Consult. Confirm. CONTROL:

with NovoSeven® (Recombinant Factor VIIa) in acquired haemophilia (AH)[1]

Henry, 78 years old, *presented with severe and extensive skin bruising and blood in the stool. Henry had no prior history of bleeding.*

This advertisement is intended for Healthcare Professionals

Your primary treatment objective in AH is to STOP THE BLEED*

NovoSeven® is one of the first-line treatment options in AH based on:†[2,3]

• Rapid bleed control with consistently high efficacy[4-11] • Established tolerability profile[1,4,12-15] • Simple, rapid reconstitution and administration‡ and convenient storage[1]

*Published guidelines also recommend eradicating the inhibitor with immunosuppressive therapy.
†Other first-line haemostatic treatments are also recommended.
‡NovoSeven® vial-to-vial reconstitution 2–5 mins to infuse.

Prescribing Information NovoSeven® Eptacog alfa (activated); recombinant Factor VIIa (rFVIIa) **Please refer to Summary of Product Characteristics for full information. Presentation:** Powder (vial) and solvent (pre-filled syringe) for solution for injection. Available in packs containing 1, 2, 5 or 8 mg rFVIIa (8 mg only available in the UK). **Uses:** Treatment of bleeding episodes and prevention of bleeding during surgery or invasive procedures in patients with:- congenital haemophilia with inhibitors to coagulation FVIII or FIX > 5 BU or who are expected to have a high anamnestic response to FVIII or FIX; - acquired haemophilia; - congenital FVII deficiency; - Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available. **Dosage:** The rFVIIa is dissolved in the accompanying solvent before use. After reconstitution the solution contains 1 mg rFVIIa/ml. Administer by intravenous bolus injection over 2-5 minutes; must not be mixed with infusion solutions or given in a drip. NovoSeven® should be administered as early as possible after the start of a bleeding episode. *Haemophilia A or B with inhibitors or expected to have high anamnestic response* Initial dose of 90 µg/kg body weight. Duration of, and interval between, repeat injections dependent on severity of haemorrhage or procedure/surgery performed. Paediatric population: Clinical experience does not warrant a general differentiation in dosing between children and adults. Children have faster clearance than adults and higher doses may be needed to obtain similar plasma concentrations as in adults. For mild to moderate bleeding episodes (including home therapy): Two dosing regimens can be recommended: i) Two to three injections of 90 µg/kg body weight administered initially at 3-hour intervals. If further treatment is required, one additional dose of 90 µg/kg can be administered. ii) One single injection of 270 µg/kg body weight. Duration of home therapy should not exceed 24 hours. Only after consultation with the haemophilia treatment centre can continued home treatment be considered. For serious bleeding episodes, initial dose 90 µg/kg body weight; dose every two hours until clinical improvement. If continued therapy indicated, dosage interval can be increased successively. Major bleeding episode may be treated for 2-3 weeks or longer if clinically warranted. For invasive procedures/surgery administer initial dose of 90 µg/kg body weight immediately before the procedure. Repeat dose at 2-3 hour intervals for first 24-48 hours. In major surgery continue dosing at 2-4 hour intervals for 6-7 days. Dosage interval may then be increased to 6-8 hours for further 2 weeks. Treatment may be up to 2-3 weeks until healing has occurred. *Acquired haemophilia* Initial dose of 90 µg/kg body weight. Further injections may be given if required. Initial dose interval should be 2-3 hours. Once haemostasis achieved, the dose interval can be increased successively *Factor VII deficiency* For bleeding episodes and for invasive procedures/surgery, in adults and children, administer 15-30 µg/kg body weight every 4-6 hours until haemostasis achieved. Adapt dose and frequency to individual. Limited clinical experience in long term prophylaxis has been gathered in paediatrics below 12 years of age, with severe clinical phenotype. *Glanzmann's thrombasthenia* For bleeding episodes and for invasive procedures/surgery administer 90 µg/kg body weight (range 80-120 µg) every 2 hours (1.5-2.5 hours). At least three doses should be administered to secure effective haemostasis. For patients who are not refractory platelets are first line treatment. In all conditions the dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred. **Contra-indications:** Known hypersensitivity to active substance, excipients, or to mouse, hamster or bovine protein may be a contraindication to the use of NovoSeven®. **Precautions:** Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. For severe bleeds NovoSeven® should only be administered in hospitals specialised in the treatment of patients with coagulation factor FVIII or FIX inhibitors or in close collaboration with a physician specialised in treatment of haemophilia. No clinical experience with administration of single dose of 270 µg/kg body weight in elderly patients. Home therapy should not exceed 24 hours. Possibility of thrombogenesis or induction of DIC in conditions in which tissue factor could be expected in circulating blood, e.g. advanced atherosclerotic disease, crush injury, septicaemia, or DIC. Since NovoSeven® may contain trace amounts of mouse, bovine and hamster proteins there is a remote possibility of the development of hypersensitivity. Monitor FVII deficient patients for prothrombin time and FVII coagulant activity; suspect antibody formation if FVIIa activity fails to reach expected level or bleeding not controlled with recommended doses. Thrombosis in FVII deficient patients receiving NovoSeven® during surgery has been reported but risk is unknown. Avoid simultaneous use of prothrombin complex concentrates, activated or not. Based on a non-clinical study it is not recommended to combine rFVIIa and rFXIII. **Interactions: (Irish requirement only)** Risk of a potential interaction between NovoSeven® and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided. Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and rFVIIa treatment is however limited. **Fertility, pregnancy and lactation:** Only administer to pregnant women if clearly needed. Not known if excreted in human milk; a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NovoSeven® should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoSeven® therapy to the woman. Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility. **Side Effects:** The frequencies of both serious and non-serious adverse drug reactions are: Uncommon (≥ 1/1,000, < 1/100): venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia); rash (including allergic dermatitis and rash erythematous); pruritus and urticaria; therapeutic response decreased - it is important that the dosage regimen of NovoSeven® is compliant with the recommended dosage; pyrexia. Rare (≥1/10,000, <1/1,000): disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT; coagulopathy; hypersensitivity; headache; arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia); angina pectoris; nausea; injection site reaction including injection site pain; increased fibrin degradation products; increase in alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known. Not known: anaphylactic reaction; intracardiac thrombus, flushing; angioedema. *Inhibitory antibody formation:* Post-marketing there have been no reports of inhibitory antibodies against NovoSeven® or FVII in patients with haemophilia A or B. Development of inhibitory antibodies to NovoSeven® has been reported in post-marketing observational registry of congenital FVII deficient patients. Patients with FVII deficiency, formation of antibodies against NovoSeven® and FVII is the only adverse drug reaction reported (frequency: common (≥ 1/100 to < 1/10)). Risk factors may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived FVII, severe mutation of FVII gene, and overdose of NovoSeven®. Patients with FVII deficiency treated with NovoSeven® should be monitored for FVII antibodies. *Thromboembolic events:* When NovoSeven® is administered outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (5.6% in patients treated with NovoSeven® versus 3.0% in placebo-treated patients) has been shown in trials conducted outside current approved indications. Safety and efficacy of NovoSeven® have not been established outside approved indications; NovoSeven® should not be used in these cases. Thromboembolic events may lead to cardiac arrest. *Patients with acquired haemophilia:* Clinical trials showed certain adverse drug reactions were more frequent (1% based on treatment episodes): arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products. The Summary of Product Characteristics should be consulted for a full list of side effects. **Marketing Authorisation numbers:** NovoSeven® 1 mg (50 KIU) EU/1/96/006/008 NovoSeven® 2 mg (100 KIU) EU/1/96/006/009 NovoSeven® 5 mg (250 KIU) EU/1/96/006/010 NovoSeven® 8 mg (400 KIU) EU/1/96/006/011 (UK only) **Legal Category:** POM **(UK ONLY)- Basic NHS Price:** NovoSeven® 1 mg £525.20 NovoSeven® 2 mg £1,050.40 NovoSeven® 5 mg £2,626.00 NovoSeven® 8 mg £4,201.60 For complete prescribing information, please refer to The Summary of Product Characteristics which is available: **For Ireland from** - www.medicines.ie or by email from info@novonordisk.ie or from Medical Department, Novo Nordisk Limited, 1st Floor, Block A, The Crescent Building, Northwood Business Park, Santry, Dublin 9, Ireland; Tel: 1 850 665 665 **For UK from** – www.medicines.org.uk or from Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA; Tel: 01293 613555 or Fax: 01293 613535

Ireland only

Adverse events should be reported. Information about adverse event reporting is available at www.hpra.ie Adverse events should be reported to the Novo Nordisk Medical department; Tel: 1 850 665 665.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 600 5055). Calls may be monitored for training purposes.

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NovoSeven® Recombinant Factor VIIa

bjh guideline

Guideline on the management of acute chest syndrome in sickle cell disease

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Keywords: sickle cell disease, acute chest syndrome, respiratory disease.

Summary of key recommendations

- Acute chest syndrome (ACS) is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray. Severe hypoxia is a useful predictor of severity and outcome (1B).
- ACS has a multifactorial aetiology and an infective cause is common and this should be considered in treatment algorithms (1B).
- Patients with sickle cell disease (SCD) can present with ACS, or it may develop sometime after onset of severe pain. Therefore, vigilance should be maintained throughout hospital admission (1B).
- Clinicians should maintain a high index of suspicion of ACS in patients who have chest symptoms and signs, especially if hypoxic, even in the presence of a normal chest X-ray (1C).
- Pulmonary embolism, fluid overload, opiate narcosis and hypoventilation may cause or trigger ACS and should be considered when a diagnosis of ACS is made as these conditions may require additional treatment (1B).
- Acute chest syndrome can be a severe life-threatening condition. Early recognition of progression to acute respiratory failure is vital (1B).
- Patients should be monitored for predictors of severity which include worsening hypoxia, increasing respiratory rate, decreasing platelet count, decreasing haemoglobin concentration, multilobar involvement on chest X-ray and neurological complications (1B).
- Patients should be treated aggressively irrespective of their sickle genotype (1C).
- Essential investigations for the diagnosis and management of ACS are plain chest X-ray, full blood count, basic biochemistry tests (creatinine and liver function) and blood group and screen (or crossmatch). Blood cultures, sputum for microscopy and culture and sputum and nasopharyngeal aspirate for viral testing including influenza A (and H1N1 subtype), influenza B, metapneumovirus, adenovirus, parainfluenza and respiratory syncytical virus should also be performed if clinically indicated (1B).
- Arterial blood gases analysis should be performed in adults with oxygen saturation (SpO_2) ≤94% on air (2C).
- Computerized tomography (CT) of the chest and V/Q scanning are not helpful in the acute setting. A CT pulmonary angiogram (CTPA) is recommended if there is a high clinical suspicion of pulmonary embolism (2B).
- All hospitals should have a treatment pathway for ACS, which should include a referral pathway to the high dependency unit (HDU-level 2) and intensive care unit (ICU – level 3) (1B).
- All patients with ACS should be given prompt and adequate pain relief according to National Institute of Health and Care Excellence (NICE) guidance (1B).
- Incentive spirometry has proven benefit in preventing ACS in patients with chest or rib pain (1A) and should be also considered in all patients with ACS (2C).
- Antibiotics, with cover for atypical organisms, should be used even if blood cultures and sputum cultures are negative. Anti-viral agents should be used if there is a clinical suspicion of H1N1 infection (1B).
- Early simple ('top-up') transfusion should be considered early in the hypoxic patient but exchange transfusion is necessary if there are severe clinical features or evidence of progression despite initial simple transfusion (1B).
- Blood should be sickle-negative and fully matched for Rh (C, D and E type) and Kell. A history of previous red cell

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antibodies should be sought and appropriate antigen-negative blood given (1A).
- The critical care team should be consulted early for respiratory support (2C).
- Bronchodilators should be used if there are clinical features suggestive of a history of asthma or evidence of acute bronchospasm (1B).
- Ensure that all patients are offered penicillin V prophylaxis and pneumococcal polysaccharide vaccination in addition to pneumococcal conjugate vaccine, and appropriate seasonal vaccination (1A/2B).
- Hydroxycarbamide should be recommended for prevention of recurrent ACS (1A).
- Consider chronic transfusion for prevention of recurrent ACS if hydroxycarbamide therapy is not effective (2B).
- In children, consider stem cell transplantation for prevention of recurrent ACS if hydroxycarbamide therapy is not effective (2B).

Sickle cell disease (SCD) affects 12 000–15 000 individuals in the UK. Whilst homozygous SCD (sickle cell anaemia — HbSS) is the most common and severe genotype, and is where most of the evidence exists, this guidance should be used for all genotypes of SCD.

Acute chest syndrome (ACS) is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray (Charache *et al*, 1979; Ballas *et al*, 2010). This definition encompasses cases both where an infective organism is isolated and where no infective cause is identified. It is unique to SCD but in some cases ACS may appear to be similar to bacterial pneumonia in a patient without SCD. ACS may have a severe clinical course and can progress rapidly from mild hypoxia to respiratory failure and death. The presence of hypoxia is not included in the definition, but in clinical practice, hypoxia is a useful predictor of severity and outcome (Vichinsky *et al*, 1997, 2000).

Historically, ACS is one of the most common causes of death in patients with SCD (Platt *et al*, 1994; Lucas *et al*, 2008), although mortality is improving with improved medical management (Fitzhugh *et al*, 2010). ACS can also be associated with significant morbidity, including long-term parenchymal lung damage, pulmonary vascular abnormality and neurological sequelae. Patients may present to hospital acutely unwell with ACS or ACS may develop during a hospital admission following a painful crisis or post-operatively.

This guideline will be useful for clinicians working in both high and low prevalence areas and may serve as the foundation for clinical governance measures that can be introduced in individual units with the aim of improving care for patients with SCD. It can be used to inform local pathways and protocols, and we recommend that all acute healthcare organizations should have a protocol for management of this condition (Sickle Cell Society, 2008). In specialist centres such pathways and protocols will be developed locally, but smaller centres should consider linking with a nearby specialist centre and using a shared protocol. Units in acute healthcare organizations in low prevalence areas who may only rarely be confronted with ACS should have clear guidance on: (i) which specialist centre to seek advice from, (ii) criteria for transfer to the specialist centre and (iii) criteria for transfer to a critical care intensive care unit (ICU) (level 3) or high dependency unit (HDU) (level 2).

Guideline writing methodology

The guideline group was selected by the British Committee for Standards in Haematology (BCSH) to be representative of UK-based medical experts. MEDLINE and EMBASE were searched systematically for publications from 1966 until April 2013 using a variety of key words. The writing group produced the draft guideline, which was subsequently considered by the members of the General Haematology Task Force of the BCSH. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists and members of the BCSH and British Society of Haematology Committee, patient representatives and other interested parties. Comments were incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found in Appendix I. Criteria used to quote levels and grades of evidence are as outlined in the Procedure for Guidelines Commissioned by the BCSH (Appendix I).

Pathophysiology/aetiology

Acute chest syndrome refers to a spectrum of disease from a mild pneumonic illness to acute respiratory distress syndrome and multi-organ failure. The initial insult, which may be pulmonary infection, fat embolism and/or pulmonary infarction, causes a fall in alveolar oxygenation tension, which causes HbS polymerization. This, in turn, leads to decreased pulmonary blood flow that exacerbates vaso-occlusion, producing more severe hypoxia such that a vicious cycle of hypoxia, HbS polymerization, vaso-occlusion and altered pulmonary blood flow ensues.

There is evidence that VCAM1, which is up-regulated by hypoxia and fat embolism, has a role in the development of ACS as an inducer of red cell adhesion It contributes to increased adherence of red cells to the respiratory endothelium and increased vaso-occlusion within the pulmonary circulation, leading to increased hypoxia (Stuart & Setty, 1999).

Pulmonary infection

Acute chest syndrome may occur secondary to infection, and infectious organisms were identified in 38% of cases who underwent detailed investigations including blood culture, nasopharyngeal sampling for viral culture, sputum culture and serum samples for antibody response and bronchoscopy

(Vichinsky *et al*, 2000). The identification of a specific infectious organism is less likely with standard investigations alone. An infective aetiology is more common in children than in adults and shows seasonal variation in children, being three times more common in winter (Vichinsky *et al*, 1997). Viral infection is the commonest cause of ACS in children under 10 years of age. The most common bacterial organism identified in adults is *Chlamydophila pneumoniae* and in children is *Mycoplasma pneumoniae* and the commonest virus identified is the respiratory syncytical virus (RSV). *Mycoplasma* has been isolated in 12% of episodes in children under 5 years of age, 14% of episodes in children aged 5–9·9 years but only 3% of episodes in the 15 years and over age group (Neumayr *et al*, 2003). *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and respiratory viruses other than RSV are also seen (Vichinsky *et al*, 2000; Dean *et al*, 2003; Neumayr *et al*, 2003). The prevalence of both viruses and atypical bacteria as common causes of infection suggest that the clinician must carefully consider the antimicrobial agents prescribed, which should provide coverage against atypical bacteria. The clinical course of ACS is significantly different to that of infectious pneumonia in non-sickle individuals, which is probably because of the damaged microvasculature of the lung in individuals with SCD (Ballas *et al*, 2010).

Fat embolism

Acute chest syndrome may also be caused by fat embolism. During a painful crisis, vaso-occlusion within the bones leads to bone marrow necrosis and the release of fat emboli. These enter the blood stream and lodge in the pulmonary vasculature causing acute hypoxia. Evidence of fat emboli has been shown on autopsy studies, and fat-laden macrophages have also been found in bronchoalveolar fluid and in induced sputum (Vichinsky *et al*, 1994).

Microvascular pulmonary infarction

In situ microvascular occlusion and pulmonary infarction can also be associated with ACS and it can be secondary to hypoventilation, causing pulmonary atelectasis, hypoxia and pulmonary intravascular sickling. Microvascular pulmonary infarction must be distinguished from pulmonary embolism, which can present with chest pain and tachypnoea but without a new infiltrate on chest X-ray. Whilst this group of patients have a hypercoagulable state and are at an increased risk of pulmonary embolism, the clinical picture is usually distinct from ACS.

Hypoventilation/atelectasis

Severe bony pain from rib infarcts can lead to splinting and regional hypoventilation in the areas of pain (Rucknagel *et al*, 1991; Gelfand *et al*, 1993). Alveolar hypoventilation can also occur secondary to opiate narcosis or in the post-operative period, following a general anaesthetic (Vichinsky *et al*, 2000).

Asthma

A pre-existing diagnosis of asthma has been shown to be associated with an increased incidence of ACS in children (Boyd *et al*, 2006). A cohort of 291 infants followed by the Cooperative Study of Sickle Cell Disease for up to 20 years found that 16·8% had asthma and those with asthma has almost twice as many episodes of ACS (0·39 episodes per patient year vs. 0·20 episodes per patient year; $P < 0{\cdot}001$) (Boyd *et al*, 2006). Those with SCD and asthma were younger at their first presentation with ACS with a median age of 2·4 years (Boyd *et al*, 2006). Bronchospasm and wheeze are common in the context of ACS, and may contribute to local hypoxia. They are most frequently seen in children and commonly have a viral aetiology.

Recommendations

Acute chest syndrome is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray. Severe hypoxia is a useful predictor of severity and outcome (1B).

Acute chest syndrome has a multifactorial aetiology and an infective cause is common and this should be considered in treatment algorithms (1B).

Clinical features

Acute chest syndrome is the second most common reason for hospitalization in SCD and is a leading cause of morbidity and mortality. The clinical features of ACS may not be evident at the time of admission. Nearly half of patients present initially with a painful vaso-occlusive crisis and then develop this complication whilst in hospital. ACS will often develop 24–72 h after the onset of severe pain (Gladwin & Vichinsky, 2008). All patients admitted with painful crisis should be considered to be potentially in the prodromal phase of ACS. Additionally, ACS can develop post-operatively, especially following abdominal surgery and in patients not given a pre-operative blood transfusion (Howard *et al*, 2013). Patients with minimal clinical features may become critically unwell rapidly and vigilance throughout admission for the development of ACS is mandatory, particularly in patients presenting with rib or chest pain. Regular monitoring of vital signs and at least daily chest examination are essential. Often, the clinical diagnosis is sought when a patient is found to be hypoxic.

Symptoms and signs

The most common respiratory symptoms of ACS are cough, chest pain and shortness of breath. Chest pain may be pleu-

Table I. Signs and symptoms of acute chest sydrome in children and adults (data from Vichinsky *et al*, 1997, 2000).

	Children	Adults
Fever	+++	++
Cough	++	++
Chest pain	+	++
Dyspnoea	+	++
Tachypnoea	+	+
Wheezing	+	+/−
Intercostal recession/nasal flaring	+	+/−
Skeletal pain	+	++
Hypoxia	++	+++
Haemoptysis	+/−	+

+++ frequent (>80%), ++ common (50–79), +less common (10–49%), +/− infrequent (<10%).

ritic in nature and cough productive. Rib and sternal pain, chills, wheezing and haemoptysis may also occur.

The clinical features vary depending on age. Young children more often present with fever, cough and wheeze whereas pain and dyspnoea are predominant features in adults. Pain is a less prominent feature in children (Table I).

Features include.

- Hypoxia – Evidence of ACS should be sought in any patient who is unwell and hypoxic. Oxygen saturation (SpO_2) ≤94% (on air) on pulse oximetry or a fall in SpO_2 of 3% or more from baseline steady state values should prompt further action. Oxygen desaturation may not always correlate with degree of hypoxia and can be influenced by other factors, including chronic anaemia, so hypoxia may need to be confirmed by arterial blood gas (ABG) measurement. A number of patients are chronically hypoxic for reasons such as pulmonary hypertension and chronic sickle lung disease and any further deterioration should be considered significant. Hypoxia may precede clinical signs and chest X-ray abnormalities.
- Fever.
- Tachypnoea.
- Tachycardia.
- Wheeze.
- Chest signs including dullness to percussion, reduced air entry, crepitations, bronchial breath sounds, rhonchi and pleural rubs.
- Pleural effusions (more common in adults).
- Intercostal recession, nasal flaring and other signs of increased work of breathing may be may be seen in children.

Clinical signs often precede the chest X-ray findings. In addition to the rather general nature of these signs, which could indicate a primary bacterial or viral pneumonic process, the chest examination may be normal. It is important if this is the case, that the diagnosis is not excluded at this stage. If there is strong clinical suspicion, close monitoring should be undertaken and, perhaps, therapy initiated. A normal chest examination is more likely to be encountered in children.

Challenges in the diagnosis of ACS

Clinical features overlap with those of pneumonia in a patient without SCD. ACS is often precipitated by infection but treating ACS as a purely infective episode may lead to progression and rapid clinical deterioration.

Other considerations when making a diagnosis of ACS should include:

- Pulmonary embolism. May present with chest pain, dyspnoea and hypoxia. D-dimers are unhelpful in SCD as levels are usually elevated, so testing should be avoided. If there is a high clinical suspicion of pulmonary embolism (i.e. sudden onset unilateral pleuritic pain that is not typical of sickle pain) treat for both conditions pending a computerized tomography pulmonary angiogram (CTPA). ACS may be complicated by pulmonary embolism or may occur secondary to pulmonary embolism and treatment will be required for both conditions simultaneously.
- Fluid overload. Fluid replacement is an integral part of the management of ACS. However, overhydration may lead to pulmonary vascular congestion and pulmonary oedema, especially in patients with decreased cardiac function. Close attention should be paid to fluid balance and a fluid balance chart must be maintained. Acute deterioration in a patient after blood transfusion should prompt consideration of this complication or transfusion-related acute lung injury (TRALI).
- Opiate narcosis. Careful attention should be paid to avoid this untoward effect of opiates. Monitoring of respiratory rate, sedation and pain scores should be in place, with opiate narcosis being associated with a falling respiratory rate. Dose modification or discontinuation may be necessary and naloxone may be required if there is evidence of opiate toxicity. Opiate narcosis may trigger or worsen ACS.
- Alveolar hypoventilation due to pain. Effective analgesia is necessary to prevent hypoxia and hypercapnia developing due to a restrictive ventilatory defect as a consequence of ongoing chest pain, in particular, in the context of patients with chronic sickle lung disease. This may contribute to the development of ACS.

Recommendations

- Patients with SCD can present with ACS, or it may develop sometime after onset of severe pain. Therefore, vigilance should be maintained throughout hospital admission (1B).
- Clinicians should maintain a high index of suspicion of ACS in patients who have chest symptoms and signs,

especially if hypoxic, even in the presence of a normal chest X-ray (1C).
- Pulmonary embolism, fluid overload, opiate narcosis and hypoventilation may cause or trigger ACS and should be considered when a diagnosis of ACS is made as they may require additional treatment (1B).

Course and outcome

The severity of ACS is variable, ranging from a mild illness to a severe life-threatening condition. In addition to the age-dependent variation of clinical presentation, the age of the patient also influences severity. Although ACS is more common in children (21 events per 100 person years in children vs. 8·7 events per 100 person years in adults) it tends to follow a milder course with infection frequently implicated in the aetiology. In contrast, ACS in adults tends to be a more severe illness marked by severe hypoxia, a higher requirement for transfusion and higher mortality. It can be considered as a form of acute lung injury that can progress to acute respiratory distress syndrome progressing, albeit infrequently, to acute multi-organ failure.

Acute chest syndrome can be severe in all sickle genotypes, with similar death rates per event in HbSS and HbSC (Vichinsky *et al*, 1997). All patients should be treated aggressively, irrespective of their sickle genotype.

Hospital stay is often shorter in children (5 d vs. 10 d in adults) (Vichinsky *et al*, 1997). Recurrence is a feature and some patients have multiple episodes with previous episodes increasing the likelihood of further similar events.

Acute respiratory failure (partial pressure of arterial oxygen on room air ≤8 kPa)

All patients, in particular, those with chest signs and symptoms can progress rapidly during ACS to acute hypoxic respiratory failure and therefore regular SpO_2 monitoring is essential. Predictors of acute respiratory failure include extensive lobar involvement and a history of cardiac disease (Vichinsky *et al*, 2000).

Invasive and non-invasive (including continuous positive airway pressure) mechanical ventilation

Mechanical ventilation has been reported as necessary in up to 20% of cases and it is more likely to be required in older patients. In the large multicentre National Acute Chest Syndrome Study, mechanical ventilation was provided for 13% of patients, of whom 81% recovered (Vichinsky *et al*, 2000).

Other morbidity

Neurological features, such as altered mental status, seizures and strokes, may be associated with ACS. Patients with neurological symptoms more often progress to acute respiratory failure and have a significantly higher mortality compared to those without neurological features (Vichinsky *et al*, 2000). A recent history of ACS is a risk factor for overt stroke, silent stroke and posterior reversible encephalopathy syndrome in children (Ohene-Frempong *et al*, 1998; Henderson *et al*, 2003).

An acute drop in haemoglobin concentration with an associated increase in markers of haemolysis prior to the onset of ACS is common. Reported falls from steady state haemoglobin values have varied from 7 g/l for all genotypes (Vichinsky *et al*, 1997), to 16–22·5 g/l depending on genotype (Maitre *et al*, 2000). A greater fall in haemoglobin values has been documented for cases with bilateral lung involvement than for unilateral disease (28·3 g/l vs. 13·3 g/l) (Davies *et al*, 1984).

Mortality

Acute chest syndrome remains a leading cause of premature mortality in SCD. In a recent national survey in the United Kingdom, ACS was the third most common cause of death reported in adults (Lucas *et al*, 2008). It is a recognized risk factor for early death in HbSS patients above the age of 20 years (Platt *et al*, 1994). Respiratory failure is the most common cause of death. Other causes of death in these patients included pulmonary haemorrhage, cor pulmonale, overwhelming sepsis and cerebrovascular events.

Mortality rates in ACS will be dependent in part on the appropriateness of medical management. Even with good medical treatment, overall mortality rates of up to 3% are reported, with the overall death rate in adults being four times higher than in children (Vichinsky *et al*, 1997, 2000).

Recommendations

- ACS can be a severe life-threatening condition. Early recognition of progression to acute respiratory failure is vital (1B).
- Patients should be monitored for predictors of severity, which include worsening hypoxia, increasing respiratory rate, decreasing platelet count, decreasing haemoglobin concentration, multilobar involvement on chest X-ray and neurological complications (1B).
- Patients should be treated aggressively irrespective of their sickle genotype (1C).

Monitoring and investigations

The diagnosis of ACS is typically straightforward when a high level of clinical suspicion is combined with the usual clinical features. In this scenario, the appearance of consolidation on a plain chest X-ray in a sickle cell patient with recent onset hypoxia, tachypnoea, chest signs, fever and chest

pain is diagnostic (Vichinsky *et al*, 2000). However, the diagnosis can be difficult because (i) adult patients are often afebrile (Vichinsky *et al*, 1997); (ii) clinical features may be few (Davies *et al*, 1984); (iii) hypoxia is difficult to determine on clinical examination unless severe (Vichinsky *et al*, 1997) and (iv) the radiological signs often lag behind the physical signs (Charache *et al*, 1979; Davies *et al*, 1984; van Agtmael *et al*, 1994).

Standard patient monitoring of patients with SCD admitted with acute pain crisis should include at least 4-hourly SpO_2 monitoring (on air), heart rate monitoring and blood pressure monitoring. SpO_2 should be measured on room air to enhance the sensitivity and specificity of the test to detect significant hypoxia and this is particularly helpful if the patient is located in a general ward environment. Daily clinical examination is also required, which should be more frequent if there is clinical concern.

Essential investigations

The investigations required for the diagnosis and management of ACS are standard tests available in acute district general hospitals. It should be stressed that clinical suspicion is vital to early diagnosis.

The following investigations are essential and should be performed on all patients with suspected ACS:

- Chest radiograph.
- Full blood count.
- Basic biochemistry (creatinine and liver function tests).
- Blood group and screen (or crossmatch).
- Blood cultures.
- ABG measurement on room air in adults (if $SpO_2 \leq 94\%$ on room air). This should not be done on room air if patient is in obvious respiratory distress or if SpO_2 saturations fall to <85% if oxygen is stopped briefly.
- Serology for atypical respiratory organisms and urine for Pneumococcal and Legionella antigen.
- Sputum for bacterial culture and sputum and nasopharyngeal aspirate for immunofluorescence or polymerase chain reaction (PCR) for viruses in patients with coryzal symptoms.

Chest X-ray. Typical findings on plain chest radiography in ACS are segmental, lobar or multilobar consolidation usually involving the lower lobes, or collapse with or without pleural effusion (Leong & Stark, 1998; Madani *et al*, 2007). Children are less likely to have pleural effusions, but are more likely to have upper or middle lobe disease (Davies *et al*, 1984; Vichinsky *et al*, 1997, 2000; Maitre *et al*, 2000). Radiological signs are often absent early in the illness (Charache *et al*, 1979; Davies *et al*, 1984; van Agtmael *et al*, 1994), or if present, may underestimate the severity of hypoxia (Bhalla *et al*, 1993), and treatment must not be delayed because the changes on chest X-ray are unremarkable. If initial chest X-ray is normal, a repeat chest X-ray should be performed if there is ongoing clinical suspicion. In the situation of unexplained hypoxia (no clinical features and no radiological signs on chest X-ray), a computerized tomography (CT) scan of the pulmonary arteries should be considered. This will provide clinical data on the pulmonary vasculature as well as the lung parenchyma.

Full blood count. An acute fall in haemoglobin concentration and platelet count are often seen in ACS. These are markers of disease severity. A decreasing platelet count to less than 200×10^9/l is an independent risk factor for neurological complications and the need for mechanical ventilation (Vichinsky *et al*, 2000; Velasquez *et al*, 2009). Measurement of reticulocytes will confirm adequate bone marrow function and exclude red cell aplasia (erythrovirus B19 infection).

Biochemical tests. Patients with ACS are at risk of developing multi-organ failure as a result of systemic fat emboli and require monitoring of their renal and liver function. C-reactive protein (CRP) levels, if elevated, may be used to follow the clinical progress of patients with ACS. If there is evidence of co-existent infection, the sensitivity and specificity of CRP levels as a biomarker of vaso-occlusion is reduced, but an increasing CRP is still a useful marker of a worsening clinical condition.

Group and screen/crossmatch. Blood must be urgently ABO-, Rh- (C, D and E) and Kell-typed with antibody screening for all sickle cell patients at increased risk of ACS (severe vaso-occlusive crisis, previous ACS), and for those with mild ACS as their clinical condition may suddenly deteriorate and require emergency transfusion. Red cell alloimmunization is a common problem in SCD patients and can pose significant difficulties in their management (Vichinsky, 2001). Blood for transfusion should be fully matched for Rh (C, D and E) and Kell type and should be sickle-negative. If the patient is not known to the hospital, they should be asked if they are carrying an antibody card with details of their latest alloantibody profile and any previous alloantibodies detected. In addition every effort must be made to obtain the red cell phenotype and latest red cell alloantibody profile from the hospital where their usual care is provided. This is especially important because red cell alloantibodies often become undetectable over time in sickle cell patients (Vichinsky, 2001), thereby increasing the risk of delayed haemolytic transfusion reaction if antigen positive blood is inadvertently transfused.

It must be remembered that in the UK red cell units for sickle cell patients will usually have to be ordered in from the National Blood Service, which will increase the time it takes to make the blood available for the transfusion. Therefore in requesting blood for emergency transfusion, it is best to liaise directly with the blood transfusion staff, informing them that the blood is required for a sickle cell patient in addition to providing relevant details on the crossmatch request form.

Blood culture. This must be performed in all patients with ACS who are febrile although the yield is low (Vichinsky *et al*, 1997).

Arterial blood gas sampling on room air (if $SpO_2 \leq 94\%$ on room air). Although pulse oximetry can be used to provide a reliable estimate of arterial SpO_2 in patients with sickle cell anaemia (Ortiz *et al*, 1999; Fitzgerald & Johnson, 2001), ABG measurement is the gold standard in determining the partial pressure of oxygen and partial pressure of carbon dioxide in adults with suspected ACS. An ABG on room air is useful for making the diagnosis of ACS, assessing severity and for guiding decisions about the need for HDU/ITU admission and for urgent blood transfusion and is the investigation of choice for this reason in patients with SpO_2 of ≤94% on room air, even if they have higher SpO_2 with oxygen therapy. Patients in clear respiratory distress or in whom SpO_2 falls rapidly to <85% when oxygen is removed need immediate medical review and escalation of therapy and ABGs on room air are unlikely to be needed to confirm a diagnosis or influence therapy. If samples for ABG measurement are taken whilst the patient is breathing oxygen then this must be acknowledged and the arterial-alveolar (A-a) gradient calculated to determine the degree of shunting and alveolar hypoventilation. This is unlikely to be feasible outside the HDU/ITU setting, but may be useful to guide the need for escalation of respiratory support. Arterial puncture is often very distressing to children and thus pulse oximetry is the mainstay of monitoring oxygenation. Venous or capillary samples give similar values to ABG in terms of pH, $PaCO_2$, base excess and bicarbonate but poor correlation with PaO_2 (Yildizdaş *et al*, 2004).

A lower than normal PaO_2 (11 kPa) on room air is common in clinical studies, but the prevalence varies with some studies reporting a prevalence of around 70% of cases (van Agtmael *et al*, 1994; Bernini *et al*, 1998). The mean PaO_2 of patients with ACS was 9·3 kPa (70 mmHg) and 9·2 kPa (69 mmHg) in two large studies (Vichinsky *et al*, 2000; Fartoukh *et al*, 2010), and in another study, nearly one-fifth of patients had a PaO_2 less than 8·0 kPa (Vichinsky *et al*, 1997). In the majority of studies $PaCO_2$ was in the normal range with a mean value of 4·7 kPa being recorded in 141 of 252 of first ACS events in adults (Vichinsky *et al*, 1997). However, an unexpectedly high prevalence of hypercapnia (46%) was reported in one study among adult patients with no evidence of opioid abuse (Maitre *et al*, 2000). We would suggest that a PaO_2 less than 8 kPa on room air should be accepted as severe hypoxia and a $PaCO_2$ of greater than 6 kPa as hypercapnia.

Infectious disease testing. Acute and convalescent samples for antibodies against atypical respiratory organisms, including *M. pneumoniae*, *Chlamyophila pneumoniae* and *Legionella* should be sent, if feasible, and for erythrovirus B19 if indicated by the clinical and haematological features (Vichinsky *et al*, 2000). Mycoplasma infection may be suggested by red cell agglutination on a stained blood film and the presence of cold agglutinins in serum. The usual screening test for Legionella is by testing for the urinary antigen. PCR/Immunofluorescence testing for viruses in sputum and nasopharyngeal aspirate are generally performed as a virus panel for a range of viruses. This may include testing for influenza A (including H1N1 subtype), influenza B, metapneumovirus, adenovirus, parainfluenza and RSV but will be dictated by the clinical picture and local microbiological advice. Identification of specific infective organisms will help to guide antibiotic prescription and appropriate use of isolation facilities.

Other investigations

Although a number of other investigations have been reported in the literature, these are not routinely used in the diagnosis and management of ACS in the UK.

High-resolution computerized tomography of the chest. In a study of ten children with moderate to severe ACS, high-resolution computerized tomography (HRCT) performed within 48 h of presentation accurately detected microvascular occlusion in areas of the lungs that looked normal on chest X-ray, with an average sensitivity and specificity of 84% and 97% respectively (Bhalla *et al*, 1993). In contrast to chest X-ray, the extent of microvascular occlusion on HRCT correlated with the clinical severity and degree of hypoxia (Bhalla *et al*, 1993).

However, in view of the high radiation dose delivered by CT, the use of this modality for diagnosis of ACS is not recommended. The routine use of CT is also to be discouraged because of the tendency of ACS to recur and also because people with SCD frequently require other radiological tests for a range of other indications. These considerations should not, however, detract from the use of HRCT where it is judged to be clinically appropriate. Likewise, a CTPA should be done if there is a clinical suspicion of pulmonary embolism.

Ventilation/perfusion (V/Q) lung scan. This usually reveals widespread perfusion defects with normal ventilation (Noto, 1999; Feldman *et al*, 2003; Kaur *et al*, 2004). However, the appearances may be confused with pulmonary emboli or diminished by the presence of other pathology, such as pleural effusions. The role of V/Q lung scanning in the diagnosis of ACS has not been formally investigated in prospective studies and therefore it has a limited role in the investigation of this syndrome.

Bronchoalveolar lavage for bacterial and viral studies. The complication rate of bronchoscopy in patients with ACS has been reported as 13%. The commonest reported complication was a transient fall on SpO_2, but there was a small risk of mechanical ventilation following the procedure (Vichinsky *et al*, 2000). In practice, bronchoalveolar lavage is only ever

likely to be done in patients who have progressed to intubation and ventilation. These data, combined with the lack of immediate availability of bronchoscopy in most hospitals, support the use of bronchoscopy only to answer specific clinical questions based on the clinical features and first line investigations.

Additional investigations. Secretory phospholipase A2 (sPLA2) is an enzyme that is thought to release inflammatory free fatty acids from bone marrow lipid (Styles *et al*, 1996) and it was initially shown to be elevated in ACS with the levels of phospholipase A2 correlating with the severity of ACS. It has been suggested that measurement of levels of this enzyme may be useful in diagnosis of ACS, but the test is not widely available (Styles *et al*, 1996, 2000, 2007) and more recent studies have shown a positive predictive value of only 24% in ACS (Styles *et al*, 2012).

Oil-Red-O staining of bronchoalveolar lavage samples has been used to diagnose pulmonary fat embolism (Vichinsky *et al*, 1994, 2000; Maitre *et al*, 2000). Although ACS patients with pulmonary fat embolism have a more severe clinical course (Vichinsky *et al*, 1994), this is not standard practice as it is not necessary to demonstrate the occurrence of fat embolism in routine clinical practice.

Recommendations

- Essential investigations for the diagnosis and management of ACS are plain chest X-ray, full blood count, basic biochemistry tests (creatinine and liver function) and blood group and screen (or crossmatch). Blood cultures, sputum for microscopy and culture and sputum and nasopharyngeal aspirate for viral testing including influenza A (and H1N1 subtype), influenza B, metapneumovirus, adenovirus, parainfluenza and RSV should also be performed if clinically indicated (1B).
- Arterial blood gases analysis should be performed in adults with $SpO_2 \leq 94\%$ on air (2C).
- CT chest and V/Q scanning are not helpful in the acute setting. A CTPA is recommended if there is a high clinical suspicion of pulmonary embolism (2B).

Treatment of ACS

The immediate aim of treatment in ACS is to prevent or reverse acute respiratory failure. Rapid resolution in the majority of patients will occur with application of the simple measures described below. The key to success is early recognition of ACS and institution of treatment without delay. Prompt and effective treatment will potentially minimize the occurrence of irreversible lung damage and its associated long-term sequelae. These aims are best achieved if haematological, acute medical and critical care support are provided at an early stage.

General aspects of management of ACS

Acute chest syndrome may present as a medical emergency. Sickle cell patients with ACS are often very ill and require close monitoring and management by a multi-disciplinary team. Close cooperation within and between clinical teams (haematology, acute medicine and critical care) is essential to ensure the optimal delivery of care.

1 The haematology team should be informed by the admitting acute medical team as soon as ACS is suspected. The critical care team should also be made aware of the patient, even in mild cases of ACS, because clinical deterioration often occurs rapidly and unexpectedly. This will facilitate the prompt transfer of the patient to the HDU (level 2) or to an ICU (level 3) should the patient deteriorate. In specialist sickle cell units, patients who have less severe disease may be managed on the haematology ward, but a referral pathway to level 2 and level 3 care must still be put in place in case of clinical deterioration. In low prevalence areas, it is probably better to manage ACS patients on the HDU from the outset and the management plan and need for transfer should be discussed with the linked specialist centre (via telephone). Transfer of children in low prevalence paediatric units to a specialist sickle centre should be considered as soon as the condition is suspected. Depending on the child's clinical condition, this may require retrieval by a regional paediatric intensive care team.
2 Pulse rate, systemic blood pressure, respiratory rate and SpO_2 should be monitored at least 4-hourly or more frequently depending on the patient's condition. SpO_2 should be monitored on air initially, but once the diagnosis is established, monitoring of SpO_2 can continue whilst on oxygen therapy. Patients who are receiving patient-controlled analgesia must be on hourly monitoring.
3 Monitoring of ABGs will be determined by the patient's clinical status.
4 Chest X-ray should be repeated in the deteriorating patient.
5 Daily blood counts, urea and electrolytes and liver function tests must be performed until a trend towards normalization of abnormal values is observed.
6 In adults, thromboprophylaxis should be administered as per National Institute of Health and Care Excellence (NICE) guidelines (NICE, 2010).

Specific treatment of ACS

Oxygen. It is not clear what the optimum SpO_2 is and a pragmatic approach is that oxygen should be given to maintain $SpO_2 \geq 95\%$ or within 3% of the patient's baseline. SpO_2 should be monitored at least 4-hourly so that any deterioration indicated by increasing oxygen requirement can be easily detected. If the patient is becoming increasingly dependent on oxygen a senior member of the clinical team should

be informed. More frequent or continuous monitoring is required when there is clinical concern.

Intravenous fluids. Patients with ACS are usually too unwell to maintain adequate hydration orally. Intravenous crystalloid infusion should be given until the patient is able to drink adequate amounts of fluid. Fluid requirements should be individualized and be guided by the patient's fluid balance and cardiopulmonary status. Clinical consideration must be given to avoiding fluid overload and the development of acute pulmonary oedema. Daily fluid balance should be monitored using a fluid balance chart of input and output with a daily target for fluid balance.

Pain relief. Vaso-occlusive sickle cell crisis affecting the thorax (ribs, sternum and thoracic spine) causes chest splinting and alveolar hypoventilation, which can be complicated by lung atelectasis. There is a high correlation between thoracic bone infarction and ACS (Rucknagel *et al*, 1991; Gelfand *et al*, 1993). Therefore effective pain relief, using the World Health Organization analgesic ladder is an important aspect of the management of ACS (Rees *et al*, 2003). However, care must be taken to avoid alveolar hypoventilation from opioid overdose, as this would heighten the risk of ACS. Two studies have found that the use of morphine may increase the likelihood of developing ACS (Kopecky *et al*, 2004; Buchanan *et al*, 2005). However, a small case-crossover study did not support these findings (Finkelstein *et al*, 2007). Adequate analgesia allows deeper breathing (Needleman *et al*, 2002), therefore careful monitoring with frequent review and assessment of pain and sedation scores, in addition to cardiorespiratory monitoring, is required.

Incentive spirometry and chest physiotherapy. Incentive spirometry coupled with effective pain relief helps to reduce the risk of ACS in children and young adults admitted with thoracic bone ischaemia and infarction by reducing chest splinting and atelectasis (Bellet *et al*, 1995). Whilst there are no studies on its specific use in prevention of ACS in adults or as treatment for ACS it is likely to be an important adjunct to other forms of therapy. The use of the incentive spirometer should be tailored to the patient's needs as determined by the physiotherapist, but as a guide, 10 maximum inspirations every 2 h during the day and while the patient is awake during the night is a reasonable starting point (Bellet *et al*, 1995). Incentive spirometry may also be useful in the prevention of post-operative ACS. Although most evidence of its use is in children, it could be of benefit in adults as well. Input from a chest physiotherapist and adequate pain relief are both essential to achieve optimal benefit from incentive spirometry, as patients with ACS are often not able to achieve the recommended targets on their own, and their ability to use it may be limited by pain. Alternative manoeuvres, such as positive expiratory pressure devices, can be used in younger children who may not be able to co-ordinate incentive spirometry (Hsu *et al*, 2005). The skills of respiratory physiotherapists are also essential in the management of patients with more severe ACS, who require non-invasive ventilation or invasive mechanical ventilation.

Antimicrobials. As it is usually not possible to distinguish between the different causes of ACS, the presence of infection must be assumed. There are currently no randomized controlled trials on the antibiotic management of ACS (Martí-Carvajal *et al*, 2013). Based on published data, atypical respiratory pathogens predominate in cases of ACS due to infection (Vichinsky *et al*, 2000). It is therefore prudent to treat **all** patients empirically for severe community acquired pneumonia unless there are clinical data to suggest another type of infection. The antibiotic combination must always cover atypical respiratory organisms such as *Mycoplasma* and *Chlamydophila* (Lim *et al*, 2009; Harris *et al*, 2011) (see Table II). The H1N1 subtype of the Influenza A virus must be aggressively treated according to local microbiology advice if suspected or proven (van Tuijn *et al*, 2010).

Blood transfusion. The role of blood transfusion in the management of ACS has not been formally investigated in

Table II. Suggested antibiotic regimens (Lim *et al*, 2009).

	Adults	Children	Adults (penicillin-allergic)	Children (penicillin-allergic)
Recommended antibiotics*	Co-amoxiclav 1·2 g tds iv plus Clarithromycin 500 mg bd iv/po Alternative regimen Ceftriaxone 2 g od iv plus Clarithromycin 500 mg bd iv/po	Co-amoxiclav plus Clarithromycin **OR** Ceftriaxone plus Clarithromycin (May substitute azithromycin for clarithromycin)	Ceftriaxone 2 g od iv plus Clarithromycin 500 mg bd po/iv If true penicillin anaphylaxis: vancomycin 1 g bd iv plus Clarithromycin 500 mg bd po/iv	Ceftriaxone plus Clarithromycin If true penicillin anaphylaxis, seek microbiology advice

*This is a recommendation only and should be discussed with the local microbiology team, taking local antibiotic resistance profiles into consideration.

iv, intravenously; po, orally; tds, three times a day; bd, twice a day; od, once daily.

randomized controlled trials (Alhashimi *et al*, 2010), but there is observational and case control evidence for its efficacy in ACS and it can be lifesaving in severe cases. Blood transfusion can produce rapid and dramatic improvements in clinical, radiological and oxygenation parameters (Emre *et al*, 1995; Vichinsky *et al*, 1997, 2000). Both simple ('top up') and exchange transfusion increase oxygenation to similar extents (Vichinsky *et al*, 2000; Turner *et al*, 2009). Exchange blood transfusion may have additional benefits as, by reducing the number of circulating sickle cells, it prevents their further participation in vaso-occlusive events and reduces the deleterious effects of haemolysis without an unacceptable increase in blood viscosity (Swerdlow, 2006).

Not all patients with ACS will require a blood transfusion and the decision to transfuse may be difficult so a senior decision maker should be involved. Patients may deteriorate rapidly so the need for transfusion should be frequently reassessed and samples should be taken early for blood grouping and antibody screening. A simple ('top-up') transfusion should be considered in patients with a PaO_2 of less than 9·0 kPa on room air, but may also be needed at less severe degrees of hypoxaemia, depending on the individual patient's history and clinical features, or if the patient's oxygen requirements are increasing. An exchange transfusion is indicated for patients who show features of severe disease, in those who deteriorate despite an initial simple transfusion or in those with a higher haemoglobin concentration (>90 g/l).

In general, it is better to initiate transfusion early as acute respiratory failure can develop rapidly and early simple transfusion, aiming for a final haemoglobin concentration of 100–110 g/l, is often effective at preventing progression (Emre *et al*, 1995). Exchange transfusion may be a manual or automated procedure. Eight units of packed red cells will usually be sufficient for a full exchange transfusion in an adult and for children under 50 kg, 40 ml/kg of packed red cells will be required. With exchange transfusion the final haemoglobin target should also be 110–110 g/l but a lower HbS% will be achieved. There is no evidence for an optimal HbS% target post-exchange transfusion. In practice a target of <30–40% is often used, but clinicians should be guided by the clinical response. Some centres will aim for a lower HbS target of <20–30% in very sick patients (e.g. invasively ventilated patients) and will maintain the lowest possible levels of HbS by carrying out further exchanges until the patient has made a full recovery.

Advanced respiratory support. A minority of patients will require more intensive respiratory support. This support may be required from the outset, or more commonly, later in the course of the illness as a result of late diagnosis or delays in treatment. Worsening hypoxia, severe dyspnoea and increasing hypercapnia causing a respiratory acidosis (arterial pH <7·35) are indications for initiating advanced respiratory supportive therapies. These should be performed in a critical care environment with advanced physiological monitoring. Patients with risk factors for progression of ACS including extensive pulmonary involvement, co-existing respiratory disease and those in whom blood is not readily available should be considered for early intervention with advanced respiratory support.

(a) Non-invasive ventilation (NIV): NIV could potentially reduce the need for intubation and mechanical ventilation in ACS with acute respiratory failure, although there is limited evidence to currently support this approach in either children or adults. NIV has been used in children and adults with ACS (Padman & Henry, 2004; Fartoukh 2010). NIV has expected physiological benefits for patients with ACS as it increases mean airway pressure, resulting in recruitment of collapsed lung units, which increases both functional residual capacity and lung compliance. Consequently, this reduces the work of breathing.

Non-invasive ventilation significantly improved oxygenation, decreased the work of breathing and reduced heart rate but had no impact on the proportion of patients who were hypoxic by the third day, blood transfusion requirements, opioid use and length of stay in the step down unit and in hospital. In addition, NIV use was associated with greater patient discomfort than conventional therapy (Padman & Henry, 2004; Fartoukh 2010). It is not possible to draw any firm conclusions from these studies and further studies are required to clarify its precise role in ACS.

(b) Invasive ventilation: Endotracheal intubation and ventilation will be required in patients with worsening acute respiratory failure despite maximal NIV or continuous positive airway pressure support, patients with a falling level of consciousness and those patients who are unable to protect their airway. In this situation, standard lung protective ventilation should be provided with a (i) target tidal volume of 6 ml/kg (ii) a PaO_2 of 8 kPa and (iii) a peak airway pressure less than 30 cm H_2O (Brower *et al*, 2001; ARDS Definition Task Force *et al*, 2012). The majority of patients can be managed with conventional mechanical ventilation. There are occasional case reports of the use of high frequency oscillatory ventilation (Wratney *et al*, 2004) and using systems such as extracorporeal membrane oxygenation (Gillett *et al*, 1987; Pelidis *et al*, 1997; Kuo *et al*, 2013). It is impossible to make recommendations based on these historical case reports, particularly as the techniques involved have progressed in the time since the reports were published, and they do not reflect current practice. Furthermore the patients in these reports would have been massively transfused and this may have had a substantial role in the therapeutic benefit. However, for fulminant ACS refractory to standard conventional therapy, these measures may be appropriate in centres with sufficient expertise.

Other measures

Bronchodilators. There are no studies investigating bronchodilator use in ACS (Knight-Madden & Hambleton, 2003).

However, there is evidence for an association between asthma and ACS in children with asthma (Boyd *et al*, 2006). Bronchodilators should be used in individual patients with (i) demonstrable reversible airways disease (ii) a history suggestive of asthma, e.g. intermittent wheeze and nocturnal cough or (iii) acute bronchospasm. There is no evidence to support the use of bronchodilators in all patients with ACS.

Inhaled nitric oxide. Several case reports have described the use of inhaled nitric oxide (NO) in the treatment of ACS (Atz & Wessel, 1997; Sullivan *et al*, 1999; Laurie, 2010). However, there are no randomized controlled trials on the use of inhaled NO in the management of ACS and there is currently insufficient evidence to support its routine use (Al Hajeri *et al*, 2008).

Corticosteroids. Corticosteroids have been used for the treatment of ACS, but there is significant variability in their efficacy (Sobota *et al*, 2010). Corticosteroids have been shown to decrease the length of hospitalization with ACS, however, the use of corticosteroids for ACS is associated with longer overall lengths of stay and with higher readmission rates as a result of rebound sickling (Bernini *et al*, 1998; Strouse *et al*, 2008; Sobota *et al*, 2010; Quinn *et al*, 2011). With current evidence, routine use of corticosteroids in the treatment of mild and moderate ACS cannot be recommended due to its adverse effects. The exception to this is the use of corticosteroids in children and adults with acute asthma (British Thoracic Society/Scottish Intercollegiate Guidelines Network, 2008) in combination with ACS.

Recommendations

- All hospitals should have a treatment pathway for ACS, which should include a referral pathway to the HDU-level 2 and ICU – level 3 (1B).
- All patients with ACS should be given prompt and adequate pain relief according to NICE guidance (1B).
- Incentive spirometry has proven benefit in preventing ACS in patients with chest or rib pain (1B) and should be also considered in all patients with ACS (2C).
- Antibiotics, with cover for atypical organisms, should be used even if blood cultures and sputum cultures are negative. Anti-viral agents should be used if there is a clinical suspicion of H1N1 infection (1B).
- Early simple ('top-up') transfusion should be considered early in the hypoxic patient but exchange transfusion is necessary if there are severe clinical features or evidence of progression despite initial simple transfusion (1B).
- Blood should be sickle-negative and fully matched for Rh (C, D and E type) and Kell. A history of previous red cell antibodies should be sought and appropriate antigen-negative blood given (1A).
- The critical care team should be consulted early for respiratory support (2C).
- Bronchodilators should be used if there are clinical features suggestive of a history of asthma or evidence of acute bronchospasm (1B).

Chronic complications and prevention

Acute chest syndrome may lead to scarring, pulmonary fibrosis and chronic sickle lung disease. In both children and adults, previous episodes of ACS are associated with worse lung function (Sylvester *et al*, 2006; Knight-Madden *et al*, 2010) and in adults sickle chronic lung disease is associated with previous ACS (Powars *et al*, 1988). Prevention of infection with antibiotic prophylaxis, administration of annual influenza vaccination (including vaccination against H1N1) from the age of 6 months and the avoidance of smoking may decrease the risk of ACS. Penicillin V prophylaxis is clearly of benefit in decreasing mortality in young children (Gaston *et al*, 1986) and, despite evidence of improvement in mortality being less clear in older children and adults, penicillin V prophylaxis is routinely recommended to all patients with SCD. The pneumococcal conjugate vaccine (PCV 13 – Prevenar) is given at 2, 4 and 12 months as part of routine childhood vaccinations, but individuals with SCD should also be strongly recommended the pneumococcal polysaccharide vaccine (PPV –Pneumovax) at 2 years of age and every 5 years thereafter. Children with SCD will have *H. influenzae* type b and meningitis C vaccine as part of routine childhood vaccinations but it should be recommended that children moving to the UK, or adults who did not receive these vaccines should receive them.

Hydroxycarbamide has been shown to significantly decrease the incidence of ACS in patients with recurrent severe pain (Charache *et al*, 1995) and also in unselected children with HbSS (Wang *et al*, 2011). The benefits and side effects of hydroxycarbamide should be discussed with patients and/or parents, and supported with an information leaflet. Physicians in a low prevalence area may need to refer patients to their local specialist centre for advice on initiation of hydroxycarbamide and shared care using a common protocol may be appropriate (Sickle Cell Society, 2008). Hydroxycarbamide should be recommended for patients who have had a single-life threatening episode or recurrent ACS and are not already prescribed it. If hydroxycarbamide is not effective, long-term blood transfusion may be considered as an alternative, and has been shown to decrease the incidence of ACS in patients who are being transfused for stroke prevention (Miller *et al*, 2001) or for secondary prevention of silent cerebral infarcts (DeBaun *et al*, 2014). Long-term blood transfusion may result in iron accumulation and overload and iron chelation therapy will need to be considered at an early stage (Sickle Cell Society, 2008). Patients who receive a pre-operative transfusion have a significant reduction in the incidence of post-operative ACS and pre-operative transfusion is now recommended in patients with HbSS

and HbSβ^{o}thalassaemia prior to surgery (Howard *et al*, 2013). Stem cell transplantation may be considered in children with recurrent ACS that is refractory to hydroxycarbamide treatment. There may be a role for nocturnal oxygen therapy in those patients with nocturnal hypoxia (Ip *et al*, 2013) to prevent ACS, but this needs to be proven in larger multicentre trials.

Recommendations

- Ensure that all patients are offered penicillin V prophylaxis, pneumococcal polysaccharide vaccination in addition to pneumococcal conjugate vaccine, and appropriate seasonal vaccination (1A/2B).
- Hydroxycarbamide should be recommended for prevention of recurrent ACS (1A).
- Consider chronic transfusion for prevention of recurrent ACS if hydroxycarbamide therapy is not effective (2B).
- In children, consider stem cell transplantation for prevention of recurrent ACS if hydroxycarbamide therapy is not effective (2B).

Appendix I

Strength of recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of evidence and definitions

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws, e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Date for guideline review

The guideline will be reviewed within 5 years of completion of the final draft.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology (BSH) not the publishers accept any legal responsibility for the contents of these guidelines.

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