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Contents

Contents

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Anaesthesia

Intensive care medicine in rural sub-Saharan Africa - who to admit?

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Summary

This article describes some of the factors to be weighed up when considering which patients are appropriate for admission to an intensive care unit in a country with limited resources. The authors describe their experience running an ICU in a rural part of Uganda, and use the audited outcomes of a cohort of 2,202 patients admitted over a six-year period.

INTRODUCTION

St.Mary's Hospital Lacor is a not-for-profit, church hospital situated in northern Uganda. It is in a rural area which, until recently, has suffered considerable insecurity and is in one of the poorest areas of rural sub-Saharan Africa.[1] The hospital has significant overseas support and patient care is subsidised in order to fulfil its mission of serving the poorest patients to the highest standards possible. There are approximately 500 hospital beds and 5000 operations are performed in the theatre block per year. Since July 2005 we have prospectively collected data on outcomes of all patients admitted to the ICU. The data of over 2000 patients is stored on an Access® database.

ICU STAFFING AND INFRASTRUCTURE

The eight-bed ICU has 8 trained nurses and 4 assistant nurses. There is one anaesthetic officer assigned to the ICU who also covers the emergency theatres in the night, with one nurse anaesthetist. One overseas anaesthesiologist, has been attached to the ICU for the last 9 years and he is the only physician with a clinical responsibility totally to the ICU. All patients are admitted under the care of the admitting physicians, who also have duties in the main wards, labour ward, outpatients and theatre. There are no other dedicated ICU medical staff.

The majority of the nurses on the ICU are not rotated around the main wards, as is often the custom in other institutions, so that a core of locally trained specialised ICU nurses has been retained.

The ICU has no capacity for peritoneal dialysis or haemodialysis. There are no infusion pumps or blood gas analysis and it is only occasionally possible to estimate serum electrolytes. There are currently three Glostavent ventilators (Diamedica, UK) in ICU with a fourth in theatre and an adequate number of pulse oximeters and non-invasive blood pressure machines. The ratio of trained nurses to patients varies from 1 to 4 to 1 to 8. The ICU is a large open-planned area with two cubicle spaces, situated close to theatre (Figure 1).[2] With a physical capacity of eight beds, and with the added possibility of admitting more patients on trolleys if required, the ICU is rarely physically short of beds to accept referrals from the hospital clinicians. However the nursing staff number is fixed so in busy times the ratio of nurses to patients suffers.

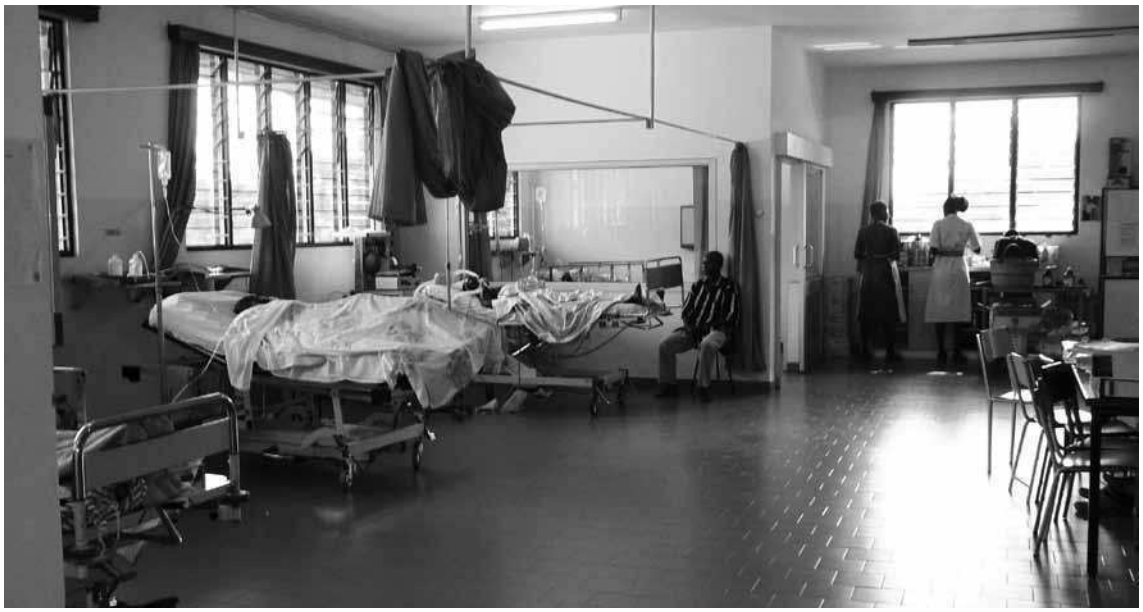

Figure 1. *The intensive care unit at St Mary's Hospital Lacor, Uganda.*

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ADMISSIONS POLICY

Admission of patients to the ICU is open to any clinician, with no strict policy to guide this. Clinicians have discovered by a process of clinical experience how best the ICU could serve their patients and inappropriate admissions have been identified by ward round feedback on a daily basis.

The difficulty of deciding who to admit to the ICU has both ethical and clinical factors. The concept of futility remains an issue no matter what resources are available and it remains an issue of continuous discussion in many guises. If ICU admission is refused then the patient will receive the level of care that is offered on the general wards, and so this must also be evaluated in order to compare that offered in the ICU.

General ward care

The patient ratio on the wards may range from one trained nurse to 30 patients to one trained nurse to 60 patients, with the night shifts often the most stretched. Any critically ill and unstable patient who is denied access to the ICU will then be admitted to the ward, where both the nurse to patient ratio, and the experience of the individual nurses to deal with these patients, is far less favourable than in ICU. However, we do not have data from ward patients for direct comparison to the ICU patient population.

The issue of who to admit to the ICU and also who to discharge back to the ward is, in practice, an ongoing discussion between the ICU and ward-based clinicians. ICU ward rounds are conducted three times per day and the suitability of each patient for discharge back to the wards is discussed, in light of new referrals and the need to maintain a good nurse to patient ratio.

ANALYSIS OF ADMISSIONS TO ICU

The annual rate of admissions to ICU has grown over the last 5 years, from 264 patients in 2006 to 449 patients in 2010. The ICU mortality has remained at a steady level, ranging between 26 to 36% (Figure 2).

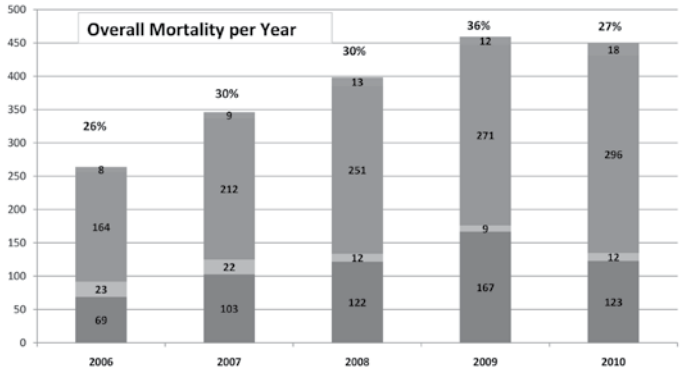

Figure 2. *Analysis of admission to ICU at St Mary's Hospital Lacor, with mortality data. Upper section of bar = number referred; second section from top = number discharged to ward; third section from top = number discharged home; bottom section = number died*

The work of Fenton and colleagues, assessing the mortality of Caesarean sections in Malawi, demonstrated that 80% of deaths occur in the postoperative period.[3] It is likely that general surgical deaths have a similar postoperative emphasis in Africa. Figure 3 shows our outcomes in 2202 patients over the last 6 years, shown according to their admission specialty.

Thirteen arbitrary diagnostic groups were used. The development of our ICU has largely been driven by a need to meet the demands of the surgical, obstetric and gynaecological services. Medical admissions comprise 7% of admissions with a mortality of 47%. We have encouraged the development of a high dependency area within the general medical ward, containing oxygen concentrators and pulse oximeters, so that rational oxygen therapy can be administered without the need for ICU admission for this reason alone.

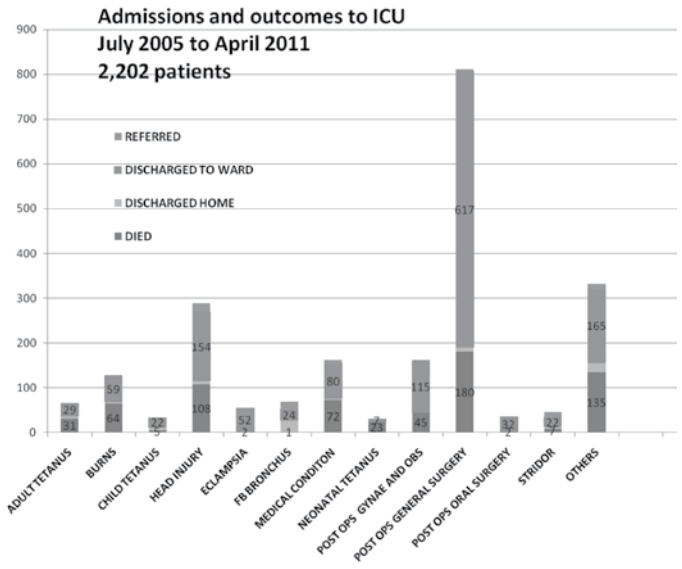

Figure 3. *Outcomes in 2202 patients over the last 6 years, shown according to their admission specialty. 'Referred' means admitted to the ICU but later referred to another hospital, usually the teaching hospital in Kampala.*

Head injured patients, judged clinically to be unsuitable for ward management are admitted to the ICU, but our policy has always been not to undertake advanced respiratory support, with intubation and ventilation, in these patients. The limited number of nurses and ventilators, along with the expectation of poor outcomes, even with prolonged ventilation, has ensured that this policy persists today. On rare occasions intubation and ventilation has been commenced, when sputum retention is considered to be a major factor in deteriorating coma or when early referral to an urban area is an option. Of 282 head-injured patients admitted, 108 died, 154 were discharged to the ward and 20 were referred on to Mulago Hospital, Kampala for further care. Overall mortality for head injured patients admitted to ICU was 37%.

All patients undergoing thyroidectomy are admitted to the ICU postoperatively for at least one night, as our experience is that a small number of patients develop airway problems postoperatively on the main ward. These are not reliably recognised and effectively managed on the general ward.

Figure 3 shows that postoperative general surgical patients form the largest diagnostic group in our ICU patient population. The mortality for this group is 22%, perhaps reflecting that our non-physician anaesthetists recognise the importance of adequate preoperative resuscitation. During the intraoperative period active resuscitation, cardiorespiratory monitoring and respiratory support is continuous.

We now view the postoperative period as the time of greatest risk to the patients - the general wards have a poor nurse to patient ratio, limited monitoring and limited senior staff available ward, meaning that monitoring of hypoxia and adequate blood and fluid replacement is difficult to establish. The non-physician anaesthetist assigned to the ICU is ideally situated, equipped and trained to identify high-risk postoperative patients needing blood, fluid and/or oxygen therapy, as well as pain relief.

Ventilation in ICU

Among the general surgical patients, 181 (23%) were also given intermittent positive pressure ventilation (IPPV) and the overall mortality of this sub-group was 52% (Figure 4).

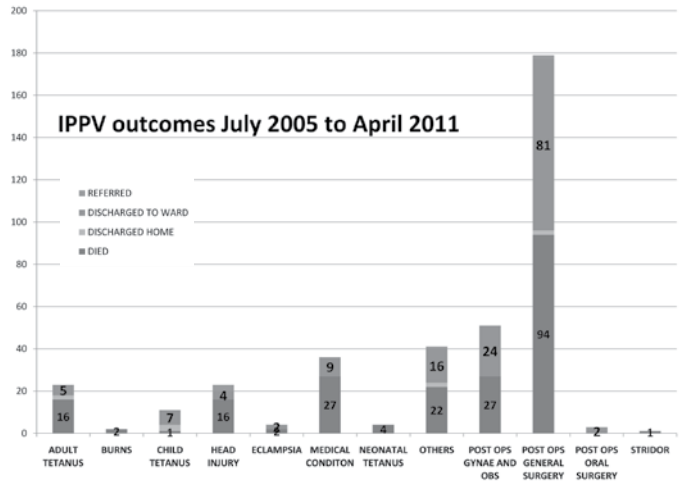

Figure 4. *Outcomes of ventilated patients by diagnostic group.*

Postoperative IPPV is the main invasive ICU intervention that we can offer. Our theatre anaesthetist is trained to identify patients with cardiorespiratory instability during surgery or in the immediate postoperative period, that may benefit from postoperative IPPV. These patients are transferred to ICU for ventilation. We use the same type of ventilator/anaesthesia machine (the Glostavent) in theatre and in ICU, and this has made this process of postoperative IPPV much easier to manage and teach.

Among the postoperative surgical patients who received IPPV, 83 (47%) survived. It is our view that the majority would have died if managed on the general ward without the facility for IPPV. A similar experience of postoperative support is seen with the 162 obstetric and gynaecological patients, in whom the overall mortality was 26%. Within this group 51 patients were given IPPV with a mortality of 53%, with 24 survivors. Again we believe that the majority would have died if they had received only ward care.

Figure 5 shows that in the 378 patients from all diagnostic groups, who received IPPV, the mortality was 56%, with 150 survivors. Eight patients suffered snakebite with a neurotoxic venom, where muscle fasciculation and respiratory distress required IPPV. Six of these patients were among the survivors. Six patients were admitted with some form of poisoning, often a pesticide (organophosphate) compound with five, all of whom received IPPV, surviving. Although they represent a small subgroup, patients suffering respiratory failure following snakebite and poisoning have a good outcome in our practice. Similarly, patients who developed acute pulmonary oedema occurring under general anaesthesia formed a small group with very good outcomes when treated with postoperatively ventilation. The majority of these patients had longstanding anaemia exacerbated by acute haemorrhage, predisposing to development of pulmonary oedema.

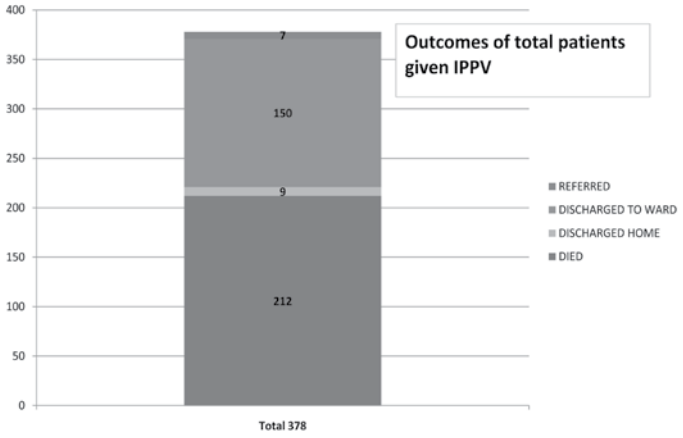

Figure 5. *Outcomes of all ICU patients treated with IPPV.*

Tetanus

Tetanus is a disease category which requires special consideration as its treatment lends itself particularly to the skills of anaesthetists and intensivists. We have classified tetanus into neonatal, child and adult. In our experience neonatal tetanus outcomes have been very poor, with a mortality of 77% in 30 neonates admitted. Four patients were given IPPV and all died. We no longer offer IPPV for neonatal tetanus.

The introduction of magnesium sulphate therapy for adult and child tetanus has, in our view, contributed to a major improvement in our outcomes, in comparison with the care previously offered in the general ward. Our protocols have been published in a previous edition of *Update in Anaesthesia*[4] and follow the advice of anaesthetists in Sri Lanka.[5] The mortality in 65 adults with tetanus receiving ICU management was 48% and in local conditions we consider this a remarkably good outcome, giving 34 survivors. In 23 of these patients tetanus was so severe that, despite large doses of magnesium sulphate, the spasms could not be controlled and so they were sedated, paralysed, ventilated and subsequently tracheostomy performed. There were 7 survivors in this group (mortality 80%).

In our experience tetanus in children has a much better prognosis with an overall mortality of 15% from 33 children. In 11 children the spasms were so severe that they were sedated, paralysed, ventilated and received tracheostomy, yet only one of these children died (mortality 9%). The management of severe tetanus in children and adults is very demanding on the ICU nurses and anaesthetists, as it may require IPPV for up to 4 weeks, but is one of the most rewarding conditions to treat. Venous access is a challenging problem in these long stay patients and femoral and internal jugular lines are usually required.

Severe burn patients are managed in the ICU and our mortality is 50%.

CONCLUSION

The majority of patients admitted to our ICU in rural sub-Saharan Africa were postoperative surgical patients. The nurse to patient ratio, close supervision and assessment by anaesthetists and basic 'ABC' interventions is superior to that available on the general wards. We believe that this has produced better outcomes for many diagnostic groups and consequently admissions rates have rapidly increased over that last six years, although we recognise that comparative data for patients receiving ward-based care is not available. The main sustainable and inexpensive invasive intervention offered in our ICU is postoperative IPPV. This is indicated in patients with reversible respiratory insufficiency and/or haemodynamic instability - conditions that would likely lead to death on the general wards.

The most dramatic effective intervention for medical patients was IPPV for poisoning by pesticides. General medical patients remain a very small percentage of our admissions over the 6 years of data collection. Tetanus patients had good outcomes compared with ward care and very early in our experience all tetanus patients were treated in the ICU. Snake bite patients with neurotoxic paralysis also did well with IPPV. Rational use of oxygen with oximetry monitoring and oxygen therapy using oxygen concentrators has proved to be a sustainable inexpensive and effective treatment for hypoxia from whatever cause. We continue to train the general ward clinicians and nurses on basic principles of rational oxygen therapy so that ICU admissions for this sole reason are reduced.

REFERENCES

1. Available at: www.lacorhospital.org
2. Towey RM, Ojara S. Intensive Care in the Developing World. *Anaesthesia* 2007; **62** (Suppl): 32-7.
3. Fenton PM, Whitty CJM, Reynolds F. Caesarean Section in Malawi: prospective study of early maternal and perinatal mortality. *British Medical Journal* 2003; **327**: 587-90.
4. Towey R. Tetanus: a review. *Update in Anaesthesia* 2005; **19**: 43-8.
5. Attygalle D, Rodrigo N. Magnesium as a first line therapy in the management of tetanus: a prospective study of 40 patients. *Anaesthesia* 2002; **57**: 778-817.

Update in
Anaesthesia

Tetanus

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Summary

Tetanus remains an important cause of death worldwide and is associated with a high mortality, particularly in the developing world. With modern intensive care management, death from acute respiratory failure should be prevented, but cardiovascular complications as a result of autonomic instability and other causes of death remain.[1] In this article, the pathophysiology, clinical features and current management of tetanus are reviewed.

INTRODUCTION

In spite of the World Health Organization's intention to eradicate tetanus by the year 1995, it remains endemic in the developing world. The WHO estimated that there were approximately one million deaths from tetanus worldwide in 1992. This included 580,000 deaths from neonatal tetanus, of which 210 000 were in South East Asia and 152,000 in Africa. The disease is uncommon in developed countries. In South Africa approximately 300 cases occur each year (6 per million population), approximately 12-15 cases are reported each year in Britain (0.2 per million) and between 50 and 70 in the USA (0.2 per million).

Tetanus is caused by a Gram-positive bacillus, *Clostridium tetani*. This is a common bacterium with a natural habitat in the soil. It can also be isolated from animal and human faeces. It is a motile, spore-forming obligate anaerobe. The spore is incompletely destroyed by boiling, but eliminated by autoclaving at 1 atmosphere pressure and 120°C for 15 minutes. It is rarely cultured and diagnosis of the disease is clinical. *Clostridium tetani* produces its clinical effects via a powerful exotoxin. The role of the toxin within the organism is not known. The DNA for this toxin is contained in a plasmid (DNA that is separate from and can replicate independently of the bacteria's chromosomal DNA). Presence of the bacterium does not always mean that the disease will occur, as not all strains possess the plasmid. Bacterial antimicrobial sensitivity has been little investigated.

As infection does not confer immunity, prevention is through vaccination. Tetanus vaccine has been available since 1923. Vaccination is started at 2 months of age with three injections performed at monthly intervals. The second injection confers immunity, with the third prolonging its duration. A booster is given before the age of 5. Similar responses occur in older children and adults. Neonatal immunity is provided by maternal vaccination and transplacental transfer of immunoglobulin. This may be impaired in the presence of maternal HIV infection. Immunity is not life-long. Revaccination at 10-yr intervals is recommended in the USA. In the UK, two boosters spaced 10 years apart are recommended in adulthood, so the recommendations do not extend to vaccination beyond the third decade. Thus in the UK, after these 5 injections patients are considered immune, and there is no value in giving further prophylactic doses. In the USA, more than 70% of cases and 80% of deaths occur in those over 50. Similar proportions are reported in Europe.

PATHOPHYSIOLOGY

Under the anaerobic conditions found in necrotic or infected tissue, the tetanus bacillus secretes two toxins: *tetanospasmin* and *tetanolysin*. Tetanolysin is capable of locally damaging viable tissue surrounding the infection and optimizing the conditions for bacterial multiplication.

Toxins

Tetanospasmin leads to the clinical syndrome of tetanus. It binds to neural membranes and the amino terminus facilitates cell entry. It acts pre-synaptically to prevent neurotransmitter release from affected neurones. Released tetanospasmin spreads to underlying tissue and binds to gangliosides on the membranes of local nerve terminals. If toxin load is high, some may enter the bloodstream from where it diffuses to bind to nerve terminals throughout the body. The toxin is then internalized and transported intra-axonally and retrogradely to the cell body. Transport occurs first in motor, and later in sensory and autonomic, nerves. Once in the cell body the toxin can diffuse out, affecting and entering nearby neurones. When spinal inhibitory interneurones are affected, symptoms occur. Further retrograde intraneural transport occurs with toxin spreading to the brainstem and midbrain. This passage includes retrograde transfer across synaptic clefts by a mechanism that is unclear.

Toxins and the CNS

The effects of the toxin result from prevention of neurotransmitter release. Synaptobrevin is a membrane protein necessary for the export of intracellular vesicles containing neurotransmitter. The tetanospasmin cleaves synaptobrevin, thereby preventing neurotransmitter release. The toxin has a predominant effect on inhibitory neurones, inhibiting release of glycine and gamma-aminobutyric acid (GABA). The term 'disinhibition' is used as the main effect of tetanus. This

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results in a failure of inhibition (relaxation) of muscle groups, leading to increased muscle tone and muscular spasms because the muscles are unable to relax. In normal muscles, when one muscle group contracts there has to be a corresponding relaxation of the opposing muscle group. In tetanus this is prevented and results in intermittent spasms. Interneurones inhibiting alpha motor neurones are first affected and the motor neurones lose inhibitory control. Later (because of the longer pathway), pre-ganglionic sympathetic neurones in the lateral horns and the parasympathetic centres are also affected.

Motor neurones are similarly affected and the release of acetylcholine into the neuromuscular cleft is reduced. This effect is similar to the action of the closely related botulinum toxin, which produces a flaccid paralysis. However, in tetanus the disinhibitory effect on the motor neurone overwhelms any diminution of function at the neuromuscular junction. Medullary and hypothalamic centres may also be affected. Tetanospasmin has a cortical convulsant effect in animal studies. Whether these mechanisms contribute to intermittent spasm and autonomic storms is unclear. The pre-junctional effect on the neuromuscular junction may lead to considerable weakness between spasms, and might account for both the paralysis of cranial nerves observed in cephalic tetanus, and myopathies observed after recovery.

Uninhibited efferent discharge from motor neurones in the spinal cord and brainstem leads to intense muscular rigidity and spasm, which may mimic convulsions. The reflex inhibition of antagonist muscle groups is lost, and agonist and antagonist muscles contract simultaneously. Muscle spasms are intensely painful and may lead to fractures and tendon rupture. Muscles of the jaw, face, and head are often involved first because of their shorter axonal pathways. The trunk and limbs follow but peripheral muscles in the hands and feet are relatively spared.

Disinhibited autonomic discharge leads to disturbances in autonomic control, with sympathetic overactivity and excessive plasma catecholamine levels. Neuronal binding of toxin is thought to be irreversible. Recovery requires the growth of new nerve terminals, which explains the prolonged duration of tetanus.

CLINICAL FEATURES

Tetanus usually follows a recognized injury. Contamination of wounds with soil, manure, or rusty metal can lead to tetanus. It can complicate burns, ulcers, gangrene, necrotic snakebites, middle ear infections, septic abortions, childbirth, intramuscular injections, and surgery. Injuries may be trivial, and in up to 50% of cases the injury occurs indoors and/or is not considered serious enough to seek medical treatment. In 15-25% of patients, there is no evidence of a recent wound.

Presentation

There is a clinical triad of rigidity, muscle spasms and autonomic dysfunction. Neck stiffness, sore throat, and difficulty opening the mouth are often early symptoms. Masseter spasm causes trismus or 'lockjaw'. Spasms progressively extend to the facial muscles, causing the typical facial expression risus sardonicus (literally a 'sarcastic smile' - Figure 1), and muscles of swallowing, causing dysphagia. Rigidity of the neck muscles leads to retraction of the head. Truncal rigidity may lead to opisthotonos, which is the severe arching of the back during a spasm caused by the stronger extensor muscle group (Figure 2). Respiratory difficulty with decreased chest wall compliance may also result.

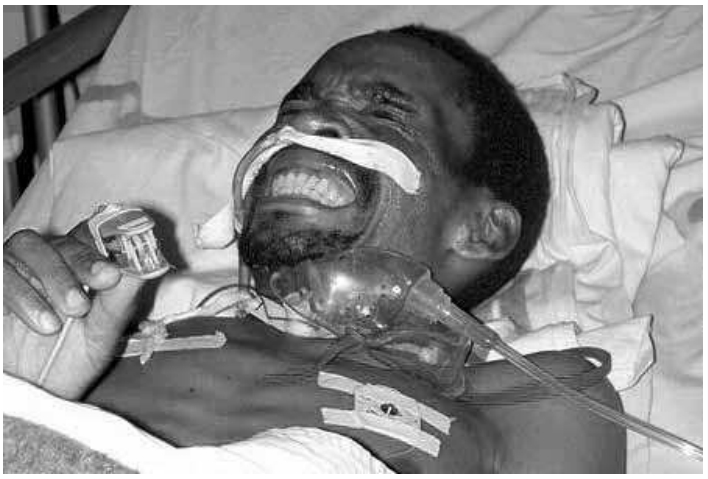

Figure 1. *Risus sardonicus.*

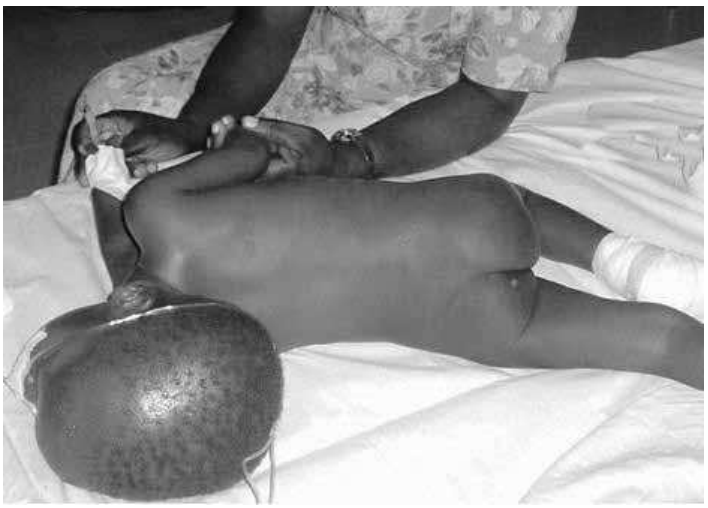

Figure 2. *Opisthotonus in a 21-month-old with a foot wound.*

In addition to increased muscle tone, there are episodic muscular spasms. These tonic contractions have a convulsion-like appearance affecting agonist and antagonist muscle groups together. They may be spontaneous or triggered by touch, visual, auditory or emotional stimuli. Spasms vary in severity and frequency, but may be strong enough to cause fractures and tendon avulsions. Spasms may be almost continual, leading to respiratory failure. Pharyngeal spasms are often followed by laryngeal spasms and are associated with aspiration and life threatening acute airway obstruction.

Generalized tetanus, the commonest form of tetanus, affects all muscles throughout the body. The muscles of the head and neck are usually affected first, with progressive caudal spread of rigidity and spasm to affect the whole body. The differential diagnosis includes orofacial infection, dystonic drug reactions, hypocalcaemia, strychnine poisoning and hysteria.

Local tetanus is seen with lower toxin loads and peripheral injuries. Spasm and rigidity are restricted to a limited area of the body. Mortality is greatly reduced. An exception to this is cephalic tetanus when

localized tetanus from a head wound affects the cranial nerves; paralysis rather than spasm predominates at presentation, but progression to generalized tetanus is common and mortality is high.

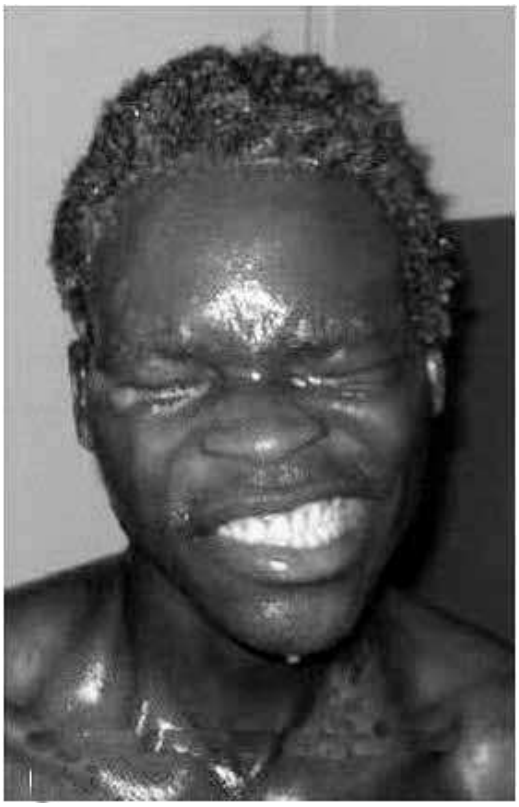

Figure 3. *Cephalic tetanus with right facial nerve palsy.*

Tetanus neonatorum causes more than 50% of deaths from tetanus worldwide but is very rare in developed countries. Neonates present within a week of birth with a short history of failure to feed, vomiting, and 'convulsions'. Seizures, meningitis and sepsis are differential diagnoses. Spasms are generalized and mortality is high. Poor umbilical hygiene is the cause of the disease but it is entirely preventable by maternal vaccination, even during pregnancy.

Autonomic effects

Prior to the introduction of artificial ventilation, many patients with severe tetanus died from acute respiratory failure. With the development of intensive care and the ability to ventilate patients it became apparent that severe tetanus was associated with marked autonomic instability. The sympathetic nervous system is most prominently affected. Clinically, increased sympathetic tone causes persistent tachycardia and hypertension. Marked vasoconstriction and pyrexia are also seen. Basal plasma catecholamine levels are raised.

'*Autonomic storms*' occur with marked cardiovascular instability. Severe hypertension and tachycardia may alternate with profound hypotension, bradycardia, or recurrent cardiac arrest. These changes are a result of rapid alterations in systemic vascular resistance, rather than problems with cardiac filling or performance. During these 'storms' plasma catecholamine levels are raised up to 10-fold, to levels similar to those seen in phaeochromocytoma. Norepinephrine (noradrenaline) is affected more than epinephrine (adrenaline). Neuronal hyperactivity, rather than adrenal medullary hyperactivity, appears to predominate.

In addition to the cardiovascular system, other autonomic effects include profuse salivation and increased bronchial secretions. Gastric stasis, ileus, diarrhoea, and high output renal failure may all be related to autonomic disturbance.

The involvement of the sympathetic nervous system is established. The role of the parasympathetic system is less clear. Tetanus has been reported to induce lesions in the vagal nuclei, while locally applied toxin may lead to excessive vagal activity. Hypotension, bradycardia, and asystole may arise from increased vagal tone and activity.

Natural history

The incubation period (time from injury to first symptom) averages 7-10 days, with a range of 1-60 days. The onset time (time from first symptom to first spasm) varies between 1-7 days. Shorter incubation and onset times are associated with more severe disease. The first week of the illness is characterized by muscle rigidity and spasms, which progressively increase in severity. Autonomic disturbance usually starts several days after the spasms, and persists for 1-2 weeks. Spasms reduce after 2-3 weeks, but stiffness may persist considerably longer. Recovery from the illness occurs because of re-growth of axon terminals and by toxin destruction.

SEVERITY GRADING

There are several grading systems but the system reported by Ablett is most widely used (Table 1).

Table 1. *Ablett classification of tetanus severity*

Grade		Clinical features
1	Mild	Mild trismus, general spasticity, no respiratory embarrassment, no spasms, no dysphagia.
2	Moderate	Moderate trismus, rigidity, short spasms, mild dysphagia, moderate respiratory involvement, respiratory rate > 30, mild dysphagia.
3	Severe	Severe trismus, generalized spasticity, prolonged spasms, respiratory rate > 40, severe dysphagia, apnoeic spells, pulse > 120.
4	Very severe	Grade 3 with severe autonomic disturbances involving the cardiovascular system.

Altered cardiovascular physiology

In uncomplicated tetanus, the cardiovascular system mimics that of a normal patient undergoing intense exercise. There is a hyperdynamic circulation, largely because of increased basal sympathetic activity and muscle metabolism, with a lesser effect from raised core temperature. There is low-normal systemic vascular resistance and raised cardiac output, because of extensive vasodilatation in metabolically active muscles.

As the oxygen extraction ratio does not alter in tetanus, the increased demand must be delivered by increased blood flow. Poor spasm control exaggerates these effects. In severe tetanus, patients are less able to increase cardiac performance and are more susceptible to profound hypotension and shock during acute vasodilatory storms. The mechanism is unclear, but may relate to sudden reduction of catecholamine secretion or a direct action of tetanus toxin on the myocardium. Altered myocardial function may occur due to persistently raised catecholamine levels, but abnormal function may occur even in the absence of sepsis or high catecholamine levels.

Altered respiratory physiology

Muscular rigidity and spasms of the chest wall, diaphragm and abdomen lead to a restrictive defect. Pharyngeal and laryngeal spasms predict respiratory failure or life threatening airway obstruction. Poor cough from rigidity, spasms, and sedation leads to atelectasis and the risk of pneumonia is high. The inability to swallow copious saliva, profuse bronchial secretions, pharyngeal spasms, raised intra-abdominal pressure and gastric stasis all increase the risk of aspiration, which is common. Ventilation/perfusion mismatch is also common. Consequently, hypoxia is a uniform finding in moderate or severe tetanus, even when the chest is radiologically clear. When breathing air, oxygen tensions are often between 5.3-6.7kPa (40-50mmHg), with the oxygen saturation commonly falling below 80%.

In artificially ventilated patients, increased alveolar-arterial gradients persist. Oxygen delivery and utilization may be compromised even without super-added lung pathology. Acute respiratory distress syndrome may occur as a specific complication of tetanus. Minute ventilation may be altered by a variety of causes. Hyperventilation may occur because of fear, autonomic disturbance, or alteration in brainstem function. Hypocarbia ($PaCO_2$ 4.0-4.6kPa, 30-35mmHg) is usual in mild to moderate disease. Hyperventilation 'storms' may lead to severe hypocarbia ($PaCO_2$ < 3.3kPa, 25mmHg). In severe disease, hypoventilation from prolonged spasms and apnoea occurs. Sedation, exhaustion and altered brainstem function may also lead to respiratory failure. Respiratory drive may be deficient, leading to recurrent life threatening apnoeic periods.

Altered renal physiology

In mild tetanus, renal function is preserved. In severe disease reduced glomerular filtration rate and impaired renal tubular function are frequent. Contributory causes of renal failure include dehydration, sepsis, blocking of the renal tubule with myoglobin (as a result of muscle breakdown) and alterations in renal blood flow secondary to catecholamine surges. Renal failure may be oliguric or polyuric. Clinically important renal impairment is associated with autonomic instability and histology is normal or shows acute tubular necrosis.

MANAGEMENT

Treatment strategies involve three management principles:

- Organisms present in the body should be destroyed to prevent further toxin release,
- Toxin present in the body, outside the CNS should be neutralized, and
- The effects of toxin already in the CNS should be minimized.

Adult tetanus protocol

St.Mary's Hospital Lacor, Gulu, Uganda

1. Start metronidazole intravenously 500mg three times a day.
2. Give tetanus human immune globulin IM 3,000-6,000 IU if available. If not available Equine ATS 10 000 IU IM.
3. Admit to ICU, commence oxygen, obtain IV access and attach monitoring.
4. Alert surgeon to perform radical debridement.
5. Slow loading dose diazepam IV to control spasms. Up to about 40mg may be required. Give a loading dose of 5g magnesium sulphate slowly over 20 minutes IV.
6. Start diazepam 10mg 6 hourly and increase to hourly if required. Titrate to symptoms.
7. Start magnesium 2.5g IV 2 hourly and increase to hourly if required. Titrate to symptoms. Stop diazepam if symptoms controlled by magnesium alone. Anaesthetist to pass nasogastric tube for feeding when patient stabilised.
8. Phenobarbitone up to 200mg IV twice a day for breakthrough spasms using 50mg doses.
9. Tracheostomy if airway compromised by above treatment.
10. Intermittent positive pressure ventilation with muscle relaxants if respiration compromised by treatment or uncontrolled spasms.

Removal of the source of infection

Obvious wounds should be surgically debrided. The surgeon should be encouraged to perform a radical debridement to eliminate as much of the source of infection as possible. Penicillin has been widely used for many years, but is a GABA antagonist and is associated with convulsions. Metronidazole is probably the antibiotic of choice. It is safe and comparative studies with penicillin suggest at least as good results. Erythromycin, tetracycline, chloramphenicol and clindamycin are all accepted as alternatives.

Neutralization of unbound toxin

If available human tetanus immune globulin 3,000-6,000 units is given intra-muscularly (IM). If this is not available (which is often the case in the developing world), then anti-tetanus horse serum (ATS) should be given after sensitivity tests, in a dose of 10,000 units IM. All these injections should be administered within 24 hours of the diagnosis.

Control of rigidity and spasms

The principle of management is to prevent spasms and rigidity with the minimal dose of pharmacological agent, so that the side effects of the drugs themselves do not become life threatening. Administering the correct dose of agent cannot be judged without frequent assessment by the clinician, especially in the early stages. Clinical symptoms may change rapidly.

Avoidance of unnecessary stimulation is mandatory, but the mainstay of treatment is sedation with a benzodiazepine. Benzodiazepines increase GABA activity, by inhibiting an endogenous inhibitor at the GABA-A receptor. Diazepam may be given by various routes. It is cheap and widely used, but long acting metabolites (oxazepam and desmethyldiazepam) may accumulate and lead to prolonged coma. Doses vary between individuals, but a starting dose of 10mg every 6 hours is usual. Higher doses of 20 or 40mg 6 hourly may be necessary. Midazolam has been used with less apparent accumulation.

Additional sedation may be provided by anticonvulsants, particularly phenobarbitone at a dose of up to 200mg IV twice a day. Phenobarbitone has a GABA agonist effect. However, it is a potent respiratory depressant and should be used with caution, starting with low doses of 50mg twice a day.

Phenothiazines, usually chlorpromazine, have often been used. However caution is essential to avoid deep depression of protective airway reflexes and the risk of pulmonary aspiration.

In situations where full intensive care facilities are available, the classical teaching is to proceed to tracheostomy and IPPV when sedation does not control the spasms, or when the necessary sedative dose produces such deep depression of the airway reflexes or respiration, that the patient is no longer safe. However, in many parts of the developing world there is little capacity to perform a tracheostomy or give IPPV. Even if a surgeon is available to perform a tracheostomy, the nursing care demands of a tracheostomy over several weeks puts a major strain on nursing capacity. This should not be undertaken without firstly considering other treatment options.

Magnesium sulphate may offer some new hope in this context. In Sri Lanka, Attygalle and Rodrigo reported a series of 40 patients with tracheostomy, in which IPPV was avoided by using magnesium sulphate.[2] There has also been a report from the USA where the need for tracheostomy was avoided through the use of magnesium sulphate.[3] The dose suggested is 1g increasing to 2.5g per hour in adults, following a 5g loading dose. The therapeutic serum magnesium levels were 2-4mmol.L^{-1} (normal 1.2mmol.L^{-1}).

Magnesium is a presynaptic neuromuscular blocker. It blocks catecholamine release from nerves and the adrenal medulla. It also reduces receptor responsiveness to released catecholamines, is an anticonvulsant and a vasodilator. It antagonises calcium in the myocardium and at the neuromuscular junction and inhibits parathyroid hormone release, lowering serum calcium. If too large a dose is given, it causes weakness and paralysis with central sedation (although the latter is controversial). Attygalle advises using the presence of patella tendon reflexes as a monitor of a safe serum magnesium level.[2] Hypotension and bradyarrhythmias may occur. It is therefore mandatory to maintain magnesium levels in the therapeutic range. In a series of patients with very severe tetanus magnesium was found to be inadequate alone as a sedative and relaxant, but was an effective adjunct in controlling autonomic disturbance.[4] The author's experience of using magnesium to manage severe tetanus in rural Africa has been positive, with good outcomes. The future role of magnesium will require further studies, but it offers hopeful new possibilities.

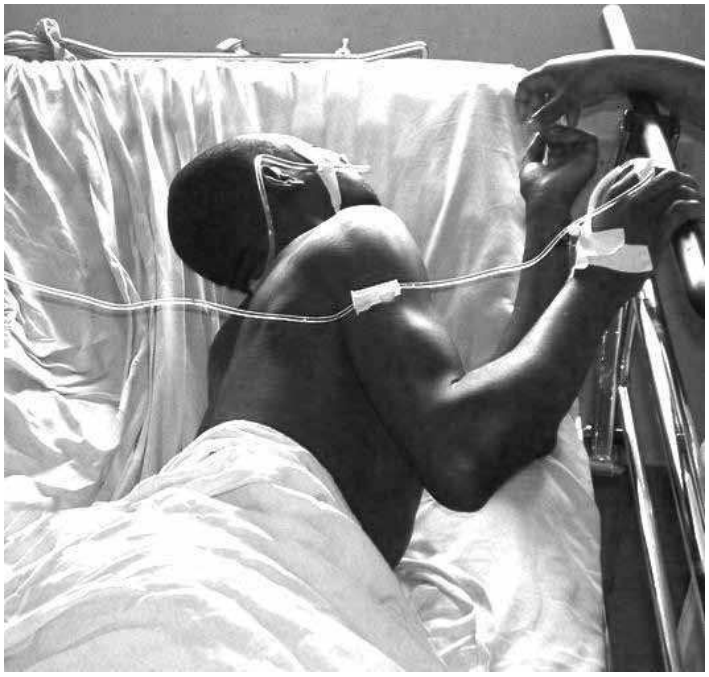

Figure 4. *Opisthotonus modified by treatment with magnesium.*

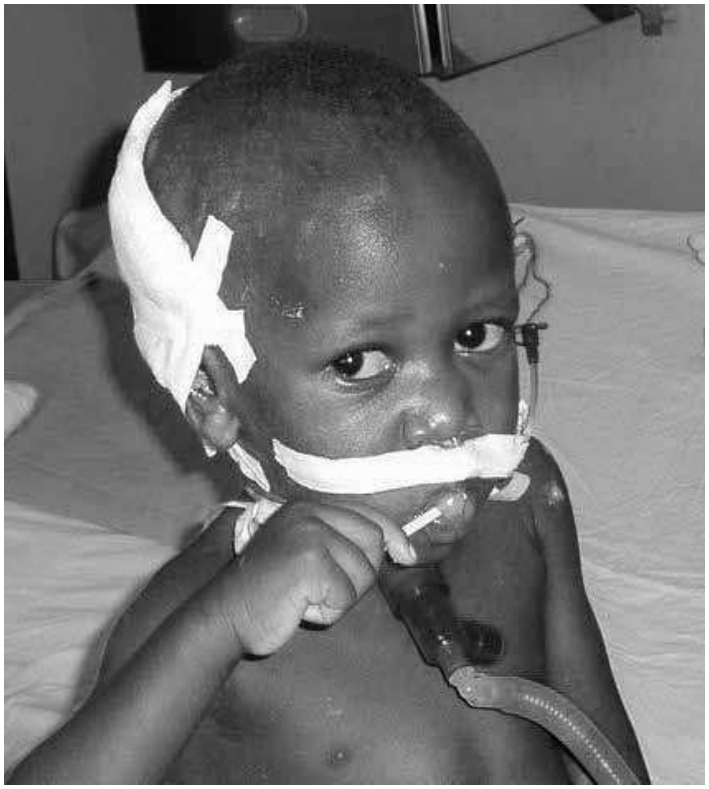

Figure 5. *Seven weeks after admission and treatment with invasive ventilation and magnesium.*

Neuromuscular blocking agents and intermittent positive pressure ventilation may be required for a prolonged period when sedation alone is inadequate. Traditionally, the long acting agent pancuronium has been used and it is cheaper than the more modern non-depolarising muscle relaxants. Vecuronium, atracurium and rocuronium have also been used.

Propofol sedation may allow control of spasms and rigidity without the use of neuromuscular blocking drugs. However, drug levels are closer to anaesthetic than sedative concentrations and mechanical ventilation is likely to be needed.

Control of autonomic dysfunction

Many different approaches to the treatment of autonomic dysfunction have been reported. Most are presented as case reports or small case series. There is a lack of comparative or controlled studies. In general, outcome measures have been limited to haemodynamic data, rather than survival or morbidity.

Sedation is often the first treatment. Benzodiazepines, anticonvulsants, and morphine are frequently used. Morphine is particularly beneficial as cardiovascular stability may be achieved without cardiac compromise. Dosages vary between 20 and 180mg daily. Proposed mechanisms of action include replacement of endogenous opioids, reduction in reflex sympathetic activity and release of histamine. Phenothiazines, particularly chlorpromazine are also used; anticholinergic and adrenergic antagonism may contribute to cardiovasular stability.

β-adrenergic blocking agents, such as propranolol, were used in the past to control episodes of hypertension and tachycardia, but profound hypotension, severe pulmonary oedema and sudden death were all found to occur. Labetolol, which has combined α and β-adrenergic blocking effects has been used, but no advantage over propranolol has been demonstrated (possibly because its α activity is much less than its β activity). In recent years, the short-acting agent, esmolol, has been used successfully. Although good cardiovascular stability is achieved, arterial catecholamine concentrations remain elevated.

Sudden cardiac death is a feature of severe tetanus. The cause remains unclear, but plausible explanations include sudden loss of sympathetic drive, catecholamine-induced cardiac damage and increased parasympathetic tone or 'storms'. Persisting β-blockade could exacerbate these causes because of its negatively inotropic effect or vasoconstrictor activity. This may lead to acute cardiac failure, particularly as sympathetic crises are associated with high systemic vascular resistance and normal or low cardiac output. Isolated use of α-adrenergic block, with long acting agents, cannot therefore be recommended.

Postganglionic adrenergic blocking agents such as bethanidine, guanethidine and phentolamine have been used successfully with propranolol, along with other similar agents such as trimetaphan, phenoxybenzamine and reserpine. Disadvantages of this group of drugs are that induced hypotension may be difficult to reverse, tachyphylaxis occurs and withdrawal can lead to rebound hypertension.

The α-adrenergic agonist clonidine has been used orally or parenterally, with variable success. Acting centrally, it reduces sympathetic outflow, thus, reducing arterial pressure, heart rate, and catecholamine release from the adrenal medulla. Peripherally, it inhibits the release of norepinephrine from pre-junctional nerve endings. Other useful effects include sedation and anxiolysis.

Magnesium sulphate has been used both in artificially ventilated patients to reduce autonomic disturbance and in non-ventilated patients to control spasms. The dose suggested is 1g, increasing to 2.5g, per hour for an adult.

Supportive intensive care treatment

Weight loss is universal in tetanus. Contributory factors include inability to swallow, autonomic induced alterations in gastrointestinal function, increased metabolic rate (due to pyrexia and muscular activity), and prolonged critical illness. Nutrition should therefore be established as early as possible. Enteral nutrition is associated with a lower incidence of complications and is cheaper than parenteral nutrition. Nasogastric tube feeding should be started as soon as possible. In experienced units, percutaneous gastrostomy may be more suitable as a route for feeding.

Infective complications of prolonged critical illness, including ventilator-associated pneumonia, are common in tetanus. Securing the airway early in the disease and preventing aspiration and sepsis are logical steps in minimizing this risk. As artificial ventilation is often necessary for several weeks, tracheostomy is usually performed after intubation. In experienced hands the percutaneous dilatational method may be particularly suitable for patients with tetanus. This bedside procedure avoids transfer to and from the operating theatre, with the attendant risk of provoking autonomic instability. Prevention of respiratory complications also involves meticulous mouth care, chest physiotherapy and regular tracheal suction, particularly as salivation and bronchial secretions are greatly increased. Adequate sedation is mandatory before such interventions in patients at risk of uncontrolled spasms or autonomic disturbance. The balance between physiotherapy and sedation may be difficult to achieve.

Other important measures in the routine management of patients with tetanus (as with any long-term critical illness), include prophylaxis of thromboembolism, gastrointestinal haemorrhage and pressure sores. The importance of psychological support should not be underestimated.

Venous access is a major problem when diazepam has been used for many days using peripheral veins. An elective placement of a central or femoral line improves general care and outcomes.

COMPLICATIONS

Complications may occur as a result of the disease (e.g. laryngospasm, hypoxia), or as a consequence of treatment (e.g. sedation leading to coma, aspiration or apnoea; ventilator-associated pneumonia; complications of tracheostomy; acute respiratory distress syndrome). Gastro-intestinal complications include gastric stasis, ileus, diarrhoea and haemorrhage. Cardiovascular complications include tachycardia, bradycardia, hypertension, hypotension and asystole. High output renal failure and oliguric renal failure are reported and thromboembolism and overwhelming sepsis also occur.

MORTALITY AND OUTCOME

Fatality rates and causes of death vary dramatically according to the

facilities available. Without doubt the introduction of intensive care treatment will reduce mortality. In developing countries, without facilities for prolonged intensive care and ventilatory support, deaths from severe tetanus exceed 50% with airway obstruction, respiratory failure, and renal failure as prominent causes. A mortality of 10% has been suggested as an acceptable goal in developed countries. Modern intensive care should prevent death from acute respiratory failure, but as a result, in severe cases, autonomic disturbance becomes more apparent. Before ICU care was established about 80% of patients died as a result of early acute respiratory failure. Important complications of ICU care include nosocomial infections (particularly ventilator-associated pneumonia), generalized sepsis, thromboembolism, and gastrointestinal haemorrhage. Mortality varies with patient age. In the USA, mortality in adults below 30 years may approach zero, but in those over 60 years is 52%. In Africa, mortality from neonatal tetanus without artificial ventilation is over 80%.

Severe cases of tetanus generally require ICU admission for approximately 3-5 weeks. Recovery can be expected to be complete, with return to normal function, although some survivors of tetanus may have persistent physical and psychological problems.

CONCLUSION

Tetanus is entirely preventable by vaccination. However it remains a major health problem worldwide. In developed countries, several cases present every year in the elderly and unimmunised population. Mortality in these cases remains high. Prolonged intensive care support may be necessary, but most treatment is based on limited evidence. Major therapeutic challenges lie in the control of muscular rigidity and spasms, the treatment of autonomic disturbance and the prevention of complications associated with prolonged critical illness. For the developing world tetanus is a major challenge with a high mortality among all age groups. The use of magnesium to avoid long term ventilation is a hopeful development that will need further evaluation. Return to normal function can be expected in those who survive.

REFERENCES

1. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. *British Journal of Anaesthesia* 2001; **87**: 477-87.
2. Attygalle D, Rodrigo N. Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients. *Anaesthesia* 2002; **8**: 778-817.
3. Ceneviva G, Thomas N, Kees-Folts D. Magnesium Sulfate for control of muscle rigidity and spasms and avoidance of mechanical ventilation in pediatric tetanus. *Pediatric Critical Care Medicine*: 2003;.**4**: 480-4.
4. James MFM, Manson EDM. The use of magnesium sulphate infusions in the management of very severe tetanus. *Intensive Care Medicine* 1985; **11**: 5-12.