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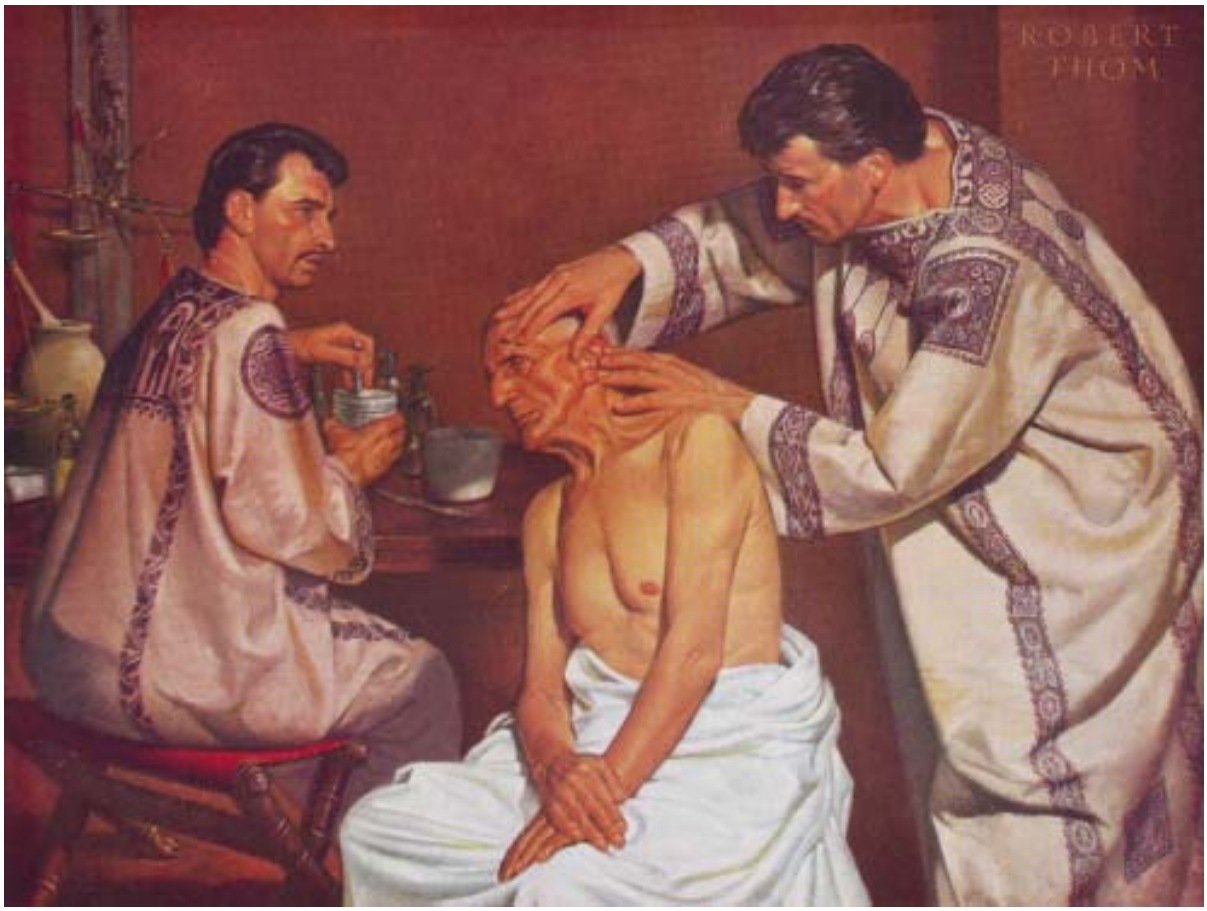

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The State Pharmaceuticals Corporation has served the people of our country for forty years. The Editorial Board of the *Sri Lanka Prescriber* remembers the late Professor Senaka Bibile on this occasion with respect, esteem and affection, for it was Senaka Bibile's genius that conceptualised and created that unique institution. The State Pharmaceuticals Corporation was an integral part of his national medicinal drug policy. The institution has demonstrated its sustainability under both natural and man-made disasters, and various political vicissitudes that would have destabilised or destroyed a less robust or less resilient institution.

Editors
Sri Lanka Presciber

Cover picture

DAMIAN AND COSMAS (300 A.D.)

Typifying twinship of Pharmacy and Medicine, Arabian Christian twin brothers, Damian and Cosmas, practiced together until martyred in 304 A.D. Canonized 200 years later, they became patron saints of Pharmacy and Medicine.

One of a series: *A History of Pharmacy in Pictures,* presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Adverse events following immunisation

Introduction

The WHO defines an adverse event following immunisation (AEFI) as a medical incident that takes place after an immunisation, causes concern and is believed to be caused by the immunisation [1]. There are no absolutely safe vaccines. Unlike many medicines, vaccines are usually given to healthy children. The real benefit of vaccines for children is not witnessed by the parents as vaccines prevent infectious diseases, so when infectious diseases become less common, parents become more concerned about adverse effects of vaccines [2]. It is necessary for doctors to have a clear understanding about AEFIs as their effective management is important to sustain the immunisation programme. This article presents a general outline about AEFIs and immunisation safety surveillance. Clinical management of common AEFIs is beyond the scope of this article.

Classification of AEFIs

AEFIs are classified into 5 categories [1] (table 1). It is important to determine the category of an AEFI for successful preventive measures and effective communication to the public.

Vaccine reactions

Vaccine reactions are due to an inherent property of the vaccine. They are classified as common, minor reactions (table 2) and rare, more serious reactions (table 3). For established vaccines (e.g. BCG, DPT, measles, etc), the range of vaccine reactions is well known through post-marketing surveillance programmes as these vaccines have been in the market for many years. They could be fatal in a small number of vaccine recipients. The vaccine reactions for established vaccines depend on their quality and composition. For example, type and frequency of vaccine reactions of the Diphtheria-Tetanus-Pertussis (DTP) whole cell vaccine and DTP acellular vaccine are different. Consequently, in Sri Lanka, cost difference restricts the availability of DTP acellular vaccine only in the private sector [3]. For new vaccines, the need for post-marketing surveillance is greater as not many recipients would have received these vaccines. Some new vaccines are kept under active surveillance for a specific AEFI which has been identified either during pre-, or post-marketing safety surveillance. For example, rota virus vaccine and risk of intussusception [4], pandemic influenza A (H1N1) 2009 vaccines and narcolepsy [4], and human papilloma virus (HPV) vaccine and syncope with injury following a faint [5].

Programme errors

Programme error and injection reactions are common to all vaccines, and in most instances do not depend on an inherent property of the vaccines. Non-sterile injection, incorrect preparation, injecting at wrong site, incorrect storage or transport, and ignoring contraindications have been identified as common programme errors that may lead to serious or fatal AEFI [1]. They may occur in clusters and the origin of the cluster could be traced to a particular health facility, a particular batch, or a particular vial of a vaccine. It is essential to detect programme errors, investigate them thoroughly and take preventive measures, because AEFI can be detrimental to an immunisation programme.

Table 1. Classification of adverse events following immunisation (AEFIs) [1]

Vaccine reaction	Event caused or precipitated by the vaccine when given correctly, due to inherent properties of the vaccine (the active component/excipients)
Programme error	Event caused by an error in vaccine preparation, handling, or administration
Coincidental	Event that happens after immunisation, but NOT caused by the vaccine – a chance association
Injection reaction	Event from anxiety about, or pain from, the injection itself rather than the vaccine
Unknown	Event's cause cannot be determined

Table 2. Common, minor immunisation reactions [1]

Vaccine	Local reaction (pain, swelling, redness)	Fever >38 ºC	Irritability, malaise and systemic symptoms
BCG	90-95%	–	–
HiB	5-15%	2-10%	–
Hepatitis B	Adults (15%) Children (5%)	1-6%	–
Measles / MR / MMR	10%	5-15%	55 (rash)
OPV		< 1%	< 1%
Tetanus / DT / Td	10%	10%	25%
Pertussis (DTP-Whole cell vaccine)	Up to 50%	Up to 50%	Up to 55%

HiB – *Haemophilus influenzae* Type B; OPV – oral poliomyelitis vaccine; MR – measles-rubella; MMR – measles-mumps-rubella; DT – diphtheria-tetanus vaccine; Td – adult tetanus-diphtheria vaccine

Injection reaction

This is a reaction to anticipating or actually receiving the injection, and is not related to the content of the vaccine. It is often precipitated when a child witnesses an AEFI in another vaccine recipient. Such anticipatory vaccine reactions are reported from school immunisation programmes when one child who shows symptoms of an AEFI (such as anaphylactic shock) is taken away for emergency treatment. Other children in the same group may then faint or vomit as a result of an injection reaction. When investigating AEFIs, the cluster of injection reactions may draw attention away from the initial case of anaphylactic shock. Hence meticulous recording of clinical events at the site by the attending health care team is crucial to differentiate a vaccine reaction from injection reactions.

Coincidental and unknown reaction

Assigning an AEFI to coincidental and unknown category should be done on positive evidence rather than as a diagnosis of convenience.

Immunisation safety surveillance

Immunisation safety surveillance has two major goals: (1) pharmacovigilance of AEFI, (2) ensuring sustainability of the immunisation programme by appropriate quick response to AEFIs, and removing the negative impact.

Pharmacovigilance of AEFI: Pharmacovigilance is the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems" [6]. Some refer to pharmacovigilance of AEFI as vaccinovigilance.

The objectives of pharmacovigilance of AEFI should include:

1. Early detection, assessment and management of the AEFI.
2. Root cause analysis of the AEFI and recommending preventive measures.
3. Estimating AEFI rates and generating new hypotheses about vaccine reactions (signal).
4. Active surveillance programme for newly marketed vaccines.
5. Maintaining public confidence in the immunisation programme.

Pharmacovigilance should be a joint venture involving the national immunisation programme, drug regulatory authority and the pharmacovigilance centre. Reported AEFIs should be defined, classified in terms of type and system involved, assessed in terms of seriousness, causality, and outcome, quantified, and analysed in terms of root cause and preventability. This should be done regularly, and the results should be communicated to all stakeholders to implement appropriate preventive measures. Some AEFI should be subjected to further investigation. Each country should decide the criteria which demand further investigation of an AEFI. The WHO recommendations include, AEFIs that may have been caused by programme error, AEFIs under active surveillance, serious AEFIs of unexplained cause, and AEFIs causing significant parental or community concern [1] (table 4).

List of reportable AEFIs

This list must include all serious AEFIs, and AEFIs which require immediate reporting for rapid and prompt response, eg. programme error, BCG lymphadenitis, severe local reaction, injection site bacterial abscess, AEFI occurring in cluster. A cluster is defined as two or more cases of the same or similar events related in time, geography, and vaccine administered. There is no universal list of reportable AEFIs. For example, when a new vaccine is introduced into the programme, or when there is a change in the immunisation schedule, the list should cover the AEFIs associated with these changes.

Table 3. Rare, serious immunisation reactions (onset interval and rates of most frequently reported AEFI and anaphylaxis) [1]

Vaccine	*Reaction*	*Onset interval*	*Reactions/million doses*
BCG	Suppurative lymphadenitis	2-6 months	100-1000
	BCG osteitis	1-12 months	0.01-300
	Disseminated BCG infection	1-12 months	0.19-1.56
HiB	None known		
Hepatitis B	Anaphylaxis	0-1 hour	1-2
Measles / MR / MMR	Febrile seizures	6-12 days	330
	Thrombocytopenia	15-35 days	30
	Anaphylactoid reaction	0-2 hours	10
	Anaphylaxis	0-1 hour	1
	Encephalopathy	6-12 days	< 1
OPV	Vaccine associated paralytic poliomyelitis	4-30 days	0.4*
Tetanus	Brachial neuritis	2-28 days	5-10
	Anaphylaxis	0-1 hour	0.4-10
Tetanus-diphtheria	None extra to tetanus reactions		
Pertussis (DTP-Whole cell vaccine)	Persistent (>3 hours) inconsolable screaming	0-24 hours	1000-60 000
	Seizures	0-2 days	80-570#
	Hypotonic, hyporesponsive episode (HHE)	0-24 hours	30-990
	Anaphylaxis	0-1 hour	20
	Encephalopathy	0-2 days	0-1

HiB – *Haemophilus influenzae* Type B; OPV – oral poliomyelitis vaccine; MR – measles-rubella; MMR – measles-mumps-rubella; DT – Diphtheria- tetanus vaccine; Td – adult tetanus-diphtheria vaccine

* Risk is higher for first dose (1 in 750,000 compared to 1 in 5.1 million, and for adults and immunocompromised

Seizures mostly febrile and risk depends on age, with much lower risk in infants under the age of 4 months.

Serious AEFIs

AEFIs that result in death, require inpatient hospitalisation or prolongation of existing hospitalisation, result in actual or potential persistent or significant disability/incapacity, or life-threatening are defined as serious AEFIs.

Case definition

Since most AEFIs do not have a gold standard of confirmatory investigation, case definitions are vital to diagnose them. The WHO gives case definitions for most of the serious AEFIs [1]. Using case definition permits uniformity in diagnosis and facilitates dissemination of surveillance data. For anaphylaxis following immunisations, Brighton case definition [7] is also available which ascertains diagnostic certainty and classifies it into 3 levels. The level 1 classification is associated with the greatest diagnostic certainty.

Frequency

Unlike in adverse drug reactions (ADR), determination of frequency of AEFIs is feasible during post-marketing surveillance as denominator data, ie. number of vaccine recipients or number of doses administered is generally documented. So if the post-marketing surveillance yields data on the numerator, ie. number of particular AEFIs as completely as possible, frequency of AEFIs could be determined fairly accurately (table 2, 3).

Causality

This is the assessment of the strength of association between the implicated vaccine and an AEFI. Causality assessment is required mainly for AEFIs that are subjected to further detailed investigation. Many causality assessment methods are reported in the literature with most utilising a few basic elements such as time relationship between the event and administration of the vaccine, presence of alternative explanations, previous experience with the suspected vaccine, and dechallenge and rechallenge. The Uppsala Monitoring Centre (WHO) classifies causality as certain, probable, possible, unlikely, conditional/ unclassified and unassessible / unclassifiable [9]. For AEFI, the first three categories are used [1]. Accurate causality assessment requires detailed documentation of the AEFI and the patient's history. In the absence of these data, the degree of causality could be an underestimate.

The Department of Immunisations, Vaccines and Biologicals of the WHO spearheads the global immunisation safety surveillance programme. Under its auspices, the Global Advisory Committee on Vaccine Safety was established in 1999, which is tasked with the duty of handling vaccine safety issues of potential global importance [4]. A major current activity of the WHO in immunisation safety surveillance is "The Global Network for Post-Surveillance of Newly Prequalified Vaccines" which is a post-marketing surveillance programme to monitor the safety of vaccines that are newly pre-qualified and introduced into routine national immunisation programmes.

Sri Lanka is a participating country in this programme. The Epidemiology Unit of the Ministry of Health spearheads the National Immunisation Safety Surveillance Programme. It has an AEFI reporting system in place, and necessary action is taken based on the reports. It is advised by an expert committee which handles vaccine safety issues of potential national importance. The vaccine safety information is published in the *Quarterly Epidemiological Bulletin.*

Individual countries have their own immunisation safety surveillance programmes with national objectives and activities depending on the respective country's needs and priorities. For example, in the United States of America, Vaccine Adverse Event Reporting System (VAERS), a joint programme of Centers for Disease Control and Prevention (CDC) and the Food and Drugs Administration (FDA) engage the public in many of its activities. AEFI data are made available to the public, parents can report a suspected AEFI (online or via the paper version), vaccine safety data are disseminated to the public, and most importantly, has a National Vaccine Injury Compensation Programme (VICP) in place under National Childhood Vaccine Injury Act of 1986. It permits a victim of AEFI to claim compensation from the State, and when the Courts determine that a claim is justifiable, the victim is paid up to 250 000 USD. The VICP is regarded as a no-fault alternative to the traditional tort system for resolving injury claims, that provides compensation to people found to be injured by vaccines.

Immunisation may cause adverse events, and some of them may be serious or even fatal. However, given the enormous benefits of immunisation and the rare nature of fatal and serious AEFIs, the benefits greatly outweigh the risks. Nevertheless, this does not remove the need for a strong immunisation safety surveillance programme.

Table 4. List of reportable AEFIs (recommendations of the WHO) [1]

Occurring within 24 hours of immunisation	1. Anaphylactoid reaction 2. Anaphylaxis 3. Persistent (more than 3 hours) inconsolable screaming 4. Hypotonic hyporesponsive episode (HHE) 5. Toxic shock syndrome (TSS)
Occurring within 5 days of immunisation	1. Severe local reaction 2. Sepsis 3. Injection site abscess (bacterial/sterile)
Occurring within 15 days of immunisation	1. Seizures, including febrile seizures (6-12 days for measles / MMR; 0-2 days for DTP) 2. Encephalopathy (6-12 days for measles / MMR; 0-2 days for DTP)
Occurring within 3 months of immunisation	1. Acute flaccid paralysis (4-30 days for OPV recipient; 4-75 days for contact) 2. Brachial neuritis (2-28 days after tetanus containing vaccine) 3. Thrombocytopenia (15-35 days after measles/MMR)
Occurring between 1 and 12 months after BCG immunisation	1. Lymphadenitis 2. Disseminated BCG infection 3. Osteitis/Osteomyelitis

No time limit: Any death, hospitalisation, or other severe and unusual events that are thought by health workers or the public to be related to immunisation

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Conflict of interest: None declared.

Citalopram hydrobromide: drug safety communication – abnormal heart rhythms associated with high doses

AUDIENCE: Psychiatry, Cardiology

ISSUE: FDA notified healthcare professionals and patients that the antidepressant citalopram hydrobromide should no longer be used at doses greater than 40 mg per day, because it can cause abnormal changes in the electrical activity of the heart, (prolongation of the QT interval of the electro-cardiogram) which may lead to an abnormal heart rhythm including torsade de pointes, which can be fatal. Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low levels of potassium and magnesium in the blood.

Studies did not show a benefit in the treatment of depression at daily doses higher than 40 mg. Previously, the citalopram drug label stated that certain patients may require a dose of 60 mg per day. The citalopram drug label has been revised to include the new drug dosage and usage recommendations, as well as the information about the potential for QT interval prolongation and torsade de pointes.

BACKGROUND: Citalopram hydrobromide is in a class of antidepressants called selective serotonin reuptake inhibitors (SSRIs).

RECOMMENDATION: Citalopram causes dose-dependent QT interval prolongation. Citalopram should no longer be prescribed at doses greater than 40 mg per day. Citalopram should not be used in patients with congenital long QT syndrome, patients with congestive heart failure, bradyarrhythmias, or predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or drugs, who are at higher risk of developing torsade de pointes. Safety of Medicines and Risk Evaluation Sub Committee (SAFRESC) has recommendations for healthcare professionals and patients.

Healthcare professionals and patients are encouraged to report adverse events or side-effects related to the use of citalopram products to the Adverse Drug Reporting Program "Info_Vig".

NOTE: Trade names of citalopram hydrochloride marketed in Sri Lanka are Celepra 20, Citap, Citopam, Feliz 20, Feliz 40, Lopram, Pramcit and Ultidep 20.
Download the adverse drug reaction reporting form from:

www.cmb.ac.lk/academic/medicine/ext_pages/pharmacology/documentation/ADR.pdf

or **call 0094 112 697483** to request a reporting form, then complete and return to The Head, Drug Information Centre (Info_Vig), Department of Pharmacology, Faculty of Medicine, PO Box 271, Kynsey Road, Colombo 8, Sri Lanka, or submit by **fax to 0094 112 697483**.

Reference

www.fda.gov

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Conflict of interests: None declared

Management of dengue haemorrhagic fever

Introduction

In the year 2009 the disease burden of dengue in Sri Lanka was 35 010 cases with 346 deaths – our highest recorded mortality to date. Given the known epidemiological trend we cannot foresee a reduction in the disease burden in the near future. Under the circumstances our role should be to ensure that no patient dies of dengue. This is a realistic goal which responsible clinicians should strive to achieve. The current management approach includes a new dimension, particularly to fluid therapy. A clear understanding of the course of the disease makes for high predictability of outcomes. Blind therapy is undesirable in the management of dengue fever (DF) and dengue haemorrhagic fever (DHF). Properly timed and appropriate interventions regarding the quality and quantity of fluid, as well as adjuvant therapy, can minimise a fatal outcome amidst cascading complications triggered by profound shock, provided this is detected early and addressed aggressively within 4 hours of onset.

Management

Proper management of dengue requires early diagnosis of dengue infection, preferably within the first 3 days of the onset of fever. The next step requires identification of the clinical type as DF or DHF. These are two distinct clinical entities with different management approaches and outcomes. There is no plasma leakage in DF, and consequently, it has an excellent prognosis. DHF, on the other hand, is characterised by plasma leakage and goes through a fairly predictable course comprising febrile, critical and convalescent phases.

Panel 1. Key points in the diagnosis

- Dengue is hyperendemic. Therefore be vigilant to detect dengue in all acute fevers.
- Symptoms of a viral fever
- Absence of coryza
- Diffuse blanching erythema
- Leucopenia with thrombocytopenia

Dengue fever

- No plasma leakage

Dengue haemorrhagic fever

- Plasma leakage with platelet count <100,000/ microlitre

Note

Bleeding manifestations and thrombocytopenia are common to both DF and DHF and hence not discriminative of identifying the clinical type

Panel 2. Evidence of plasma leakage

Suspect

- Tachycardia in an afebrile patient
- Pulse pressure <20 mmHg
- CRFT >2 seconds
- Rise in HCT

Confirm

- Chest xray – R lateral decubitus – mild pleural effusion
- US SCAN abdomen – gall bladder wall oedema, mild ascites, fluid in pouch of Douglas

Additional evidence to be checked when in doubt

- Non-fasting serum cholesterol <100 mg/dl
- Serum albumin <3.5 g/dl

CRFT = capillary refilling time
HCT = haematocrit
US SCAN = ultrasound scan

Once DHF is confirmed by detecting evidence of plasma leakage it is essential to determine the time of entry into the critical phase and its predicted end. It is computed by analysing all the full blood counts done during the febrile phase arranged in chronological order. The time at which the total WBC is at a low nadir, differential count shows a lymphocyte predominance, HCT has increased, and platelet count is <100 000 per microlitre is usually taken as the point of entry into the critical phase. This information, as well as the ideal body weight of the patient are vital for rational and precise fluid therapy. Blind fluid therapy is no longer advocated. Fluid therapy has to be precise, and should not be started until this basic information is accurately determined and documented.

Throughout the entire course of the illness the clinician has to be aware of the stage of the illness, and if in the critical phase, the precise point in the time scale. Accurate monitoring of the clinical status, vital signs, and hourly urine output, and their accurate documentation according to the phase of the illness form an integral part of management.

Obesity, pregnancy, and comorbid states such as diabetes, asthma, hypertension and ischaemic heart disease tend to give rise to severe disease. This should be anticipated and such patients warrant more comprehensive monitoring.

Symptomatic therapy

Paracetamol is the only antipyretic agent that should be used to control fever, myalgia and headache. NSAIDs of any form including diclofenac suppositories and mefenamic acid should not be used in any patient with suspected dengue. Antibiotics also should not be used at any stage of the disease unless there is a bacterial infection.

Fluid therapy

Fluid therapy is the cornerstone of management of DHF. Its quantity, quality and route of administration are determined by the phase of the illness and the status of the variables. Plasma leakage is the pathological hallmark in DHF, and it is the result of increased vascular permeability specifically into the pleural and peritoneal surfaces. If left unattended hypotension and shock are inevitable owing to intravascular volume depletion. The objective of fluid therapy is to offset this tendency by judicious fluid therapy aimed at matching the plasma leakage, thereby preventing intravascular volume depletion.

Febrile phase

In the majority, oral fluid is here sufficient. Parenteral fluid is not mandatory, and should be considered only if oral feeding is hampered by vomiting. Prescribe only the maintenance quantity (for an adult 2 - 2.5 l / 24 hours). Additional fluid will be needed to compensate for vomiting and diarrhoea. Water alone is insufficient, electrolytes too are essential. Oral rehydration fluid, rice kanjee, fresh fruit juices and soups are good options. However, black and red drinks should be avoided.

Critical phase

Administer only the calculated fluid quota of ***M+5%*** (panel 3), which is the total quantity for the entire 48 hour period of the critical phase. This includes the total of both oral and IV fluids. Fluids should not be given at a flat rate; it should be adjusted hour by hour to match the dynamics of fluid leakage. Most will require only crystalloids for the entire phase of plasma leakage. Few patients will need colloids (Dextran 40 or 6% starch solution) as well. Isotonic saline is a good crystalloid to start with at the rate of 1.5ml/kg /h. Infusion rate should be progressively increased every 4 - 6 h to 3 ml/kg /h and then 5 ml/kg/h at about 24 hours into the critical phase, when plasma leakage is maximal (7 ml/kg/h), after which it should be gradually decreased. It should always be kept in mind that there is no hard and fast rule to fluid therapy, it has to be flexible, and sometimes adjusted hour by hour based on the dynamics of the monitoring variables and individual patient requirements.

When the desired goal of an adequate hourly urine output of 0.5 - 1 ml/kg and satisfactory pulse pressure of >25 mm Hg cannot be maintained, and there is a need to frequently increase the crystalloid infusion rate, rapid plasma leakage should be suspected and a colloid in the form of Dextran 40 should be substituted for saline without delay. Dextran 40 causes volume expansion, remains in the circulation for about 4 hours, and provides a more sustained improvement in the haemodynamic status. Colloids should also be considered if the calculated fluid quota is being exhausted while still in the early part of the critical phase. Colloids enable the clinician to restrict and conserve the fluid quota while maintaining the desired haemodynamic stability, which otherwise would have needed a larger volume of crystalloid. Under these circumstances, although Dextran 40 is the preferred colloid near the peak of plasma leakage, 6% starch would be a better choice towards the end of plasma leakage. Colloids should be given as boluses and not as infusions. Capillary haematocrit should be checked before and 15 minutes

after each bolus. Haematocrit drops by 10 points after a Dextran bolus. Haematocrit should be checked as frequently as necessary throughout the critical phase to make decisions, along with the relevant data from the monitored vital signs.

Accurate identification of the time of entry into the critical phase, precise calculation of the fluid quota based on the ideal body weight (maximum 50 kg) for the entire period of 48 hours of plasma leakage, and careful selection between isotonic saline, Dextran 40 and 6% starch solution enables the clinician to work within the fluid quota and prevent shock as well as fluid overload.

Convalescent phase

A wide pulse pressure and an hourly urine output in excess of 1 ml/kg body weight heralds the onset of the convalescent phase. Fluid requirement is only the maintenance quantity, which should be given orally. Parenteral fluids are not essential and could even be harmful. Leaked fluid gets reabsorbed during this phase, so colloids, particularly Dextran 40 should never be given in this phase of the illness, because volume expansion can precipitate pulmonary oedema.

Adjuvant therapy

1. Antibiotics should be given only if there is infection with a bacterial pathogen. It should not be given at any stage even in the presence of fever if there is no infection.
2. Platelet transfusions. There is no place for prophylactic platelet transfusions even with platelet counts as low as 10 000/ per microlitre. It is indicated for significant bleeding in association with a platelet count of <10 000/microlitre, DIC, and in patients with intracranial haemorrhage or patients who have to undergo urgent surgery.
3. Fresh frozen plasma. Prophylactic transfusions are not recommended.
4. Steroids and intravenous immunoglobulins are not recommended in the light of currently available evidence.
5. Factor VII. It is used only to buy time to arrest bleeding when a specific and definitive intervention is planned to treat the cause of bleeding, eg. band ligation of oesophgeal varices.
6. Tranexamic acid. This is given at a dose of 1gram 8 hourly when there is bleeding per vaginam.

Management of complications

Prolonged shock and the resulting hypoxaemia trigger the cascading life-threatening complications such as hepatic failure, acute renal failure, severe bleeding and disseminated intravascular coagulopathy. Fluid overload is the other major complication which, by causing pulmonary oedema, aggravates hypoxaemia.

Shock

This should be prevented by good monitoring of vital signs and evaluation of all the haematological variables in the febrile phase and then by frequent monitoring and judicious fluid therapy in the critical phase.

Panel 3. Calculation of fluid quota

M = 100 ml/kg for first 10 kg B.W.
+ 50 ml/kg for next 10 kg B.W.
+ 20 ml/kg for the balance B.W.

5% of body weight = 50 ml x ideal body weight

Maximum body weight taken for calculations is **50 kg**

4600 ml of fluid is the maximum for the **entire 48 hours** of the critical phase for a patient whose body weight is 50 kg or more

Panel 4. Monitoring

Clinical status

Vital signs

- Heart rate
- BP and pulse pressure
- CRFT

Hourly urine output

HCT – priority during critical phase

FBC – priority during febrile phase

Shock with a narrow pulse pressure and hypotension is treated initially with a crystalloid (isotonic saline) bolus of 10 ml/kg body weight over 1 hour to open up the microvasculature. If there is no haemodynamic improvement a second crystalloid bolus is infused. A colloid bolus is given at a dose of 10 ml/kg body weight over 1 hour if there is no improvement after two crystalloid boluses. If the haematocrit drops by more than the expected value after these interventions and the patient remains unstable, concealed haemorrhage should be suspected, and packed red cells (PRC) transfused early. Volume of PRC to be transfused should be computed on the basis that 5 ml/kg of PRC will raise the HCT by 5%.

Profound shock (unrecordable blood pressure) is treated in the same way except that the initial crystalloid bolus is given faster over 15 minutes.

In all patients with shock HCT should be checked before and after each fluid bolus, and venous blood samples collected to check for acidosis, hypocalcaemia, hypoglycaemia and electrolyte disturbances. Acidosis should be corrected with intravenous sodium bicarbonate if the pH is <7.35 and HCO_3 is <15 mmol/l. Early correction of acidosis can minimise the tendency for severe bleeding and DIC in patients with dengue shock; hence, if facilities for blood gas analysis are not available 50 ml of 8.4% sodium bicarbonate diluted in 50 ml of isotonic saline can be given intravenously. Similarly 10 ml of 10% calcium gluconate over 10 minutes can be given intravenous as these patients are invariably hypocalcaemic, which contributes to haemodynamic instability.

Fluid overload

This is usually encountered in the convalescent phase. It is treated aggressively with repeated doses of intravenous frusemide at 1mg/kg body weight. For fluid overloaded patients who are haemodynamically unstable frusemide may be given midway during a colloid infusion or blood transfusion.

Panel 5. Essential management alerts

- Is the fever due to dengue? Full blood count (FBC) is an urgent mandatory investigation.
- When did fever start? Document date and time.
- Has the ideal body weight been recorded?
- What is the clinical type? DF or DHF? Be alert to detect plasma leakage. Monitor vital signs even when stable.
- Has the time of entry into the critical phase been computed? Review all the FBCs in chronological order
- Why is there haemodynamic instability despite correct fluid therapy?
- Concealed bleeding has to be suspected and PRC transfusions given early.
- Always be aware of the phase of the illness.

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Managing aggressive and violent patients

Summary

All healthcare workers, especially general practitioners and staff in emergency departments, are likely to encounter aggression and violence. This behaviour may be caused by a medical illness, a psychiatric illness or drug intoxication or withdrawal. These problems can occur in combination. It is important that a diagnosis is made, but in some cases the patient may need sedation before they can be examined. If non-drug management, such as de-escalation techniques, does not work, a benzodiazepine or antipsychotic can be considered. It is essential that sedated patients are monitored for signs of over-sedation. Practice design and policies as well as staff training can help to reduce the risk of violence.

Key words: antipsychotics, benzodiazepines, de-escalation, sedation.

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Introduction

Aggression and violence may be a manifestation of underlying psychiatric disorders. These include drug psychosis, delusional states, mania and personality disorder. Some patients try to use aggression as means of achieving a particular goal, such as being seen earlier or obtaining drugs.

Medical illness may result in behaviour disturbance. It can also coexist in patients with mental health, drug and alcohol problems or other conditions (see Box 1).

Prevention

Some simple preparatory steps may be helpful in averting trouble or in dealing with difficult situations as they arise. A sign should make clear that aggression and violence are not tolerated. The practice or emergency department should have a functioning duress system and protocols for responding. Ideally the assessment area should have no dangerous objects easily at hand and should have more than one exit. Some medical practices and hospitals have systems to alert staff that a presenting patient may be difficult to manage, or pre-agreed management plans for particular patients.

A number of studies have found benefits from education and training programs to help healthcare workers develop skills and increase confidence in managing these situations. Staff should be advised that their personal safety is a priority. They should not see patients for a late appointment when they are alone. It is appropriate to avoid confrontation and to call for help if they feel at risk. Keeping patients informed of waiting times and providing a comfortable waiting area is helpful.

Clinical scenarios

An elderly woman with known mild dementia is brought in by her family as she has become increasingly agitated and is confused and aggressive. A calming low stimulus environment assists the initial assessment. The underlying cause turns out to be a urinary tract infection, dehydration and hyponatraemia. Treatment with antibiotics and appropriate fluids in hospital returns her to her usual state.

Box 1

Medical conditions which can cause aggression

Hypoxia, hypercarbia – pneumonia, worsening chronic airway disease

Hypoglycaemia – diabetes, malnourished alcoholic

Cerebral insult – stroke, tumour, seizure, encephalitis, meningitis, trauma

Sepsis – systemic sepsis, urine infection in the elderly

Metabolic disturbance – hyponatraemia, thiamine deficiency, hypercalcaemia

Organ failure – liver or renal failure

Withdrawal – alcohol, benzodiazepines

Drug effects – amphetamine, steroids, alcohol, prescribed medications and interactions

A drug-affected young man is brought in by friends as he has become increasingly irrational and aggressive. An ambulance and police are called, a schedule is written, he is taken to the emergency department for a short-stay mental health and drug and alcohol admission, and sedated. The diagnosis is methamphetamine intoxication.

A middle-aged man with a long-standing brain injury is often threatening and disruptive while in the waiting room for his regular attendances. His future visits are always scheduled as an early long appointment and it is made clear he must be accompanied by his carer.

A 65-year-old man is tremulous, agitated and aggressive. He seems irrational and is experiencing visual hallucinations. He is admitted to hospital where the diagnosis is acute alcohol withdrawal. He is given fluids, nutrition, thiamine and diazepam in relatively high doses according to an alcohol withdrawal protocol. Antipsychotics and other drugs which lower the seizure threshold are avoided.

Managing an acute episode

Before treating the behavioural disturbance consider what may be causing it.

Assessment

Look for clues that the behaviour disturbance may be due to an organic cause, for example a previously stable elderly patient presenting with behaviour change may have sepsis, stroke, trauma or a drug interaction. The history is relevant, for example a patient with known epilepsy may present with post-ictal confusion, or a patient who is taking long-term anticoagulation may have had a head injury.

A general physical examination including neurological examination looking for higher function, orientation, meningism and localising signs should be performed as soon as possible. Measure the pulse, blood pressure, temperature, respiratory rate and if possible, oxygen saturation and blood glucose.

The clinical scenario will determine the extent of investigation required to exclude an organic cause or contributing comorbidity. Initial basic blood tests such as a full blood count, chemistry, blood sugar, liver and renal function are appropriate if results can be quickly obtained. Further tests including blood alcohol level, urine drug screen, urinalysis and culture and cerebral CT scanning may be required if the patient is hospitalised.

Common clues that a psychiatric cause is likely include past history of mental illness, drug use or alcoholism, current medications, general physical appearance including self-care, appropriateness of mood and engagement, manner and content of speech, posture and movement. Wherever possible collateral and corroborating history should be sought from family, friends and healthcare providers.

Non-pharmacological management

Some basic verbal de-escalation and distraction techniques can be used (see Box 2). It is often safer to call for help early and to remain at a safe distance until support, such as police and ambulance, arrives. A show of force may persuade the patient to cooperate.

Box 2

De-escalation

- Use an empathic non-confrontational approach, but set boundaries
- Listen to the patient, but avoid giving opinions on issues and grievances beyond your control
- Offer food, drink and a place to sit
- Avoid excessive stimulation
- Avoid aggressive postures and prolonged eye contact
- Recruit family, friends, case managers to help
- Address medical issues especially pain and discomfort
- Try to ascertain what the patient actually wants and the level of urgency

Suspected or identified medical problems must be addressed before treating the behavioural disturbance. If the patient is uncooperative they may need to be scheduled if they are a danger to themselves or others and mental illness is suspected. While there are state by state differences in the Mental Health Act the principles are very similar. When involuntary care is needed, an initial schedule is written to allow safe care and transport to a mental health unit (this may be an emergency department, psychiatric unit or hospital). It should be remembered that in some jurisdictions a Mental Health Schedule can now be written by police and ambulance officers as well as by a doctor, and that it is a legal order that a patient be taken to a place where they can be assessed by a mental health specialist. If there is a potentially serious medical emergency it may be necessary to provide treatment without immediate scheduling of an uncooperative patient. Restraint and forced sedation should be considered a last resort.

Pharmacological management (Table 1)

In some situations sedation may be appropriate. The choice of drug and dosage used is influenced by the patient's age, size, other prescribed or non-prescribed drugs taken, known illness such as long-term benzodiazepine abuse, alcoholism, liver or renal failure.

Physical signs such as hypotension and hyperthermia indicate a need for resuscitation as well as adjustment of drug choice and dosage. Position the patient appropriately, for example lay them flat, elevate their legs if hypotensive, and ensure a safe airway position if they are post-ictal.

Table 1. Drugs for sedation

Drug	Usual adult dose	Adverse events and management
Diazepam	5-10 mg oral or intravenously. Max 30 mg per event. Longer acting than midazolam.	Oversedation – maintain airway, coma position, provide oxygen Hypotension – lay down, intravenous fluids Airway or respiratory compromise – support airway, give oxygen Parodoxical reactions
Lorazepam	2 mg. Max 10 mg in 24 hours.	
Midazolam	5-10 mg intramuscularly. Max 20 mg per event. Rapid onset	
Olanzapine	5-10 mg oral. Max 30 mg per event.	Hypotension – lay down, intravenous fluids Seizure – coma position, clear airway, benzodiazepines
Halpoeridol	5-10 mg intramuscularly. Max 20 mg per event.	Acute dystonia - benztropine 2 mg oral or intramuscularly or intravenously Hypotension – lay down, intravenous fluids

Note: Lower doses (titrate to effect) should be used in those who are elderly, have low body weight, are dehydrated, have significant other medical illnesses or have ingested significant amounts of alcohol or other drugs. All sedatives can cause oversedation.

When possible administer oxygen, intravenous fluids and glucose (plus thiamine if Wernicke's encephalopathy is a possibility). Gather information, continue to manage clinically and arrange transfer if indicated.

For disturbed patients, in the first instance an oral sedative should be offered in a non-threatening collaborative way: 'I know you feel very distressed and this will help while we work out what to do next'. Oral diazepam 5 mg or olanzapine 5 mg are common choices.

The dosage should be titrated to clinical effect whilst watching for over-sedation and other adverse effects such as hypotension in the patient who has ingested other drugs or alcohol, is dehydrated or has a medical illness.

Parenteral sedation is more difficult although a number of patients may accept this if it is offered: 'You will feel better far more quickly if I can give you this now'. Forced parenteral sedation is not usually possible outside hospital. It requires trained staff in numbers (usually five or more) to either convince the patient to accept without violent struggle or to restrain the patient while medication is given. This needs training and equipment such as gowns, gloves and face masks and requires some skill to avoid injury to the patient or staff.

All patients who have been given parenteral sedation will require a level of monitoring and ambulance transfer to hospital should be arranged as soon as possible. The need for transfer and monitoring becomes even more urgent when higher doses of benzodiazepines are used or when other drugs such as haloperidol have also been given.

Benzodiazepines

Increasing doses of benzodiazepines produce a progressive spectrum of effect from anxiolysis and anticonvulsant effects to amnesia, sedation and eventually hypnosis and anaesthesia. Toxicity is usually related to very high doses and results in excessive sedation and airway obstruction. While benzodiazepines are essentially safe drugs, at very high doses or when given to a patient with hypovolaemia or other significant physiological compromise, they may contribute to cardiovascular and respiratory depression. Extra care should be taken if there is a possibility that the patient has consumed other sedating drugs (for example methadone).

Diazepam is used as an oral or intravenous preparation (not for intramuscular injection). It is quickly absorbed, but has a long half-life (up to 36 hours or more) so it can accumulate after repeated doses. Lorazepam has a shorter half-life (12-16 hours).

Midazolam is water-soluble and can be given intravenously or intramuscularly. It has a rapid onset, an elimination half-life of 2-4 hours and a much steeper dose-response curve than diazepam.

Antipsychotics

Olanzapine is an 'atypical antipsychotic' which can be given orally or as an intramuscular injection. It has a rapid onset of action with a half-life of about 30 hours. In clinical trials doses of 5-10 mg have been effective. A second dose should not be given for at least two hours. Olanzapine should not be given with benzodiazepines

because of the risk of cardiorespiratory depression. Extrapyramidal effects may occur but are less likely than with typical antipsychotic drugs. Other potential adverse effects include excessive drowsiness, hypotension and tachycardia.

Haloperidol can be given as an intramuscular injection. It has a rapid onset of action with effects lasting two to four hours. Toxicity manifests as over-sedation or hypotension. There may be extrapyramidal adverse effects such as dystonia (or even neuroleptic malignant syndrome) and it may lower the seizure threshold.

Post-sedation management

In almost all circumstances the patient will need to be transferred for further medical and then psychiatric assessment as soon as possible. After sedation the patient must be closely observed and monitored. They should be managed in a safe position with a clear airway and if possible supplemental oxygen given. The degree of sedation (for example as assessed by the Glasgow Coma Score), pulse, temperature, blood pressure, respiratory rate and pupils should be checked. If equipment is available check the blood glucose (or give glucose if hypoglycaemia is possible but glucose cannot be checked), ECG rhythm and oxygen saturation. A physical examination looking for possible organic medical illness should be performed.

Arranging urgent transfer and managing a patient post-sedation is critical. An awareness of the potential adverse effects and possibility of overdosage is essential. Documentation including recorded observations is required.

Conclusion

Preparedness involves a level of awareness and some planning for the possibility of aggression and violence, in particular facility design, policies and procedures and staff training. It should always be remembered that organic illness can mimic or coexist with psychiatric illness and that both may cause behaviour disturbance. Verbal de-escalation is a useful technique.

In the uncommon situation that sedation is needed in a non-hospital setting, an early call for police and ambulance assistance should be made. Oral sedation can be effective, but intramuscular or intravenous medication is needed in some cases. Post-sedation physical assessment and monitoring is essential. A review of practice preparedness and staff debriefing should be undertaken after an event.

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