiness and impaired concentration. Sleepiness may also be manifested as irritability or hyperactivity.*

[b] CSF hypocretin-1 deficiency
- hypocretin-1 concentration below 110 pg/ml in crude, unextracted CSF.
AND
- measured by the Phoenix radioimmunoassay
AND
- performed in a laboratory according to published guidelines and by using the Stanford reference sample [31], [128]

[c] Unambiguous cataplexy
In adults (≥16 years):
- sudden AND unexpected onset of episodes
AND
- presence of all of the following criteria during episodes (before initiation of treatment):
- partial or generalized muscle weakness
- preserved consciousness
- clear emotional trigger in ≥2 episodes
- duration of <30 s
OR
- episodes with documented, reversible areflexia AND
- duration of <30 s
NOT
- partial or generalized seizure OR
- neuromuscular disorders

In children and adolescents (<16 years):
- episodes of cataplexy that fulfill the criteria for adult cataplexy
OR
- the following criteria of pediatric cataplexy:

Pediatric Cataplexy
- sudden AND unexpected onset of episodes
AND
- loss of muscle tone, e.g., falling during routine activity (i.e. while walking or running), wide-based gait, head droops, prominent facial involvement resulting in "cataplectic facies," eyelid ptosis, mouth opening, tongue protrusion, facial weakness, facial grimacing, abnormal postures, swaying of the head and trunk, stereotypic movements or chorea-like patterns. Hypotonia and wide-based gait may also be disclosed at neurological examination
AND
- preserved consciousness
AND
- duration of episodes is a few seconds to several minutes (sometimes present in protracted clusters if emotional triggers continue)

Note: cataplexy in children may or may not be triggered by 'emotional' circumstances (e.g., watching funny cartoons, eating certain foods, playing games or videogames)
NOT
- partial or generalized seizure OR
- neuromuscular disorders
- any other known explanation

[d] 4 or 5 nap MSLT performed according to the American Academy of Sleep Medicine (AASM) protocol [101]

[e] Exclusion of other conditions
The following conditions must be clinically/instrumentally assessed, since they could either mimic one or more narcolepsy symptoms (mainly excessive daytime sleepiness) or constitute co-morbidities with narcolepsy:
- other sleep disorders, according to ICSD-2 criteria:
- sleep related disorder breathing
- behaviorally induced insufficient sleep
- circadian rhythm disorders
- recurrent hypersomnias secondary to medical or psychiatric conditions
- use of sedating medication and antidepressants
- focal cerebral lesions, indicated by neurological examination and/or brain imaging

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## 9. Vaccine-associated enhanced disease (VAED)

a. Vaccine associated enhanced disease (VAED)
Is an illness that occurs in persons who receive a vaccine and who are subsequently infected with the pathogen that the vaccine is meant to protect against.
This definition assumes previously antigen-naïve vaccine containers, which can be assessed by determining seronegative status prior to vaccination, when feasible. The need for documentation of seronegativity prior to vaccination, which can be done retrospectively, is particularly relevant in Phase II-III clinical trials. In the context of such trials, the working group acknowledged the difficulty in distinguishing between vaccine failure and VAED. Thus, all cases of vaccine failure should be evaluated for VAED.

b. VAED may present as severe disease or modified / unusual clinical manifestations of a known disease presentation. The illness presumably is more severe or has characteristics that distinguish it from illness that might occur in unvaccinated individuals.

c. VAED may involve one or multiple organ systems.
VAED may also present as an increased incidence of disease in vaccinees compared with controls or known background rates.

*Vaccine-associated enhanced respiratory disease (VAERD*):
a. Refers to the predominant lower respiratory tract presentation of VAED. The mechanisms of pathogenesis might be specific to the lower respiratory tract or part of a systemic process

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## 10. Multisystem inflammatory syndrome in children.

According to ACCESS case definition:

Multisystemic inflammatory syndrome in children, also known as MIS-C, is a syndrome that appears to be a rare complication of COVID-19 in children. Although it had previously been thought that COVID-19 did not affect children, it now appears that children who were previously healthy can become seriously ill with COVID-19. The syndrome is similar to incomplete Kawasaki disease (KD), a febrile childhood disease involving inflammation of the blood vessels that can result in coronary artery aneurysms. Symptoms usually occur 1 to 6 weeks after infection with COVID-19 and may overlap with an acute respiratory presentation of COVID-19. The diagnostic criteria for KD compared to MIS-C, show that there are some similarities and differences.
MIS-C can be present similar to the criteria above, or at least some of them. Besides these symptoms, children can present with evidence of multi-organ failure.

The main difference between KD and MIS-C is that classic KD typically affects infants and young children, whereas MIS-C affects mostly older children and adolescents. Children with MIS-C have a median age of 9 years old, which is 2.7 years for those with KD. Gastrointestinal symptoms are often dominant in children with MIS, whereas these symptoms are less prominent in classic KD. This also applies to myocardial dysfunction and shock, which occurs more commonly in MIS-C than in classic KD.

It is unclear if the risk of developing MIS-C varies by race. It seems to affect primarily people of African American, Caribbean, and Hispanic ancestry, which is different from KD that mostly affects children of Asian ancestry.

The presenting symptoms of MIS-C are the following:

- Persistent fever;
- Gastrointestinal symptoms like abdominal pain, vomiting and diarrhea;
- Rash;
- Conjunctivitis;
- Mucous membrane involvement;
- Neurocognitive symptoms like headache, lethargy, and confusion;
- Respiratory symptoms, not prominent in most of the cases;
- Swollen hands/feet;
- Sore throat.

Clinical findings when children are admitted to the hospital are the following:

- Shock;
- Criteria met for complete Kawasaki disease;
- Myocardial dysfunction;
- Acute respiratory failure requiring non-invasive or invasive ventilation;
- Acute kidney injury;
- Serositis (small pleural, pericardial and ascitic effusions);
- Acute hepatic failure.

The distinction between KD and MIS-C can be made by the fact that MIS-C is COVID-19 associated. Some children have a positive serology for SARS-CoV-2 but have a negative polymerase chain reaction (PCR) testing. Some children have it the other way around.

The pathophysiology of MIS-C is not well understood. It has been suggested that the syndrome results from an abnormal immune response to the virus, with some similarities to KD, macrophage activation syndrome (MAS), and cytokine release syndrome. A post-infectious process is suggested based on the timing of the rise of these cases relative to the peak of COVID-19 cases in communities.

WHO, the Centers for Disease Control and Prevention (CDC) and Royal College of Pediatrics and Child Health (UK) came up with a case definition for MIS-C. There are some differences between these definitions. The CDC requires that the child must have severe symptoms requiring hospitalization, whereas the WHO case does not. An advantage of the WHO definition is that it provides more detail regarding clinical signs of multisystem involvement.
Another difference is that WHO states that the child must have fever for three or more days, whereas the CDC states that the child must have fever for 24 hours or more.

The case definition put forth by WHO is as follows:
Age 0 to 19 years old
AND
Fever for ≥3 days
AND
Elevated markers of inflammation (e.g., erythrocyte sedimentation rate, C-reactive protein, or procalcitonin)
AND
No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal / streptococcal shock syndromes
AND
Evidence of SARS-CoV-2 infection (positive reverse transcription PCR [RT-PCR], antigen test, or serology) or contact with an individual with COVID-19
AND
*Clinical signs of multisystem involvement (at least two of the following):*

- Rash, bilateral no purulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
- Hypotension or shock
- Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/brain natriuretic peptide [BNP])
- Evidence of coagulopathy (prolonged prothrombin time or partial thromboplastin time; elevated D-dimer)
- Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain).

**(go back 10)**

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## 11. Anaphylaxis

According to Brighton Collaboration case definition:

*For all levels of diagnostic certainty anaphylaxis is a clinical syndrome characterized by:*

- sudden onset; AND
- rapid progression of signs and symptoms; AND
- involving multiple (≥2) organ systems, as follows.

*Level 1 of diagnostic certainty:*

- ≥1 major dermatological; AND
- ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion.

*Level 2 of diagnostic certainty:*

- ≥1 major cardiovascular AND ≥1 major respiratory criterion; OR
- ≥1 major cardiovascular OR respiratory; AND
- ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems); OR

- (≥1 major dermatologic) AND (≥1 minor cardiovascular; AND/OR minor respiratory criterion).

*Level 3 of diagnostic certainty:*

- ≥1 minor cardiovascular OR respiratory criterion; AND
- ≥1 minor criterion from each of ≥2 different systems/categories.

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Major and minor criteria used in the case definition of anaphylaxis.

*Major criteria:*

Dermatologic or mucosal

- generalized urticaria (hives) or generalized erythema
- angioedema*, localized or generalized
- generalized pruritus with skin rash

Cardiovascular

- measured hypotension
- clinical diagnosis of uncompensated shock, indicated by the combination of at least three of the following:
    - tachycardia
    - capillary refill time >3 s
    - reduced central pulse volume
    - decreased level of consciousness or loss of consciousness

Respiratory

- bilateral wheeze (bronchospasm)
- stridor
- upper airway swelling (lip, tongue, throat, uvula, or larynx)
- respiratory distress—2 or more of the following:
    - tachypnoea
    - increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)
    - recession
    - cyanosis
    - grunting

* Not hereditary angioedema.

*Minor criteria:*

Dermatologic or mucosal

- generalized pruritus without skin rash
- generalized prickle sensation
- localized injection site urticaria
- red and itchy eyes

Cardiovascular

- reduced peripheral circulation as indicated by the combination of at least two of

- tachycardia and
- a capillary refill time of >3 s without hypotension
- a decreased level of consciousness

Respiratory
- persistent dry cough
- hoarse voice
- difficulty breathing without wheeze or stridor
- sensation of throat closure
- sneezing, rhinorrhea

Gastrointestinal
- diarrhea
- abdominal pain
- nausea
- vomiting

Laboratory
- Mast cell tryptase elevation > upper normal limit

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

(go back 11)

## 12. Acute aseptic arthritis

According to the ACCESS case definition:

Acute aseptic arthritis (AAA) is a clinical syndrome characterized by acute onset of signs and symptoms of joint inflammation for a period of no longer than 6 weeks, synovial increased leucocyte count and the absence of microorganisms on Gram stain, routine culture and/or PCR. AAA does not include chronic inflammatory conditions such as rheumatoid arthritis (RA), connective tissue diseases, osteoarthritis vasculitis or spondyloarthropathies. These conditions are chronic and are diagnosed later than within 6 weeks.

The case definition has been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of AAA can be captured.

*All levels of diagnostic certainty:*
- One or more of the following clinical signs and symptoms assessed by a health care provider
- Articular or peri-articular swelling
- Articular effusion
- Articular or peri-articular erythema
- Increased warmth palpable over capsular contour of the joint
- Restricted range of movement

AND

- Duration of less than 6 weeks until complete resolution of symptoms

AND

- Absence of recent articular trauma Level 1 of diagnostic certainty

*Level 1 of diagnostic certainty:*

- Increased leucocyte count in synovial fluid determined as:
  - >2,000 leukocytes/mm3 on aspirate regardless of age AND
  - <50% white blood count polymorphonuclear leukocyte (PMN) in synovial fluid

AND

- Absence of pathological synovial fluid cells
- Absence of any microorganism on Gram stain, microscopy or PCR in synovial fluid
- No bacterial growth on routine culture of synovial fluid
- Absence of antibiotic treatment before obtaining the first synovial fluid sample

*Level 2 of diagnostic certainty:*

- Negative bacterial blood cultures

AND

- Negative routine bacterial culture of synovial fluid

AND

- Absence of antibiotic treatment before obtaining the first synovial fluid sample

AND

- Absence of fever

*Level 3 of diagnostic certainty:*

- Absence of fever.

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## 13. Acute respiratory distress syndrome (ARDS)

According to Berlin case definition, 2011:

**Timing:** Within 1 week of a known clinical insult or new or worsening respiratory symptoms.
**Chest imaging**[a]: Bilateral opacities — not fully explained by effusions, lobar/lung collapse, or Nodules.
**Origin of edema:** Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present.
**Oxygenation**[b]
Mild: 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H2O[c]
Moderate: 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥5 cm H2O
Severe: PaO2/FIO2≤ 100 mm Hg with PEEP ≥5 cm H2O

**NOTES**
Abbreviations: CPAP, continuous positive airway pressure; FIO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO2/FIO2_ (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

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## 14. Acute cardiac injury

According to ACCESS case definition:

**Microangiopathy:** Cardiac microangiopathy leads to microvascular dysfunction which can manifest in different clinical scenarios:
1) Occurrence of ischemic heart disease in absence of angiographically significant coronary atherosclerosis (see definition form for acute coronary syndrome - ACS) and could result in inflammation and/or abnormal vasomotor regulation.
2) Inadequate post-PCI and/or post thrombolysis coronary reperfusion, including micro-embolic mechanism.
3) In context of epicardial vessel disease.

The signs and symptoms are:

- chest pain/angina (exercise related).
- dyspnea.
- fatigue; and
- more atypical symptoms.

Coronary microvascular dysfunction (CMD) refers to a term covering a wide spectrum of clinical situations in which the structure and function of the coronary microcirculation is affected. This leads to impaired responses of the coronary flow to vasodilator stimuli, being characterized by:

- impaired coronary flow reserve (CFR), with cut-off values below 2.0–2.5 depending on the methodology OR
- abnormal high index of coronary microvascular resistance (IMR, e.g., IMR >25). AND/OR
- focal or diffuse vasoconstriction during acetylcholine provocation testing, in the absence of any significant epicardial coronary artery obstruction (>50% lumen stenosis at coronary angiography) or preserved fractional flow reserve (FFR, value ≥ 0.80).

## Heart failure (HF)

(Chronic) heart failure
HF is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. The current definition of HF restricts itself to stages at which clinical symptoms are apparent.
HF comprises a wide range of presentations, from patients with normal left ventricular ejection fraction (LVEF) [typically considered as ≥50%; HF with preserved EF (**HFpEF**)] to those with reduced LVEF [typically considered as 40%; HF with reduced EF (**HFrEF**)]. Patients with an LVEF in the range of 40–49% represent a "gray area", which we now define as **HFmrEF**. Differentiation of patients with HF based on LVEF is important due to different underlying an etiologies, demographics, co-morbidities, and response to therapies. Most clinical trials published after 1990 selected patients based on LVEF [usually measured using echocardiography, a radionuclide technique or cardiac magnetic resonance (CMR)], and it is only in patients with HFrEF that therapies have been shown to reduce both morbidity and mortality.

**Case definition of HF**

(In all cases) Presence of symptoms and/or signs of HF
AND

- A LVEF <40%

OR

- A "preserved" LVEF (defined as LVEF as LVEF ≥50% for HFmrEF or 40–49% for HFmrEF); AND
- Elevated levels of NPs (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL); and
- Objective evidence of other cardiac functional and structural alterations underlying HF.

[1]Symptoms and signs typical of heart failure

[2]Assesement of LVEF by echocardiography, the modified biplane Simpson's rule is recommended
[3]Assesement of functional alterations by cardiac imaging and other diagnostic tests (e.g., echocardiography (see table 4.3), ECG)
[4]Left ventricular hypertrophy and/or left atrial enlargement

Acute heart failure (AHF)
AHF refers to rapid onset or worsening of symptoms and/or signs of HF. It can present as a first occurrence (de *novo*) or, more frequently, as a consequence of acute decompensation of chronic HF, and may be caused by primary cardiac dysfunction. Acute myocardial dysfunction (ischemic, inflammatory, or toxic), acute valve insufficiency or pericardial tamponade are among the most frequent acute primary cardiac causes of AHF.

**Stress cardiomyopathy:** Signs and symptoms: Acute chest pain, dyspnoea, syncope, new electrocardiogram (ECG) changes, sudden elevation of cardiac biomakers and induced by physical stress.

Diagnosis of stress cardiomyopathy is difficult because of its clinical phenotype may closely resemble acute myocardial infarction (AMI) regarding ECG and abnormalities and biomarkers. Two additional features that are helpful in distinguishing Takotsubo syndrome (TTS) from acute MI are corrected QT interval (QTc) prolongation > 500 ms during the acute phase and the recovery of left ventricular (LV) function over 2 to 4 weeks. There are rare cases described where MI and TTS coexist, e.g., MI-induced TTS or TTS with secondary plaque rupture, but this occurs where the acute regional wall motion abnormalities are more extensive than the culprit coronary artery territory and fulfill the pattern and definition of TTS.

**Coronary artery disease:** coronary artery disease or ischemic heart disease describes a set of clinical symptoms due to an inadequate blood supply to the myocardium. This pathological process is characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. This disease can have a long stable period, called chronic artery disease, but also become unstable at any time due to an acute atherothrombotic event. This blockage can restrict blood flow, which causes myocardial ischemia. When the blood flow is cut off entirely the event is called a "heart attack" or acute myocardial infarction (AMI), which is categorized as acute coronary syndrome (ACS).

So, acute coronary syndrome is a subcategory of coronary artery disease, and coronary heart disease results of coronary artery disease. Coronary artery disease is characterized by atherosclerosis in coronary arteries and can be asymptomatic, whereas acute coronary syndrome is always present with symptoms, such as unstable angina, and is often associated with myocardial infarction, which can also occur regardless of coronary artery disease.

**Arrhythmia:** in the normal situation a heart beats between 60 to 100 times per minute. A cardiac arrhythmia is an abnormality or perturbation in the normal activation or beating of the heart myocardium. The pathogenesis of these arrhythmias can be divided in three mechanisms: the enhanced or suppressed automaticity, triggered activity, or re-entry. Heart ischemia, scarring, electrolyte disturbance, heart medications, old age and other factors can cause enhanced or suppressed automaticity. The suppression of the automaticity of the sinus node can lead to sinus node dysfunction or sick sinus syndrome (SSS). Atrial and ventricular arrhythmias can be a result of enhanced automaticity. Triggered activity can occur after earlier and delayed depolarizations that can lead to spontaneous multiple depolarizations, which then can lead to precipitating ventricular arrhythmias. The re-entry mechanism can be divided into the micro level re-entry and the macro level re-entry and includes bidirectional conduction and unidirectional block. The micro level re-entry occurs with ventricular tachycardia from conduction around the scar or myocardial infarction. Macro level re-entry occurs via conduction through Wolff-Parkinson-White (WPW) syndrome concealed accessory pathways.

There are different types of cardiac arrhythmias and they can be classified by the origin in the heart of the arrhythmia: ventricular or supraventricular or whether there is an increase or decrease in the heart rate: tachycardia or bradycardia. Ventricular arrhythmias caused by heart disease can be extremely dangerous and require immediate medical attention.
The different arrhythmias that are originated in the atria are the following: Premature atrial contractions (PACs) are harmless. These arrhythmias occur most of the time in healthy people and do not give any symptoms. When they do give symptoms, it can feel like a fluttering in the chest or a sensation of a skipped beat. This can be triggered by stress, exercise, caffeine, or nicotine.

- Supraventricular arrhythmias are tachycardia's that start in the atria or the atrioventricular node. These can be divided in different types as well:
    - Atrial fibrillation (AF) is characterized by a fast, irregular rhythm originating in the atria. This occurs when the electrical signal does not begin in the sinus node where it should start. This leads to activation of the atria in a not systematic way. Most of the time it is caused by an underlying condition that interferes with the heart's ability to conduct electrical impulses. Complications of long-term AF are stroke and heart failure.
    - Atrial flutter is the electrical signals of the heart spreading in a fast and regular rhythm. In contrary to AF where the electrical signals are spreading through a fast and irregular rhythm.
    - Paroxysmal supraventricular tachycardia (PSVT) is a very fast heart rate that begins and ends suddenly. There is re-enter of the electrical signals to the atria, which leads to a fast heart rate. It is usually not dangerous.
    - Wolff-Parkinson-White (WPW) syndrome is a special type of PSVT. A condition in which the heart's electrical signals travel along an extra pathway from the atria to the ventricles. The ventricles can contract very fast because of this and it can be life-threatening.

The different arrhythmias that are originated in the ventricles are the following: Ventricular tachycardia is a contraction of the ventricles in a fast and regular rhythm; this can last for a few seconds or for much longer.

- Ventricular fibrillation (V-fib) is caused by disorganized electrical signals that lead to a lower ejection fraction. A person may lose consciousness within seconds and may die within minutes if not treated.

- Torsade des Pointes is a form of ventricular fibrillation characterized by a prolonged QT interval on the ECG. Certain medicines and imbalanced amounts of potassium, calcium or magnesium in the bloodstream can cause this condition.
- Premature ventricular complexes (PVCs) are the same as PACs but than in the ventricles. It is harmless and generally people do not get any symptoms.

Sinus irregularities are the following:

- Sinus arrhythmia is harmless. It is a name for changes in the heart rate that occur during breathing. It is common in children and adults.
- Sinus tachycardia occurs because of the sinus node that sends out electrical signals faster than usual. It can be caused by excitement, certain medications, fever, exercise, dehydration, and an overly active thyroid gland.
- Sick sinus syndrome, also known as SSS, is a syndrome where the sinus node does not fire signals properly, so the heart rate slows down. Sometimes the rate changes back and forth between a bradycardia and tachycardia.

Brady-arrhythmia is when the heart rate is going to slow. It can occur in patients that have a bundle branch block. This means that the electrical signal traveling along each ventricle, called the bundle branches, is delayed, or blocked. When this happens, the ventricles do not contract on the exact same time. This means that the heart has to pump more to get the same ejection fraction as when the ventricles to contract at the same time. The cause of bundle branch block is often an existing heart condition.

Symptom's people can experience having arrhythmias: Palpitations, which can be frequent, infrequent, or continuous

- If the arrhythmia leads to a lower blood pressure and less ejection fraction it can cause light-headedness, dizziness, or syncope
- Anxiety
- Blurred vision
- Chest pain
- Difficulty breathing
- Fatigue
- Diaphoresis

## Myocarditis/Pericarditis

**Myocarditis:** Inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immunohistochemical criteria. Myocarditis is an inflammatory disease of the myocardium caused by different infectious (viral and nonviral) and non-infectious triggers (autoimmune diseases, hypersensitivity reactions to drugs, toxic reactions to drugs, toxics, etc.). Myocarditis often results from common viral infections and post-viral immune-mediated responses.
**Pericarditis:** is the inflammation of the pericardium from various origins, such as infection, neoplasm, autoimmune process, injuries, or drug induced. Pericarditis usually leads to pericardial effusion, or constrictive pericarditis.

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## 15. Coagulation disorder

According to ACCESS case definition:

This event definition form (EDF) is about multiple groups of diseases under the overarching name of coagulation disorder. A coagulation disorder is a problem with blood clotting. This can either be to mush clotting leading to thrombosis, emboli, or stroke, or to little clotting leading to bleeding and again stroke.

The events that are in this EDF are: deep vein thrombosis (DVT), pulmonary embolus (together with DVT called venous thromboembolism), cerebrovascular stroke, limb ischemia (occlusion of an artery that supplies the limps of blood), hemorrhagic disease (bleeding disorders).
Within this EDF we excluded perioperative, congenital of drug induced causes of a coagulation disorder.

**Venous thromboembolism (VTE):** deep vein thrombosis (DVT) refers to the formation of a blood clot in one of the body's large veins. Most of the time this formation happens in the lower limb. The blood clot is called a thrombus. This thrombus can block off a part or all the blood flow. The result of this is that the leg will swell due to a higher pressure in the vein. The leg turns red and is painful. The reason why DVT is a severe condition is because of the symptoms itself but mainly because of the high risk of developing a pulmonary thromboembolism (PE). PE happens in one third of DVT patients. PE has a high mortality rate.

**Pulmonary thromboembolism (PE):** when a thrombus, origination most often in the lower limb, breaks loose from the vessel wall it travels freely thru the blood vessel on its way to the heart and lungs until it hits a point where it can no longer pass. In PE the thrombus gets trapped in the long artery and closes of the blood supply to the part of the lung after the occlusion. This ca uses a drop in lung perfusion, a declining blood oxygen saturation, and sharp chest pain.

**Stroke:** acute stroke is defined as the acute onset of focal neurological findings in a vascular territory because of underlying cerebrovascular disease. This can happen in two ways. One is a ischemic stroke, where a small thrombus gets trapped in a blood vessel transporting blood to the brain. Ischemic stroke accounts for 85% of all acute strokes. The other 15% of stroke are hemorrhagic strokes which are caused by bursting of a blood vessel i.e., acute hemorrhage.
There are numerous causes of stroke, such as prolonged hypertension, arteriosclerosis, and emboli that have formed in the heart as a result of atrial fibrillation or rheumatic heart disease.

**Limb ischemia:** acute limb ischemia is defined as a quickly developing or sudden decrease in limb perfusion. Another word for limb ischemia is peripheral artery disease (PAD) or peripheral occlusive artery disease (POAD). The decrease in perfusion is due to an occlusion of the artery leading to the leg or arm. Occlusion of the upper limp is exceedingly rare, so we focus on the lower limbs. The incidence of acute peripheral arterial occlusion causing acute lower extremity ischemia is approximately 1.5 cases per 10,000 persons per year. The clinical presentation depends upon the etiology and whether the patient has underlying peripheral artery disease. Patients who present later than two weeks after the onset of the acute event are considered to have chronic lower extremity ischemia.
If a patient has symptoms of PAD, the ankle-brachial index (ABI) should be obtained. This is a measure for the severity of the PAD. A value <0.4 is indicative of severe ischemia.

**Hemorrhagic disease:** this part of the coagulation disorders focuses on a lack of blood clotting. The blood is hypo coagulable resulting in bleeding. The cause of this bleeding lays within a problem in hemostasis. Hemostasis consists of two parts, the primary and secondary

hemostasis. The primary hemostasis consists of the production of an initial blood clot with thrombocytes sticking together. After this proses, in the secondary hemostasis, this blood clot is secured with fibrin trough a cascade of multiple coagulation factors.
Problems within the primary hemostasis result in excessive bleeding when a wound occurs. Whenever there is a problem within the secondary hemostasis, an initial blood clot if formed and the wound might be dry, but the blood clot is weak and might break from time to time resulting in recurrent bleeding.

To focus on specific diseases to be able to get incidence rates about hemorrhagic diseases, we decided to focus of acquired thrombocytopenia for the primary hemostasis and acquired hemophilia for the secondary hemostasis. Hemophilia is the absence of coagulation factors necessary for making fibrin within a primary blood clot.

Acquired hemophilia occurs rarely with the incidence of approximately 1 to 4 per million/year, with severe bleeds in up to 90% of affected patients, and high mortality between 8-22%. Most often factor VIII is inhibited by neutralizing antibodies. This form is called acquired hemophilia A.

Another distinction that is possible to make within hemorrhagic disease is between major, minor, and trivial bleeding. Major bleeding is a hemorrhagic stroke or bleeding that requires transfusion, minor bleeding is any bleeding severe enough to disturb social activities, and trivial bleeding is no clinically unusual bleeding.

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## 16. Thrombocytopenia

According to Brighton Collaboration case definition:

*Level 1 of diagnostic certainty:*
Platelet count[a] less than $150 \times 10^9$ $L^{-1}$
AND
confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding.[b]

*Level 2 of diagnostic certainty:*
Platelet count[a] less than $150 \times 10^9$ $L^{-1}$

*Level 3 of diagnostic certainty*:
Not applicable

**NOTES**

[a] Measured by an automated hematology analyzer or assessed by hand count of platelets on a cell count slide.

[b] Presentations of spontaneous (i.e., non-traumatic) bleeding include purpura (i.e., petechiae, purpura *sensu stricto*, ecchymosis), hemorrhagic oozing of skin lesions including rashes, hematoma, bruising, hematemesis, hematochezia, occult bleeding per rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding other than menstruation, conjunctival bleeding, intracranial bleeding.

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## 17. Acute kidney injury (AKI)

According to ACCESS case definition:

AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that rarely has a sole and distinct pathophysiology.

*Other symptoms can occur after major complications of AKI:*

- Volume depletion/overload:
  - Swelling or retaining fluid (in lungs, ankles, stomach), shortness of breath, high blood pressure.
  - Dehydration leading to dizzy or lightheaded, hemorrhagic shock, weight loss, orthostatic hypotension, postural tachycardia.

- Electrolyte disorders e.g., hyperkaliemia, metabolic acidosis, hyponatremia, and hypernatremia, hypo/hypercalcemia, hyperphosphatemia, hypermagnesemia.
  - Cardiac arrythmias, fatigue, lethargy, convulsions, seizures, nausea, vomiting, diarrhea or constipation, abdominal cramping, confusion, headaches, muscle cramping, muscle weakness, numbness, and tingling.

- Uremic complications: encephalopathy, pericarditis, pleuritis, bleeding due to platelet dysfunction.

- Drug toxicity

AKI case definitions
In Europe, the definition/guideline of Kidney Disease-Improving Global Outcomes (KDIGO) is leading. The guideline defined AKI as follows (not graded):

increase in SCr by X0.3 mg / dl (X26.5 lmol / l) within 48 hours.
OR
increase in SCr to X1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.
OR
urine volume <0.5 ml / kg / h for 6 hours.

AKI is staged for severity according to different criteria. The first classification system is risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE), from the Acute Dialysis Quality Initiative (ADQI). RIFLE incorporated three categories of injury and two outcomes that varied by severity. The outcomes (loss, end-stage kidney disease (ESKD)) were eliminated from the subsequent Acute Kidney Injury Network (AKIN) and KDIGO definitions. The AKIN definition incorporated smaller changes in serum creatinine (SCr) concentration, and the KDIGO definition added more definitive time frames to the definition. A key concept for the SCr-based definitions of AKI is the identification of baseline SCr concentration. Although the initial international risk-injury-failure acute kidney injury classification (RIFLE) criteria recommended the use of a SCr concentration that would equate to eGFR of 75 mL/min/1.73 $m^2$ by the Modification of Diet in Renal Disease (MDRD) Study equation (MDRD-75) if no baseline were available, this definition does not account for chronic kidney disease if present.

It is essential to look for a prior baseline/reference SCr concentration, ideally from the 365 days before hospital admission from a clinical context in which there was not concern for AKI (e.g., a stable clinic visit). This concept is discussed in detail in the KDIGO AKI clinical practice guideline.

*Abbreviations: ADQI, Acute Dialysis Quality Initiative (international); AKI, acute kidney injury; AKIN, Acute Kidney Injury Network (international); eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; MDRD, Modification in Diet in Renal Disease; RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease; RRT, renal replacement therapy; Scr, serum creatinine.*

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## 18. Chilblain

According to ACCESS case definition:

Also referred to as perniosis or pernio, is a condition of the skin which manifests as erythematous to violaceous macules, papules, plaques, or nodules in sites of cold exposure and damp environments (idiopathic chilblains). The most common sites for involvement are the fingers and toes and is frequently accompanied by a sensation of itching, burning, or pain. It is postulated that pernio results from an abnormal vascular response to cold exposure. Cold-induced vasoconstriction of vasospasm resulting in hypoxemia that stimulates an inflammatory response is potential mechanism for the formation of skin lesions. There are reports of a causative correlation between systemic diseases and chilblains. The most frequent reported and studied relationship is the relationship between (chronic) chilblains and lupus erythematosus also known as “chilblain lupus erythematosus (CHLE)”.

**Chilblain-like lesions**: During the recent COVID-19 pandemic patients with little or no symptoms presented themselves with chilblain-like lesions located on the toes and fingers. These patients had no underlying autoimmune disease (such as lupus erythematosus), Raynaud’s phenomenon or previous episodes of idiopathic chilblains. It mostly affected children and young adults and the lesions took place later during the (suspected) COVID-19 disease. The chilblain-like lesions manifest as multiple red-violaceous edematous lesions with papules and macules located on acral regions such as toes, the feet (heel, sole) and/or the fingers, asymptomatic or associated with pruritis of mild pain. Because of the presentation similar with chilblains, it is referred to as pseudo-chilblain of chilblain-like lesions. The lesions disappeared after a few weeks without treatment.

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## 19. Single organ cutaneous vasculitis

According to ACCESS case definition:

Vasculitides are a group of heterogeneous conditions characterized by inflammation of blood vessel wall, which can occur in any organ system. Cutaneous involvement occurs almost exclusively with vasculitis of small and medium-sized vessels. Cutaneous vasculitis (CV) may be: (a) a single organ disease limited to the skin, (b) primary CV with secondary systemic involvement, or (c) a cutaneous manifestation of systemic vasculitis. Disease-inducing or promoting factors are not known for more than half of cases of Cutaneous Small Vessel Vasculitis (CSVV) and are currently classified as ‘‘idiopathic”. The remainder are most often either post-

infectious or drug induced. Although non-immunologic factors such as direct infection of endothelial cells can cause vasculitis, most lesions are mediated by immunopathogenetic mechanisms. These mechanisms can be classified into "Gell and Coombs" four types of hypersensitivity reactions.

**Case definition for single organ cutaneous vasculitis**: SOCV is a syndrome characterized by clinical and histological features of small vessel vasculitis of the skin without involvement of other organ systems.

*For all levels of diagnostic certainty:*
Clinical features:
Hemorrhagic papules
OR
Urticaria-like lesions
OR
Purpuric rash involving the face, ears, and extremities AND edema AND low-grade fever (only for AHEI)

*Level 1 of diagnostic certainty:*
Histology
Perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei (leukocytoclasia)
AND
Erythrocyte extravasation or hemorrhage into the dermis
AND
Fibrinoid necrosis or degeneration of the dermal postcapillary venules.
AND
*Exclusion of other vasculitic organ system involvemen*t

- Normochromic normocytic anemia, thrombocytopenia;
- Renal involvement (proteinuria, hematuria, hypertension, increased serum creatinine);
- Pulmonary involvement (dyspnea, cough, hemoptysis, patchy or diffuse alveolar infiltrates in chest X-ray);
- Gastrointestinal involvement (abdominal pain, vomiting, gastrointestinal bleeding);
- Liver involvement (elevated liver enzymes and bilirubin);
- Serosal involvement (pericardial and or pleural effusion) with ultrasound and/or X-ray examination in case of clinical suspicion;
- Arthritis (synovitis) with synovial aspirate in case of clinical suspicion, central or peripheral nervous system involvement by neurologic physical examination;
- Presence of antinuclear antibodies, ANCA, rheumatoid factor, anticitrullinated peptides antibodies (CCP), cryoglobulins;
- Reduced serum complements factors;
- Serologic evidence of hepatitis C, hepatitis B, EBV, ParvovirusB19 serology, ant streptolysin O-Trite.

*Level 2 of diagnostic certainty:*
Histology:
Perivascular inflammatory cells infiltrate dominated by neutrophils with fragmented nuclei (leukocytoclasia)
AND
Erytrocyte extravasation or hemorrhage into the dermis
AND
Exclusion of other organ or systemic involvement (see Level 1)

*Level 3 of diagnostic certainty:*
Histology - not available
AND
Exclusion of other organ or systemic involvement (see Level 1).

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## 20. Erythema multiforme

According to ACCESS case definition:

Erythema multiforme (EM) is an acute, self-limited disease that is typically associated with hypersensitivity reactions to viruses, as well as drugs. It is characterized by targetoid erythematous lesions with predominant acral localization and can be subdivided into isolated cutaneous and combined mucocutaneous forms.

Erythema multiforme is defined by the morphology of the individual lesions and the pattern of distribution. In 1993, an international consensus defined five severe bullous skin reactions including erythema multiforme based on morphological criteria.

Erythema multiforme was only included in its major form called erythema multiforme major. In EM, the detachment of the skin affects < 10% body surface area (BSA) and localized typical and/ raised atypical targets are present. Typical targets are defined as lesions less than 3 cm in diameter and characterized by three different concentric zones. Raised atypical targets normally contain only two zones. In typical and raised atypical targets, the center zone might show bullae formation as a sign of epidermal involvement. Clinically, EM patterns can be classified into EM with and EM without mucosal involvement. EM has been further subdivided into EM minus (involvement of ≤1 mucosal site) and EM majus (involvement of ≥ 2 mucosal sites).

### Table 40. Consensus classification of Erythema multiforme

| Criterion | Erythema multiforme major |
|---|---|
| Skin detachment (BSA affected) | < 10% |
| Target lesions | Typical and/or atypical |
| Raised lesions | Yes |
| Distribution | Predominantly affects the extremities; in children, frequently affects the trunk |
| Progression to TEN | No |

Abbreviations: BSA, body surface area; TEN, toxic epidermal necrolysis

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## 21. Acute liver injury

According to ACCESS case definition:

The process of acute hepatic insufficiency (IHA) is associated with the development of a coagulopathy of hepatic etiology and alteration of the level of clinically apparent consciousness due to hepatic encephalopathy (HE). The condition of patients who develop coagulopathy is defined, but they do not present any change in their level of consciousness as acute liver injury (ALI).

The clinical course of ALF starts with a severe ALI. This is characterized by a two to three-fold increase in transaminases (liver damage marker) associated with impaired liver function, such as jaundice or coagulopathy in a patient without previous chronic disease.
Severe acute liver injury defines a syndrome characterized by markers of liver damage (elevated serum transaminases) and impaired liver function (jaundice and INR> 1.5) that usually precedes clinical encephalopathy.

## Table 41. Classification systems of acute liver failure

| | Bernuau System | O'Grady System | IASL System | Japanese System |
|---|---|---|---|---|
| **Definition of ALF** | >50% decrease in factor II or V with HE | Severe liver injury with HE without prior liver disease | Severe liver Disfunction with HE within 4 wk without prior liver disease | INR ≥ 1.5 or PT ≤40% within 8 wk of symptoms without prior liver disease |
| **Requirement for HE** | Yes | Yes | Yes | No |
| **Subclasses** | Fulminant<br>Sub fulminant | Hyperacute<br>Acute<br>Subacute | Hyperacute<br>Fulminant | With hepatic Coma:<br>• Acute<br>• Subacute<br>Without hepatic coma |
| **Duration between symptoms and HE** | Fulminant <2 wk<br>Sub fulminant 2–12 wk | Hyperacute <1 wk<br>Acute 1–4 wk<br>Subacute 4–12 wk | Hyperacute<br>Fulminant | With hepatic Coma:<br>• Acute <10 d<br>• Subacute 10–56 d<br>Without hepatic coma NA |

Abbreviations: ALF, acute liver failure; HE, hepatic encephalopathy; IASL, International Association for the Study of the Liver; INR, International Normalized Ratio; NA, not applicable; PT, prothrombin time.

**Drug-induced liver injury**
Case definitions for drug-induced liver injury (DILI) include one of the following thresholds:

- ≥5 x Upper Limit of normal (ULN) elevation in alanine transaminase (ALT).
- ≥2 ULN elevation in alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of gamma-glutamyl transferase (GGT) in the absence of known bone pathology driving the rise in ALP level).
- ≥3 x ULN elevation in ALT and simultaneous elevation of total bilirubin level (TBL) concentration exceeding 2x ULN.

In patients with abnormal liver tests prior to starting treatment with the implicated drug, ULN is replaced by the mean baseline values obtained prior to DILI onset and increases should be proportionate to this modified baseline. Three patterns of DILI are determined using earliest identified elevation of liver enzymes levels. Initially ALT activity (patients ALT/ULN of ALT) and ALP activity (patients ALP/ULN of ALP) is calculated. Then ALT/ALP ratio (R) is determined:

- Hepatocellular, when there is a 5-fold or higher rise in ALT alone or when the ratio of serum activity (activity expressed as a multiple of ULN) of ALT to ALP is 5 or more.

- Cholestatic, when there is a 2-fold or higher rise in ALP alone or when the ratio of serum activity of ALT to ALP is 2 or less.
- Mixed, when the ratio of the serum activity of ALT to ALP is between 2 and 5.

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## 22. Subacute Thyroiditis (SAT)

Subacute thyroiditis (SAT) is a self-limiting thyroid disease associated with a triphasic clinical course of hyperthyroidism, hypothyroidism, and return to normal thyroid function. The well-known clinical features of SAT include thyroid pain with symptoms of hyperthyroidism, suppressed level of thyroid-stimulating hormone (TSH), low thyroid uptake of radioactive iodine, and elevated erythrocyte sedimentation rate. Diagnosis is based on clinical and laboratory data, and tissue diagnosis is rarely required. The hallmark of painful SAT is a markedly elevated erythrocyte sedimentation rate. C-reactive protein concentration is similarly elevated. Color-flow Doppler ultrasonography may also help to make this distinction; in patients with Graves' disease, the thyroid gland is hyper-vascular, whereas, in patients with painful SAT, the glands hypoechogenic and has low-to-normal vascularity.

Subacute thyroiditis (SAT) is an inflammatory disorder that is
diagnosed based on clinical and laboratory findings, including pain in the thyroid region, symptoms of hyperthyroidism, a low thyroid-stimulating hormone (TSH) level, low thyroid uptake of radioactive iodine, and an elevated erythrocyte sedimentation rate (ESR). Tissue diagnosis is rarely required. Numerous conditions—especially infections—can cause SAT.

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## 23. Rhabdomyolysis

Rhabdomyolysis is a well-known cause of renal failure and is commonly associated with drugs, toxins, and infections. There has been one reported case of rhabdomyolysis attributed to influenza vaccine causing renal failure in native kidneys.
Adverse reactions to influenza vaccines vary and non-specific systemic side effects have been reported to occur in 5–35% of vaccinated patients. Specific adverse reactions to influenza vaccines have also been reported in the past and these include neurological disorders such as Guillain–Barre, peripheral neuropathy, and demyelinating disease.
Rhabdomyolysis (often called rabdo) is a serious medical condition that can be fatal or result in permanent disability. Rhabdo occurs when damaged muscle tissue releases its proteins and electrolytes into the blood. These substances can damage the heart and kidneys and cause permanent disability or even death.
One or more symptoms of rhabdo:
Muscle cramps, aches, or pains more intense than expected,
Dark urine (tea-colored or cola),
Weak or tired, inability to complete work tasks or finish an exercise routine,
The only way to know if a person has rhabdomyolysis is through a blood test that checks for the presence of a muscle protein, creatine kinase (CK), in the blood.
Symptoms can appear at any time after the muscle injury, or even several days after the initial injury.

(go back 23)

## 24. Acute pancreatitis

According to Henry R. Thompson, acute pancreatitis is inflammation of the pancreas with activation of pancreatic enzymes within the organ. This leads to tissue destruction. Patients classically present with pain (94%), vomiting (64%), and fever (33%). This is a relatively uncommon diagnosis in childhood and is often missed. Diagnosis is based on clinical symptoms, three times increase in pancreatic enzymes, and radiologic evaluation.

A. In the patient's history, ask about acute abdominal pain in left upper quadrant (LUQ) that radiates to the back or right upper quadrant (RUQ) and is associated with nausea and vomiting. This may be with or without fever.

B. In the physical examination, note abdominal distention with or without peritoneal signs, and ascites. There may be signs of an ileus with absent bowel sounds. Discoloration around the umbilicus or flank suggests pancreatic necrosis (Cullen sign). Note signs of respiratory distress associated with pleural effusions or pneumonitis. Assess circulatory status and peripheral perfusion to identify intravascular volume loss secondary to third spacing. Note purpura or bleeding that suggests disseminated intravascular coagulation.

C. Laboratory findings of pancreatitis include increases in serum amylase and lipase levels. Comprehensive metabolic panel including liver function test results may be abnormal when choledocholithiasis or hepatitis is present. Glucose may be increased, and calcium decreased with severe disease. The white blood cell (WBC) count is often increased (10,000–25,000 K/ml).

D. Assess degree of illness (Table 42). For mild degree of illness, observe the patient. Provide hydration and symptomatic treatment. Start with a clear or low-fat diet. For severe pain, patient should be hospitalized. For very severe illness that may include respiratory distress and shock, admit to the intensive care unit (ICU).

E. Provide fluid resuscitation intravenously and correct electrolyte abnormalities. Control pain with narcotics. Prevent stress ulcer with a proton pump inhibitor (1–3 mg/kg IV every 24 hours) or use an H2 receptor antagonist (ranitidine 1 mg/kg intravenously [IV] every 8 hours).

F. Consider evaluation with ultrasound or abdominal computed tomography (CT) if increased liver function tests or physical examination findings of shock or peritonitis. In severe cases, treat with Octreotide (1–10 mg/kg/day IV divided every 12 hours). In severe cases, use nasogastric decompression. G. Follow up by re-evaluation over 24 to 72 hours. If improved with decreased amylase and lipase, consider feeds. If not improved clinically and with increased amylase and lipase, consider repeat ultrasound or CT and consider naso jejunal feeds or total parenteral nutrition.

### Table 42. Severity of Illness in Pancreatitis

| Sever | Very Severe |
|---|---|
| Severe abdominal pain with nausea and vomiting<br>And<br>Increased serum amylase or lipase | Signs of shock<br>Or<br>Disseminated intravascular coagulation<br>Or<br>Severe respiratory distress/impending Respiratory failure<br>Or<br>Signs of pancreatic necrosis<br>Or<br>Signs of peritonitis |

(go back 24)

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