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Sickle Cell Anaemia

Progress in Pathogenesis and Treatment

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Contents

Abstract

The phenotypic expression of sickle cell anaemia varies greatly among patients and longitudinally in the same patient. It influences all aspects of the life of affected individuals including social interactions, intimate relationships, family relations, peer interactions, education, employment, spirituality and religiosity. The clinical manifestations of sickle cell anaemia are protean and fall into three major categories: (i) anaemia and its sequelae; (ii) pain and related issues; and (iii) organ failure including infection.

Recent studies on the pathogenesis of sickle cell anaemia have centred on the sequence of events that occur between polymerisation of deoxy haemoglobin (Hb) S and vaso-occlusion. Cellular dehydration, inflammatory response and reperfusion injury seem to be important pathophysiological mechanisms.

Management of sickle cell anaemia continues to be primarily palliative in nature, including supportive, symptomatic and preventative approaches to therapy. Empowerment and education are the major aspects of supportive care. Symp-

tomatic management includes pain management, blood transfusion and treatment of organ failure. Pain managment should follow certain priniciples that include assessment, individualisation of therapy and proper utilisation of opioid and non-opioid analgesics in order to acheive adequate pain relief. Blood selected for transfusion should be leuko-reduced and phenotypically matched for the C, E and Kell antigens. Exchange transfusion is indicated in patients who are transfused chronically in order to prevent or delay the onset of iron-overload. Acute chest syndrome is the most common form of organ failure and its management should be agressive, including adequate ventilation, multiple antibacterials and simple or exchange blood transfusion depending on its severity.

Preventitive therapy includes prophylactic penicillin in infants and children, blood transfusion (preferably exchange transfusion) in patients with stroke, and hydroxyurea in patients with frequent acute painful episodes. Bone marrow and cord blood transplantation have been successful modalities of curative therapy in selected children with sickle cell anaemia. Newer approaches to preventative therapy include cellular rehydration with agents that inhibit the Gardos channel or the KCl co-transport channel. Curative gene therapy continues to be investigational at the level of the test tube and transgenic mouse models.

Although sickle cell anaemia has been referred to as the 'first molecular disease'[1] and paved the way to modern molecular biology, its management has lagged behind other subsequently described molecular disorders. For decades the management of sickle cell pain, the hallmark of sickle cell anaemia, was limited to bed rest, hydration and inadequate analgesia. Lack of understanding of the nature and pathophysiology of the pain associated with sickle cell anaemia hampered rational approaches of therapy and had an adverse effect on the quality of life of an already compromised health status of affected patients.

Fortunately, during the last decade, advances in the field ushered significant changes in the attitude of care providers towards sickle cell anaemia. Most important among these has been the finding that treatment of patients with sickle cell anaemia with hydroxyurea[2-4] had a significant salutary effect on the clinical picture as shown in table I. Moreover, long-term follow-up of adult patients with sickle cell anaemia showed that hydroxyurea therapy is associated with reduced mortality.[5] This fact rekindled interest in sickle cell anaemia and opened the gates for revitalised basic and clinical research on various aspects of sickle cell anaemia.

Table I. Beneficial effects of hydroxyurea in patients with sickle cell anaemia

Decreases the frequency of acute painful episodes
Decreases the incidence of acute chest syndrome
Decreases the blood transfusion requirement
Decreases morbidity and mortality

We are amid a renaissance in the field where sickle cell anaemia is no longer regarded as an unmanageable disorder, and effective treatment and cure are achievable goals in the near future. This paper reviews recent advances in the pathogenesis and treatment of sickle cell anaemia.

1. Pathogenesis

1.1 The Nature of the Sickle Mutation

Sickle cell anaemia is a hereditary disorder of haemoglobin (Hb) where the sickle gene is inherited, homozygously, from both parents. The sickle mutation is the result of a single base change (GAT → GTT) in the sixth codon of exon 1 of the β-globin gene responsible for the synthesis of the β-globin polypeptide of the Hb molecule ($\alpha_2\beta_2$). This change, in turn, results in replacement of the normal glutamic acid with valine at position 6 of the β-globin chain and the formation of sickle Hb.[6,7] In a sense, the mutation is akin to a typographical

error where a change of one letter of a keyword of a manuscript ('punctuation mutation') corrupts the meaning of the intended message. Typographical errors in articles, however, are episodic and have a transient effect that is effaced with time. The sickle mutation, on the hand, is permanent and often afflicts a life with pain, disability and morbid existence.

1.2 Consequences of the Sickle Mutation

1.2.1 Vascular Occlusion

The most important pathophysiological event in sickle cell anaemia that explains most of its clinical manifestations is vascular occlusion which may involve both the micro- and macrovasculature.[8-11] Factors that culminate in vascular occlusion are listed in table II.[9,11-14] The primary process that leads to vascular occlusion is the polymerisation of sickle Hb upon deoxygenation which, in turn, results in distortion of the shape of red blood cells (RBCs), cellular dehydration, and decreased deformability and stickiness of RBC that promotes their adhesion to vascular endothelium. Progress in the pathogenesis of vascular occlusion pertains to cellular dehydration and adhesion to endothelial cells described in sections 1.2.2 and 1.2.3, respectively.

Table II. Factors that contribute to vascular occlusion in patients with sickle cell anaemia

Factors intrinsic to RBC
Sickle haemoglobin polymerisation
Rheology of sickle RBC
cellular dehydration
RBC deformability and mechanical fragility
dense cells
Factors extrinsic to RBC
Whole blood viscosity
White blood cell factors
Endothelial factors
adhesion of sickle RBC to endothelium
intimal hyperplasia
Haemostatic factors
Vascular factors

RBC = red blood cell.

1.2.2 Cellular Dehydration

Cellular dehydration is secondary to loss of K^+ and water. Two major transport mechanisms seem to play a significant role in cellular dehydration. The first mechanism is the KCl co-transport pathway activated by acidification and cell swelling.[15-17] This pathway is most active in reticulocytes and is a feature of low-density sickle cells (Reversibly Sickled Cells – RSC). Reticulocyte dehydration appears to contribute to the generation of dense sickle cells directly without going through repetitive cycles of oxygenation-deoxygenation.[18]

The second transport system that mediates cellular dehydration is the Ca^{2+}-activated potassium channel or the Gardos pathway, which seems to be activated by Ca^{2+} reflux-induced deoxygenation.[15-17,19-21] Although much of the intracellular Ca^{2+} in sickle cells is sequestered in endocytic vesicles,[22-24] transient reflux of Ca^{2+} during deoxygenation-induced sickling seems to be responsible for stimulating the Gardos pathway. Unlike the KCl co-transport, the Gardos pathway seems to be most active in the dense fraction of sickle cell anaemia RBCs. However, in most patients both transport systems are operative.

It should be noted, however, that the exact mechanism by which polymerisation of sickle Hb leads to cellular dehydration is not fully delineated to date. Further research in this area may refine current approaches to molecular therapy.

1.2.3 Adhesion of Sickle RBC to Vascular Endothelium

Adhesion of sickle RBC to vascular endothelium appears to be a pathophysiological contributor to vaso-occlusion. Sickle RBC adhere to cultured endothelial cells *in vitro* under both static and dynamic conditions whereas normal cells do not.[25-28] These findings suggest that sickle RBC have sticky surfaces that promote their attachment to monolayers of cultured endothelial cells. These *in vitro* observations have been documented to also occur in *ex vivo* perfusion studies in rats[29] and transgenic mice.[30] Both cellular and plasma factors have been reported to affect adhesion of sickle RBC to vascular endothelium. Thus, young deformable sickle RBC appear to be more adherent

to vascular endothelium than are dense, rigid, irreversibly sickled cells.[28,31,32]

Two receptors, $\alpha_4\beta_1$ and CD36 are present on sickle cell anaemia RBC. The former has been shown to play a role in the adherence of sickle RBC to endothelial cells via vascular cell adhesion molecule (VCAM)-1.[33,34] Plasma factors that enhance adhesion include fibrinogen, factor VIII, fibronectin, hyperosmolality, von Willebrand factor, thrombospondin and microparticles from activated platelets.[28,31,32,35-38] Thrombospondin released from activated platelets bridges the gap between endothelial cells and sickle RBC by binding to CD36 receptors on the former and CD36 receptor or sulfated glycan on the latter.[39,40]

Matsui et al.,[41] have recently reported that when endothelial cells are activated, P-selectin, a glue-like molecule, moves from their intracellular environment to their outer surface where it binds to sickle cells. This is a novel finding that sheds new light on the pathogenesis of vaso-occlusion. Previous studies (*vide infra*) showed that activated P-selectin triggers clotting in platelets and helps leucocytes to adhere to endothelial cells, and they assumed that RBC did not bind directly to P-selectin. Matsui et al.[41] presented the first evidence that P-selectin binds to normal RBC and, to a greater extent, to sickle RBC. This finding suggests that inhibition of P-selectin should be considered as a novel approach for the treatment of acute sickle cell painful episodes.

Adherence of sickle RBC to vascular endothelium results in intimal hyperplasia in larger vessels that may lead to vascular occlusion and tissue infarction.[42,43] Hebbel et al.[25] reported strong correlation between the degree of adhesion of sickle cell anaemia RBC to endothelial cells *in vitro* and the severity of the disease in patients with sickle cell anaemia or other variants of sickle cell disease. These interesting findings, however, await documentation by others. Hypofibronectinaemia seems also to be related to disease severity, the lower the level of plasma fibronectin, the more severe the disease.[44]

1.2.4 Inflammatory State and Reperfusion Injury

Recent *in vivo* studies in transgenic mice suggest that vascular occlusion results in the creation of an inflammatory state.[45,46] The sequence of events seems to be as follows: (i) reticulocytes carrying the $\alpha_4\beta_1$ receptor adhere to endothelial cells; (ii) this is followed by logjam where there is propagation of occlusion caused by the accumulation of rigid deoxygenated mature RBC proximal to the site of adhesion; (iii) the obstruction eventually clears leading to reperfusion and its associated injury; and (iv) a new cycle of adhesion starts thus creating a vicious cycle of occlusion and reperfusion. Evidence of reperfusion injury includes: (i) inflammatory response in the vascular bed of the transgenic mouse with increased leucocyte rolling, adhesion and emigration after 3 hours of mild hypoxia followed by reperfusion; (ii) local production of free radicals; and (iii) the complete inhibition of (i) and (ii) after the infusion of a monoclonal murine anti–P-selectin antibody, but not an anti–RE-selectin antibody, before reoxygenation.[45]

The implication of this sequence of events is that restoration of oxygen to ischaemic tissue results in the generation of free radicals associated with inflammatory endothelial and tissue injury.

Further evidence of the importance of adhesion in the pathogenesis of sickle cell anaemia was provided by Kaul et al.[47] who investigated the ability of two murine monoclonal antibodies (MAb) to inhibit sickle RBC–endothelium interactions induced by platelet activity factor (PAF). The MAb used were 73E and LM-609. The former MAb (73E) inhibits both $\alpha_v\beta_3$ and glycoprotein (GP) IIb/IIIa that bind primarily to fibrinogen and von Willebrand factor. LM-609, on the other hand, selectively inhibits $\alpha_v\beta_3$. Infusion of washed sickle cell anaemia RBC in the *ex vivo* mesocecum of the rat, pretreated with PAF, with or without a control antibody resulted in extensive adhesion of sickle RBC in venules associated with post-capillary blockage. Pre-treatment of the vasculature with either 73E or LM-609, but not with control antibody, inhibited the adhesion of sickle RBC in postcapillary venules. Whether the same sequence of events

occurs in patients with sickle cell anaemia or not awaits carefully designed clinical trials with antibodies that inhibit the interaction of sickle RBC and endothelial cells.

Major concerns of similar trials in humans were raised by Hebbel.[48] These include: (i) the risk associated with the inhibiting effect of MAb 73E on platelet function with an unpredictable net clinical effect (i.e. thrombosis versus bleeding); and (ii) to be effective, these antibodies have to be administered before the RBC adhere to the vessel wall (i.e., pre-treatment before the onset of a vaso-occlusive event) a scenario that is unpredictable in patients with sickle cell anaemia. Available data suggest that treatment with these MAb after the onset of vaso-occlusion may not be effective. The abnormally high base-line leucocyte count both in patients with sickle cell anaemia and in the sickle transgenic mouse seems to be a marker of this proposed chronic inflammatory state of sickle cell anaemia.[45,46]

1.2.5 Other Factors

Other factors that influence vaso-occlusion in sickle cell anaemia pertain to the α-genotype, β-haplotype, total Hb level and fetal Hb (Hb F) levels. Sickle cell anaemia can be divided into subcategories depending on the α-genotypes and β-haplotypes.[49-51] About 65% of patients with sickle cell anaemia have normal α-genotypes (β^s/β^s, αα/αα), 30% have one α gene deleted (β^s/β^s, -α/αα) and the remaining 5% have two α genes deleted (β^s/β^s, -α/-α).

The effect of α gene deletion on the clinical picture of sickle cell syndromes is controversial. Generally speaking, α gene deletion is associated with milder anaemia,[52] and hence fewer complications associated with severe anaemia and less blood transfusion. The increased haemoglobin level associated with α gene deletion, however, increases the blood viscosity, which is often accompanied by increased frequency of painful crises[53,54] and vaso-occlusive episodes such as avascular necrosis.[55,56] The effect of α gene deletion on the clinical picture is best illustrated in patients with sickle cell anaemia with two α gene deletions (β^s/β^s, -α/-α). Table III lists the unique features of this type of sickle cell anaemia.[57-60] Noteworthy is that hemoglobin A2 (Hb A2) is elevated in sickle cell anaemia with two α gene deletions, a finding that confuses this diagnosis with S-β-thalassemia that is typically also associated with elevated Hb A2 levels. This clinical picture, family history, haematological data and molecular diagnostics can differentiate the two diagnoses.[59]

β-haplotypes refer to the nucleotide sequence 5′ and 3′ to the sickle gene. Three major types have been described in Africans and African-Americans.[61] These are the Senegalese (Sen), Benin (Ben) and Central African Republic (CAR) haplotypes. The significance of these haplotypes pertains to their effect on Hb F production. It has been established that the higher the Hb F level, the milder is the sickle cell anaemia.[54] The Sen haplotype, especially in the homozygous state, is associated with relatively high Hb F levels and, hence, milder disease.[50,62] However, these conclusions are based on population data and may not apply to an individual patient.

Sickle RBC from patients with a high level of Hb F seem to be less adherent to vascular endothe-

Table III. Unique features of sickle–α-thalassemia (β^s/β^s; -α/-α) compared with sickle cell anaemia without α gene deletion (β^s/β^s; αα/αα)

Parameter	β^s/β^s; -α/-α	β^s/β^s; αα/αα
Anaemia	Milder	More severe
Haemoglobin A2 level	Increased	Normal
Splenomegaly in adults	Present	Absent
Retinopathy	Present	Absent
Cerebrovascular accidents	Rare	More common
Leg ulcers	Less prevalent	More prevalent
Tissue damage	Less frequent	More frequent

lium than those from patients with low Hb F levels. Specifically, Setty et al.[63] found that paediatric sickle cell anaemia patients with high levels of F cells had a concomitant decrease in the number of CD36+, very late antigen (VLA)4+ and CD71+ erythrocytes, and hence, less adherent RBC. Moreover, Hb F seems to affect the exposure of phosphatidylserine on the surface of RBC and coagulation activation. In vivo cycles of sickling/unsickling with resulting membrane changes and microvesicle formation are one factor responsible for phosphatidylserine exposure.[64] Phosphatidylserine-exposing RBC in the transgenic sickle mouse[65] were found to have shortened red cell survival. Children with sickle cell anaemia and high HB F levels were reported to have less phosphatidylserine-exposing RBC and, hence, milder haemolytic anaemia suggesting a possibly milder clinical picture.[66]

1.2.6 Epistatic Genes

Other factors that may effect the severity of sickle cell anaemia include gene modifiers (epistatic genes) that may affect the phenotypic expression of the sickle mutation. Styles et al.,[67] reported that specific human leucocyte antigen (HLA) alleles may influence the risk of stroke in sickle cell anaemia. Adekile et al.[68] found that the 677 C→T mutation of the methyltetrahydrofolate reduction gene is relatively frequent among Kuwaiti patients with sickle cell anaemia, but did not find any correlation with disease severity or prevalence of avascular necrosis. The role of epistatic genes in modifying the phenotypic expression is currently an active area of research. Future research findings may enable us to decipher the intricate pathophysiology of sickle cell anaemia and its complications, and usher in newer therapeutic venues.

1.2.7 Environmental Factors

In addition to the factors discussed in section 1.2, there is growing evidence that psychosocial and environmental factors may precipitate vaso-occlusion and affect the frequency and severity of painful episodes. Physical stress, trauma, dehydration and infections are such known factors.

2. Management of Sickle Cell Anaemia

2.1 Palliative Care

The clinical management of the majority of patients with sickle cell anaemia is primarily palliative in nature. Palliative care is the total comprehensive care of patients whose disease is not responsive to curative therapy.[69] It targets the numerous complications of sickle cell anaemia during the life of a patient from childhood through adulthood. The major goal of palliative care is the achievement of the best quality of life of patients and their families. Palliation in sickle cell anaemia includes: (i) general supportive care; and (ii) targeted symptomatic management of complications.

2.1.1 Supportive Care

Supportive care pertains to empowering the patients to live with their disease and be authorities on its manifestations that apply to them individually. This includes the following:

- education about sickle cell anaemia, its genetic basis, inheritance and family counselling
- adherence to regular schedule of medical follow-up
- avoidance of situations that exert an adverse effect on their disease and adoption of those activities of daily living that are beneficial to them
- knowing their rights and responsibilities as patients with sickle cell anaemia when dealing with care providers, medical facilities and the workplace
- whenever possible, participation in local support groups and communication with community leaders and advocates.

2.1.2 Targeted Management

Pain Management

Sickle cell pain is unique and like other types of pain is a complex human experience that is strongly affected not only by pathophysiological factors, but also by psychological, social, cultural and spiritual factors. The pain is the result of tissue damage generated by the sickling process and occlusion of the microvasculature. Tissue damage, in turn, releases several mediators of inflammation that ini-

Table IV. Unique features of pain associated with sickle cell anaemia

Acute, sub-acute or chronic
Acute recurrent painful episodes
Somatic or visceral
Nociceptive, occasionally neuropathic
Spontaneous, occasionally evoked
Rarely psychogenic
Psychosocial factors are important modifiers

tiate a painful stimulus that is transmitted along A-δ and C peripheral nerve fibres to the dorsal horn of the spinal cord. From there the stimulus crosses to the contralateral side and ascends along the spinothalamic tracts to the thalamus, which in turn, sends the message to the brain where the stimulus is perceived as pain.

Other concurrent processes may affect pain perception. One process pertains to descending fibres from the midbrain to the dorsal horn that inhibits the transmission of painful stimuli via endogenous endorphins. Another process pertains to communications between the thalamus, the reticular formation and the limbic system, which together modulate the emotional response to pain that may enhance or inhibit the intensity of pain perception.

The unique features of sickle cell pain are listed in table IV. It is primarily a nociceptive type of pain, i.e. the result of tissue damage. However, it could be or could have a neuropathic component.[70] The latter is characterised by burning sensation, tingling and numbness. Thus, it is important to conduct a thorough history and physical examination to determine whether sickle cell pain is associated with a neuropathic component or not. This is an important aspect of the treatment because the management of neuropathic pain utilises special approaches as will be discussed in this section. Rational and effective management of sickle cell pain includes: (i) thorough assessment; (ii) utilisation of both non-pharmacological and pharmacological agents; and (iii) a comprehensive plan for disposition and longitudinal follow-up.

Assessment is the most important initial step in effective pain management. It should be conducted before and periodically after the administration of analgesics.[71-73] Assessment relies heavily on patient self report. Other factors in the process of assessment should include the presence or absence of other complications of the disease, family member reports and vital signs. The patient self report should include multidimensional scales describing the intensity, quality, location, distribution, onset, duration, mood, sedation, pain relief and factors that aggravate or relieve pain.

The intensity of pain can be assessed by using any of several available scales such as the visual analogue scale, verbal, numerical or Wong-Baker faces scale for children. It is important, however, to stick to one scale and use it routinely so that both the patient and provider become familiar with it and its significance to a certain patient on an individual basis. Nociceptive sickle cell pain, typically, is sharp and/or throbbing in nature. Pain that is burning, shooting, lancinating or tingling in nature suggests the presence of a neuropathic component of pain that entails the utilisation of certain adjuvants as will be discussed in this section.[71,72]

Initial pain assessment establishes a baseline against which the effectiveness of analgesics in achieving pain relief can be compared. Subsequent assessment allows increasing the dose of analgesics to achieve desirable pain relief, tapering the dose of analgesics as the painful episode resolves, identification of adverse effects of therapy or the emergence of complications of the disease which allow intervention to modify the treatment plan as needed.

Non-pharmacological management of pain includes cutaneous stimulation [transcutaneous electrical nerve stimulation (TENS), heat, cold and vibration] distraction, relaxation, massage, music,

Table V. Non-opioid analgesics used in pain management in patients with sickle cell anaemia

Paracetamol (acetaminophen)
Non-steroidal anti-inflammatories
Topical agents: lidocaine/prilocaine; capsaicin
Tramadol
Corticosteroids

Table VI. Non-opioid pharmacological agents commonly used in the management of pain

Drug	Maximal daily dose (mg)	Half-life (h)
Paracetamol (acetaminophen)[a]	6000	1-3
Non-selective COX inhibitors		
Salicylates		
aspirin (acetylsalicylic acid)[a]	6000	4-15
Nonacetylated salicylates		
salsalate (salicyl salicylate)	5000	4-15
diflunisal	1500	7-15
choline magnesium trisalicylate	4000	4-15
Proprionic acid derivatives		
ibuprofen[a]	3200	2
naproxen[a b]	1500	13
fenoprofen	3200	2
ketoprofen[a b]	225	2
flurbiprofen	300	3-4
Acetic acid derivatives		
idomethacin[b]	100	3-11
ketorolac - PO	40	3-11
ketorolac - IM/IV	120	3-8
sulindac	400	16
tolmetin	1600	1-2
diclofenac[b]	200	2
etodolac[b]	1200	7.3
nabumetone	2000	22.5-30
Anthranilic acid derivatives		
mefenamic acid	1500	2-4
meclofenamic acid (meclofenamate)	400	2-3
Oxicams		
piroxicam	20	30-86
Selective COX-2 inhibitors		
celecoxib	400	11-12
rofecoxib	50	17
Partially selective COX-2 inhibitors		
meloxicam	15	15-20

a Available over-the-counter.

b Available in delayed/extended release forms.

COX = cyclo-oxygenase; **IM** = intramuscular; **IV** = intravenous; **PO** = orally.

guided imagery, self-hypnosis, self-motivation, acupuncture and biofeedback. Although there are no well-controlled clinical trials on the efficacy of these modalities on the management of sickle cell pain, there are many anecdotal reports of their efficacy in pain management.

Pharmacological management of pain includes three major classes of compounds: non-opioids, opioids and adjuvants.[71,74] A major difference between non-opioids and opioids is that the former have a ceiling effect which refers to a dose above which there is no additive analgesic effect.[75] Non-opioids (table V) include paracetamol (acetaminophen), non-steroidal anti-inflammatories (NSAIDs), topical agents, tramadol and corticosteroids.

Paracetamol has analgesic and antipyretic effects, but no anti-inflammatory component.[76] The daily total adult dose must not exceed 6g in 4 to 6 divided doses.[77] High dosages damage the liver and could be fatal. The daily dose should be decreased in the presence of liver disease. The daily dose of combination medications (medications that contain paracetamol plus an opioid) must be controlled so that the 6g limit of paracetamol is met.

NSAIDs (table VI) include non-selective cyclooxygenase (COX) inhibitors, and selective and partially selective COX-2 inhibitors.[78-80] NSAIDs have an anti-inflammatory effect in addition to their analgesic and antipyretic potential. They act primarily at the level of nociceptors where pain impulses originate and, hence, are often referred to as peripherally acting analgesics. They exert their analgesic effect by decreasing the synthesis of prostaglandins by inhibiting COX enzymes,[78] thus, decreasing or abolishing the sensitisation of nociceptors by prostanoids. The traditional non-selective NSAIDs inhibit both the housekeeping COX-1 and the inducible COX-2 enzymes. Selective NSAIDs inhibit only the COX-2 enzyme and spare COX-1, which is needed to produce physiological levels of prostaglandins.

NSAIDs have potentially serious systemic adverse effects. They include gastropathy, nephropathy and haemostatic defects. They should not be administered to patients with renal disease or with history of peptic ulcer disease. It is advisable not to administer them continuously to patients with sickle cell disease for more than 5 days. Moreover, certain NSAIDs are associated with idiosyncratic (non–prostaglandin-mediated) reactions as shown in table VII. Most recent among these is immune

Table VII. Idiosyncratic (non–prostaglandin-mediated) adverse effects associated with non-steroidal anti-inflammatories

Reaction	Manifestations	Major implicated agents
Immune reactions	Thrombocytopenia	Metabolites of naproxen and paracetamol (acetaminophen)
CNS symptoms	Headaches, dizziness, mood alterations, light-headedness, blurred vision	Indomethacin
Aseptic meningitis	Headache, stiff neck, fever, photophobia	Ibuprofen, sulindac, tolmetin
Dermatological reactions	Minor rashes to exfoliative dermatitis or toxic epidermal necrolysis	Most NSAIDs
Asymptomatic transaminasaemia	Elevated laboratory values with no clinical signs and symptoms	Most NSAIDs
Hepatitis	Variable manifestation	Sulindac, phenylbutazone, diclofenac
Bilateral pulmonary infiltrates	Dyspnoea, non-productive cough	Naproxen
Exacerbation of bronchospasm	Triad of asthma, nasal polyposis, and aspirin hypersensitivity (Samter's syndrome)	Aspirin, other NSAIDs
Necrotizing fasciitis	Soft tissue infection	Diclofenac, piroxicam
		Diflunisal, idomethacin
		Flurbiprofen

CNS = central nervous system; **NSAIDs** = non-steroidal antiinflammatories.

thrombocytopenia resulting from sensitivity to metabolites of naproxen and paracetamol.[81] The antibodies described were mostly specific for GP IIb/IIIa and less often to GP Ib/IX/V. COX-2 inhibitors are associated with significantly less gastrointestinal and haemostatic adverse effects[79,80] than the non-selective NSAIDs, but their effect on renal function seems to be the same.[82,83] The concomitant administration of ketorolac with opioids was reported to exert an additional analgesic effect and decrease the amount of opioids consumed for the treatment of acute painful episodes.[84]

Tramadol[85] is a synthetic centrally acting analgesic not chemically related to opioids. It acts as a weak agonist with preferential affinity to the μ receptors. Moreover, it inhibits neuronal re-uptake of both serotonin and norepinephrine, and stimulates the release of serotonin. Thus, functionally, it has properties of an opioid and an antidepressant. The initial enthusiasm that this drug is not associated with clinically significant respiratory depression or addiction potential[85] waned after reports indicating that seizures may be an adverse effect and an increasing abuse potential. Currently, tramadol is not a scheduled drug and it seems to be as effective as paracetamol with 30mg codeine with the added advantage of a tricyclic antidepressant-like effect. Tramadol may be administered by the oral or parenteral route, and it is available in slow-release form. Only the oral form is approved for marketing in the US at the present. Anecdotally, tramadol seems to be effective in the management of mild or moderately severe pain in some patients with sickle cell anaemia.

Opioid analgesics[86] have fewer systemic adverse effects than NSAIDs but their use in sickle cell disease is often associated with many myths about drug-seeking behaviour and addiction. There are four major classes of opioids: agonists, partial agonists, mixed agonists-antagonists, and antagonists (table VIII).

Traditionally, opioid antagonists have been regarded as having no analgesic effect and their use is primarily limited to counteract the depressive effects of opioid agonists. Recently, however,[87] there have been reports showing that small doses of antagonists in combination with agonists seem to enhance the analgesic effect, and prevent or delay tolerance to opioid agonists. Should this approach be proven by controlled trials, it would be a novel tool in the management of pain.

Opioid agonists are most often used in the management of sickle cell pain, especially in adults. They decrease or modify the perception of pain at

Table VIII. Classification of opioids

Opioid agonists
Codeine
Hydrocodone and dihydrocodeine
Oxycodone
Morphine
Pethidine (meperidine)
Hydromorphone
Levorphanol
Oxymorphone
Methadone
Fentanyl
Partial agonists
Buprenorphine
Mixed agonists-antagonists
Pentazocine
Nalbuphine
Butorphanol
Antagonists
Naloxone
Nalmefene
Naltrexone

the level of the central nervous system (CNS). They exert their effect by binding to μ, κ, and to a lesser extent, δ receptors.[86] Opioid agonists can be administered via several routes (orally, subcutaneously, intramuscularly, intravenously, transdermally, etc.) and methods, including continuous intravenous drip, patient-controlled analgesia (PCA) pump or intermittent injection. Pethidine (meperidine), morphine and hydromorphone are the major opioid analgesics used in the treatment of severe pain in the Emergency Department (ED) and hospital. Long-acting opioids, such as the oxycodone controlled-release (CR) formulation OxyContin®[1] (oxycodone CR) and morphine CR, are useful in the management of chronic pain and in combination with short-acting opioids for breakthrough pain.

Adverse effects of opioid analgesics include itching, nausea, vomiting, sedation and respiratory depression. Seizures may be associated with opioids, especially with the prolonged use of pethidine, in some patients. Tolerance and physical dependence occur in some patients, but addiction is rare.[71]

As a group, opioid analgesics have no ceiling effect (with the possible exception of codeine) and hence, the only limiting factor for dosage is adverse effects. Severe sedation and respiratory depression are the most important adverse effects. Hospitalised patients receiving opioid analgesics on a regular basis should be monitored for their respiratory rate and sedation level. A respiratory rate less than 10 per min and/or severe sedation justifies missing, decreasing or delaying the dose, or discontinuing the opioid in question until the depressive effects disappear. Opioid analgesics should be used carefully in patients with impaired ventilation, asthma, increased intracranial pressure and liver failure. The dosage of pethidine and morphine should be adjusted in the presence of renal failure. They are also histaminergic and histamine release may trigger bronchospasm or initiate an allergic reaction. Morphine is the most histaminergic of all opioids.[88] The presence of paracetamol in combination with codeine or oxycodone limits the daily dose that can be safely used so that the maximum allowable dosage of paracetamol is not exceeded. The use of paracetamol in conjunction with monoamine oxidase inhibitors may cause a severe adverse reaction characterised by excitation, hyperpyrexia, convulsions and death.[89] The co-administration of antipsychotics with pethidine may cause neuromuscular disorders including akathisia, dystonia, tardive dyskinesia and neuroleptic malignant syndrome.[90]

Adjuvants include antihistamines, antidepressants, benzodiazepines and anti-convulsants. These are heterogeneous compounds that potentiate the analgesic effect of opioids, ameliorate their adverse effects and have their own mild analgesic effect. The most commonly used adjuvants in the management of sickle cell pain are listed in table IX. The role of selective serotonin reuptake inhibitors (SSRI) in sickle cell anaemia is not clear at the present. Adjuvants must be used with care and

1 Use of trade name is for product identification purposes only, and does not imply endorsement.

patients should be monitored carefully when receiving them. Adjuvants also have adverse effects, some of which precipitate or worsen some of the manifestations of sickle cell anaemia as is discussed later in this section.[71]

Acute painful episodes of mild or moderate severity are usually treated at home using a combination of non-pharmacological and pharmacological modalities. Home treatment of pain usually follows the three step analgesic ladder proposed by the World Health Organisation (WHO).[91] Mild pain is treated with non-pharmacologic agents alone or in combination with a non-opioid. More severe pain entails the addition of an opioid ± an adjuvant. Data from the Multi-center Study of Hydroxyurea (MSH)[3,4] in sickle cell anaemia showed that a oxycodone/paracetamol formulation was the opioid most often used for the home treatment of pain.[92] However, this report was before the advent of the new formulations of opioids such as oxycodone CR. Whether oxycodone/paracetamol continues to be the first in this scenario of pain management remains to be seen.

Severe acute sickle cell painful episodes are usually treated in a medical facility using parenteral analgesics. Progress in this area pertains to the advent of day hospitals where patients are promptly evaluated by a team of experts in the management of sickle cell pain without exposure to the delay that is common in hospital emergency rooms.[73] Available data in the literature show that management of patients with severe acute painful episodes in such facilities, especially those that operate on a 24-hour basis, reduce the frequency of hospital admissions. These findings should encourage other metropolitan hospitals in cities with a large population of African-Americans to follow suit by establishing acute care facilities specifically designed for patients with sickle cell disease. The establishment of such facilities nationwide may, in turn, verify the cost-saving potential of this approach to healthcare.

Data from the MSH showed that the parenteral opioid most often used in the management of acute sickle cell painful episodes in the ED or hospital was pethidine.[92] Again, this was in 1996 and since then, there have been many anecdotal reports from many hospitals of switching to other opioids than pethidine, but detailed studies to confirm this are not available to date.

Patients with chronic sickle cell pain and those with very frequent acute painful episodes are best managed with a combination of long-acting opioids and a short-acting opioid for breakthrough pain. Again, there are anecdotal reports that this approach decreased the frequency of admissions to the ED and/or hospital, but data to confirm this are not available to date. Oxycondone CR seems to be unique in that it has both an immediate analgesic effect and a delayed long-acting effect. These properties made oxycodone CR popular among drug abusers who learned to remove the mesh and release high-dose of pure oxycodone that has immediate 'euphoric' effect.[93] Care providers should exert caution in prescribing oxycodone CR as well as other opioids and keep records of assessment and plans of management of their patients.

Table IX. Adjuvants commonly used in the management of pain in patients with sickle cell anaemia

Antihistamines
Hydroxyzine
Diphenhydramine
Benzodiazepines
Diazepam
Alprazolam
Tricyclic antidepressants
Amitriptyline
Nortriptyline
Doxepin
Anti-epileptic drugs
Phenytoin
Carbamazepine
Gabapentin
Phenothiazines
Prochlorperazine
Promethazine

Blood Transfusion

Most patients usually tolerate the chronic anaemia of sickle cell disease. Sickle Hb has decreased

Table X. Indications for blood transfusion in sickle cell anaemia

Simple transfusion		Exchange transfusion	Controversial indications
episodic transfusion	chronic transfusion		
Symptomatic anaemia due to:	Recurrent sequestration crises in young children	Acute cerebrovascular accident[a]	Pregnancy
aplastic crisis	Recurrent acute chest syndrome	Acute chest syndrome[a]	Leg ulcers
acute haemorrhage	Chronic heart failure	Multiorgan failure syndrome including fat embolism[a]	Normal MRI with abnormal neurocognitive testing
acute splenic or hepatic sequestration	Chronic renal failure associated with symptomatic anaemia and haemodialysis	Acute priapism not responsive to routine therapy[a]	Chronic organ failure including renal insufficiency
acute chest syndrome	Pulmonary hypertension or chronic hypoxia	Prevention of recurrence of stroke[a]	Before infection of hypertonic contrast media
multiple organ failure syndrome	Prevention of recurrent stroke in children with:	Surgery on the central nervous system[a]	Adults with abnormal MRI and no history of CVA
sepsis and meningitis	history of acute cerebrovascular accidents	Surgery on the posterior segment of the eye	Adults with normal MRI and history of CVA
acute neurological event	abnormal transcranial doppler study		Severe growth retardation
Preparation for major surgery	silent infarcts on MRI accompanied by abnormal neurocognitive testing		Severe ophthalmological complications
Angina or high output failure	Recurrent acute priapism not responsive to routine management		Intractable painful episodes

a The transfusion in these conditions could be either simple in exchange depending on the level of haemoglobin (Hb). Patients with Hb level of 9-10g% need exchange whereas those with Hb level of 6g% or lower need simple transfusion initially followed by exchange if needed.

CVA = cerebrovascular accident; **MRI** = magnetic resonance imaging.

oxygen affinity and, hence, is efficient in delivering oxygen to tissues. The two major objectives of blood transfusion in sickle cell anaemia are; (i) improvement of the oxygen carrying capacity of blood; and (ii) dilution of circulating sickled RBC in order to improve microvascular perfusion. Specific indications for blood transfusion are listed in table X.[94-96]

The goal of exchange transfusion is to increase or maintain a Hb level of about 10g% and to decrease the level of sickle Hb to <30%.[97,98] In patients with stroke undergoing exchange transfusion to prevent recurrence of a cerebrovascular accident, a level of sickle Hb <50% seems to be acceptable.[96,99] However, there are no controlled studies to show which target of sickle Hb is better in relief of the acute symptoms and prevention of recurrence. More blood units may be needed to decrease sickle Hb to <30% and thus, more exposure of the patient to donor blood. On the other hand, decreasing sickle Hb to <50% only may increase the frequency of blood exchanges required to keep sickle Hb at this level.

Blood selected for transfusion for patients with sickle cell anaemia should meet the criteria listed in table XI. Because the majority of patients with sickle cell anaemia are Africans or African-Americans and because they receive blood given by Caucasians, there is a high incidence of allo-immunisation in transfused patients with sickle cell anaemia.[95] The most prevalent allo-antibodies in patients with sickle cell anaemia include anti-C, -E and -K. Thus, the use of phenotypically matched blood, at least for these antigens, is highly recom-

Table XI. Desirable features of blood dedicated for transfusion to patients with sickle cell anaemia

Sickle cell negative blood
ABO and Rh compatible
Phenotypically matched to C, E and K antigens
Leuko-reduced
Irradiated in selected patients

mended.[100] Some blood banks implemented programs to increase communication between the African-American community and medical facilities to ensure the presence of a blood supply from African-American donors directed for patients with sickle cell anaemia in order to reduce the incidence of allo-immunisation to those antigens that are prevalent in African-Americans. However, there are no data to show the desirable outcome, if any, of this practice. One concern about this practice (designated donations from African-Americans to patients with sickle cell anaemia) is that it may increase the incidence of transfusion-related graft versus host disease unless such blood is routinely irradiated.

Some of the complications seen in patients with sickle cell anaemia are secondary to therapeutic interventions. Table XII lists some of these complications. Patients transfused before 1992, when a reliable second generation screening test for hepatitis C virus (HCV) was introduced in blood banks, are at a higher risk for transmission of HCV. Approximately 20 to 25% of adult patients who received a blood transfusion before 1992 are positive for HCV antibody. These patients should be followed-up regularly and the levels of hepatic enzymes monitored periodically. Increase in the enzyme level beyond what is expected in sickle cell disease is an indication for a liver biopsy. If the latter shows evidence of hepatitis, specific therapy with a combination of interferon and ribavirin[101] would be considered. Patients with sickle cell anaemia taking ribavirin should be monitored carefully because ribavirin may worsen their haemolytic anaemia.[102]

The transfusion of leucocyte-reduced components decreases the chances for allo-immunisation and febrile transfusion reactions. The transfusion of phenotypically identical RBC also minimises the chances for allo-immunisation and haemolytic reactions. Iron overload is best monitored by periodic determination of serum ferritin levels in frequently transfused patients.[103] Serum ferritin levels >1500 μg/L in the steady state are suggestive of iron overload. To confirm the diagnosis of iron overload, a liver biopsy is indicated in order to quantitate the amount of iron per gram of tissue. Hepatic iron concentration >10 mg/g liver dry weight is diagnostic of iron overload and is an indication for chelation therapy with deferoxamine.

Table XII. Complications of sickle cell disease due to therapeutic interventions

Blood transfusion
Allergic reactions, febrile reactions
Haemolytic reactions, alloimmunisation
Iron overload, immunosuppression
Transmission of infectious disease
Hydroxyurea
Toxic side effects
myelosuppression
leukopenia
thrombocytopenia
anaemia
Idiosyncratic adverse effects
nausea
vomiting
pruritus
skin rash
hair loss
Effects reported in animals
carcinogenesis
teratogenesis
Unknown long-term effects
Opioid therapy
Sedation, euphoria, emesis, constipation, skin rash, pruritus, respiratory depression, orthostatic hypotension, myoclonus, seizures, dependency, addiction
Route of opioid administration
Intramuscular: fibrosis, infection, sterile abscess
Implantable catheters: infection, septicaemia
Transdermal patches: skin rash, pruritus

Prophylaxis and Management of Infection

Prophylaxis: prophylactic oral penicillin (or a macrolide if there is sensitivity to penicillin) should be given to infants and children with sickle cell disease for a minimum of 5 years.[104] All patients with sickle cell disease should receive the polyvalent (23-valent) pneumococcal polysaccharide (23ps) vaccine starting at age 2 years and every 3 to 5 years thereafter.[105] The heptavalent pneumococcal conjugate vaccine (pc V7) should

be given to all children at 2, 4, 6 and 12 months of age. Patients with sickle cell disease should also receive the pc V7 vaccine at age 2 and 5 years. Other recommended vaccinations, in addition to routine childhood vaccines, include *Haemophilus influenza* type b conjugate vaccine at ages 2, 4 and 6 months, influenza vaccine annually, and hepatitis B vaccine at birth or the first visit of children and adults who have no serological evidence of previous exposure to the hepatitis B virus.

Immunosuppression: sickle cell anaemia has an unusual relationship to certain infectious agents. Individuals with sickle trait are resistant to infection by *Plasmodium faliciparum* but patients with sickle cell anaemia are susceptible. Individuals with Fy(a-b-) red cells are resistant to infection by other types of malarial parasites. Several acquired abnormalities render patients with sickle cell disease immunocompromised and hence susceptible to a number of infections that are a major cause of mortality and morbidity. These include immunomodulation secondary to blood transfusion and iron overload.[103] The increased susceptibility of patients to infection with polysaccharide-encapsulated bacteria (*Streptococcus pneumoniae* and *H. influenzae*) is secondary to absence of splenic function. Cellular immunity may be compromised by transfusion-related iron overload and abnormalities in B cell immunity may explain antigen processing defects. Infections due to *Escherichia coli* are usually associated with urinary tract infection (UTI) in adult patients. Patients with sickle cell anaemia are susceptible to osteomyelitis secondary to *Salmonella typhimurium* in addition to the usual causes of bacterial osteomyelitis such as *Staphylococcus aureus*.[71] The susceptibility to infection by salmonella may reflect the ability of this organism to flourish in partially necrotic bone.

Management: treatment options for infections include penicillin, cephalosporins, macrolides, tetracyclines, fluoroquinolones, aminoglycosides and cotrimoxazole (trimethoprim/sulfamethoxazole) [table XIII]. The choice of antibacterial depends on the possible pathogen, the possibility of resistance, the severity of the infection and the characteristics of the patient such as age, allergies and concomitant complications.

Table XIII. Antibacterials commonly used in the treatment of infection in patients with sickle cell anaemia

Penicillins
Penicillin V potassium (First generation)
Amoxicillin (Third generation)
Ampicillin (Third generation)
Amoxicillin/clavulanic acid (Third generation)
Cephalosporins
Cephalexin (First generation)
Cefaclor (Second generation)
Cefoxitin (Second generation)
Ceftriaxone (Third generation)
Macrolides
Erythromycin
Clarithromycin
Azithromycin
Tetracyclines
Doxycycline
Generic tetracyclines
Fluoroquinolones
Ciprofloxacin (Second generation)
Levofloxacin (Third generation)
Aminoglycosides
Gentamycin
Co-tramoxazole
Other
Vancomycin
Clindamycin

Bacterial resistance is a serious and rapidly increasing worldwide problem. Pneumococci continue to be the most important organisms causing pneumonia (especially community acquired pneumonia) and also play a very important role in other infections such as sinusitis, otitis media and meningitis.[106] Approximately 25 to 40% of *S. pneumoniae* strains are resistant to penicillin. Highly penicillin-resistant strains of *S. pneumoniae* are also resistant to amoxicillin/clavulanic acid and cephalosporins. Approximately 18% of these strains are resistant to macrolides and 13% to tetracyclines. Resistance to fluoroquinolones is currently low. Moreover, approximately 20 to 30% of *H. influenzae* strains are resistant to penicillin.

Neurological Complications

Neurological complications occur in 25% of patients with sickle cell disease and are more common in sickle cell anaemia than in other sickle cell syndromes (Hb SC disease, S-β thalassemia). Cerebral infarction (figure 1) is more frequent in children, whereas intracerebral haemorrhage is more prevalent in adults. Microaneurysms (commonly referred to as moya moya) involving fragile dilated vessels that develop as compensatory collateral circulation around areas of infarction seem to be responsible for haemorrhage in adults (figure 2). Unlike other vascular beds, large vessels rather than microvessels seem to be the site of occlusion with consequent infarction. Approximately two-thirds of children with cerebral infarction (who are not transfused) may develop further ischaemic events within 3 years[9,107]

A major breakthrough in the management of CNS complications in children has been the prevention of stroke in patients at risk for this complication.[108,109] Specifically blood transfusion prevented the occurrence of stroke in children who had abnormal results on transcranial doppler ultrasonography (TCD). Blood velocity of 200 cm/sec or more in either the internal carotid or middle cerebral artery is abnormal (normal <170 cm/sec) and is an indication for blood transfusion or exchange transfusion.

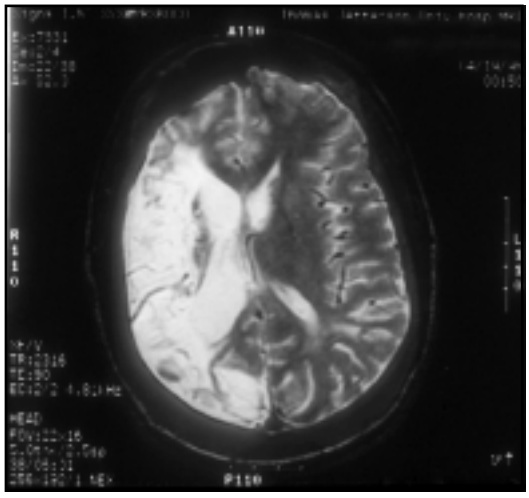

Fig. 1. Magnetic resonance imaging (MRI) of the brain of a patient with sickle cell anaemia showing an infarct (white area) in the distribution of the middle cerebral artery with gliosis, encephalomalacia and midline shift.

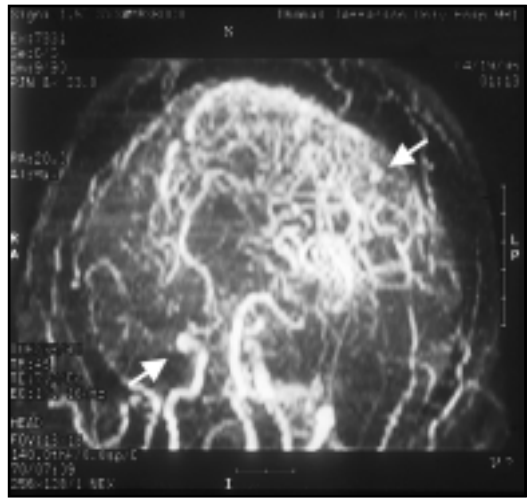

Fig. 2. Magnetic resonance arteriography (MRA) of the brain of the same patient shown in figure 1. It shows multiple microaneurysms (moya moya). The arrows point to two microaneurysms.

The appropriate therapy for a child with cerebral infarction due to vaso-occlusion or an asymptomatic patient with abnormal transcranial doppler studies is exchange transfusion or hypertransfusion to maintain the sickle Hb level below 30%. Red cell transfusions are usually continued for a minimum of 5 years after which transfusion therapy is individualised. Whether chronic transfusion therapy for adults with cerebral infarction secondary to vaso-occlusion is indicated or not remains unknown. Similarly, the appropriate treatment of an adult patient with cerebral haemorrhage has yet to be determined. A thorough search for aneurysms should be made and surgical intervention considered. Ware et al.[110] have recently suggested that some children with sickle cell disease and stroke may discontinue chronic transfusion and use hydroxyurea therapy to prevent stroke recurrence. This approach is desirable because it prevents or

decreases the risks associated with blood transfusion mentioned above. More data, however, are needed to justify this modality of therapy.

Other risk factors for stroke in children include bacterial meningitis, family history of a sibling with stroke, severe acute chest syndrome, acute anaemic episodes, recurrent episodes of seizure, impaired cognitive skills, lack of α-gene deletion and the CAR β^s-haplotype. One study suggested that high homocysteine levels may be a risk factor for cerebrovascular accidents in patients with sickle cell anaemia.[111]

Seizures in sickle cell disease may be secondary to an epileptic focus as a result of infarction or to treatment with large doses of pethidine, or they may be idiopathic. Antiepileptic therapy is recommended for patients with abnormal electroencephalograms.

Acute Chest Syndrome

Charache et al.[112] introduced the term acute chest syndrome to define acute episodes of fever, chest pain, increased leukocytosis and pulmonary infiltrates in adult patients with sickle cell anaemia, most of whom probably had pulmonary infarction. With time, the definition of acute chest syndrome has expanded to include hypoxemia, cough, shortness of breath, wheezing, chills and worsening anaemia.[113] Moreover, the current definition of acute chest syndrome stresses that the infiltrates must be 'new'. The signs and symptoms of acute chest syndrome vary from very mild to very severe and even life-threatening. Another feature of acute chest syndrome that is not included in the definition is the presence of blister cells in peripheral blood.[114] Acute chest syndrome is second to acute painful episodes as the most common cause of hospitalisation of patients with sickle cell disease and also the most common complication of surgery and anaesthesia.[115] Acute chest syndrome is the most common cause of death and is closely associated with acute painful episodes especially in adults.[116,117] Although acute chest syndrome is usually self-limited and resolves with treatment, it can be associated with respiratory failure with a mortality rate of about 1.8% in children and 4.8% in adults.[118,119]

Table XIV. Risk factors for acute chest syndrome

High white blood cell count	Rib infarction
High haemoglobin	Pregnancy
High pain rate	Aseptic necrosis of the hips
Sickle cell anaemia	Analgesics
S-β-thalassemia	Acute anaemic events
Fever	Cold weather
Age	

Risk factors for developing acute chest syndrome are listed in table XIV.[120] The incidence of acute chest syndrome is highest in sickle cell anaemia, followed by S-β^0-thalassemia, Hb SC disease and S-β^+-thalassemia in decreasing order of frequency. The single most important preventive factor is a high level of Hb F due either to endogenous genetic factors or to exogenous induction with drugs such as hydroxyurea.[3,121-124] The mean corpuscular volume (MCV) of RBCs, platelet count and α-thalassemia bear no relation to acute chest syndrome.[120] Aetiologies of acute chest syndrome include infection, especially community-acquired pneumonia, pulmonary infarction as a result of *in situ* sickling, fat-bone marrow embolism or pulmonary embolism. Infection is commonly caused by chlamydia, mycoplasma, respiratory syncytial virus, coagulase-positive *S. aureus*, *S. pneumoniae*, *Mycoplasma hominis*, parvovirus and rhinovirus in decreasing order of frequency.[118]

Adhesion of sickled RBC to endothelial cells of small or medium-sized pulmonary vessels may result in occlusion of microvascular flow and consequent pulmonary infarction.[39,124,125] This sequence of events is supported by dynamic imaging studies but confirmatory clinical data are not available. Pulmonary thromboembolism is uncommon as a cause of acute chest syndrome despite the presence of a hypercoagulable state in sickle cell disease.[126] It seems that this hypercoagulable state plays a more important role in stimulating cellular adhesion and activating the inflammatory system than in initiating the thrombotic cascade.[29,127]

Pulmonary fat-bone marrow embolism (figure 3) in patients with sickle cell anaemia appears to be more common than previously thought.[120,126] The characteristic clinical picture is that of severe bone pain, usually in long bones, followed by dyspnea, hypoxia and fever. Tissue infarction of the bone marrow within the long bones seems to generate a source of fat and necrotic tissue that has been demonstrated on autopsy. At the same time, serum levels of secretory phospholipase A2, (sPLA2), an inflammatory mediator, increase in patients with acute chest syndrome[128] and liberate free fatty acids from membrane phospholipids of damaged tissue that are believed to cause damage to pulmonary endothelium culminating in a leak syndrome which, if severe, may be similar to adult respiratory distress syndrome (ARDS). An elevated level of sPLA2 is both a marker and probably a predictor of acute chest syndrome.

Diagnostic work-up of acute chest syndrome should include serial chest radiographs, induced deep sputum and blood cultures, monitoring arterial blood gases, monitoring haemoglobin level, ventilation and perfusion scans, and ruling out thrombophlebitis in the pelvis or lower extremities. The diagnosis of fat embolism entails the identification of fat-laden macrophages in induced deep sputum, or better bronchoalveolar lavage fluid obtained by bronchoscopy.[119,126] Blister cells have been described in the peripheral blood of patients with sickle cell disease and acute chest syndrome.[114]

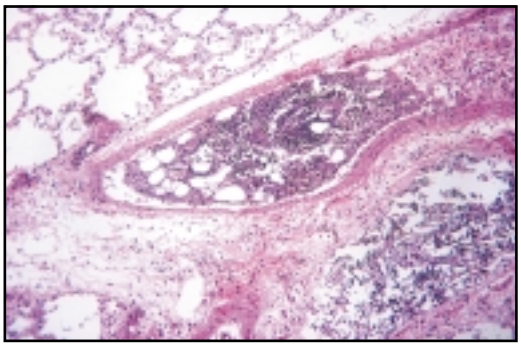

Fig. 3. Autopsy specimen of lung from a patient with sickle cell anaemia and fatal acute chest syndrome showing intravascular emboli composed of necrotic bone marrow elements. Hematoxylin & Eosin stain.

Management of acute chest syndrome includes oxygen, incentive spirometry, antibacterials, simple blood transfusion or exchange transfusion, judicious use of analgesics, careful hydration and possibly vasodilators. Incentive spirometry prevents splinting and atelectasis, and may actually prevent acute chest syndrome in patients who have rib infarction.[129] Intravenous antibacterials are indicated since it is difficult to rule out pneumonia or infected lung infarcts. A combination of a third generation cephalosporin and a macrolide or a fluoroquinolone (table XIII) should be used to cover typical and atypical pathogens. Simple transfusion or exchange transfusion is indicated in patients with worsening respiratory function. The beneficial effects of blood transfusion may not be due simply to decreasing the proportion of sickled RBC and other mechanisms may be involved. These include: (i) an immunomodulatory mechanism by which inflammatory cytokines [interleukin(IL)-8, in particular] bind to the Duffy antigen present on transfused RBCs, but often absent on RBCs of African-Americans;[130] and (ii) the albumin that is present in transfused units or used in blood exchange may bind free fatty acids, thus neutralising their damaging effect on the pulmonary endothelium.

Although intravenous corticosteroids in children with acute chest syndrome may be beneficial,[131] their use in adults with acute chest syndrome is controversial. Huang et al.[132] reported two adult patients with sickle cell disease whose clinical picture deteriorated and was complicated by worsening pain, fat embolism and coma after corticosteroid therapy. Adults, unlike children, have more adipose tissue that may hypertrophy with corticosteroids, increasing the chances of fat embolisation. Moreover, corticosteroids may induce or worsen avascular necrosis, which is more common in adults than in children.

Excessive use of opioid analgesics may precipitate acute chest syndrome because of the depres-

sive effect on respiration. Recent reports[118] recommend the use of NSAIDs. This recommendation should be considered carefully. Opioids have a few systemic adverse effects, and careful monitoring of their use ensures their safety. They should be discontinued if the respiratory rate is ≤10 per minute and their adverse effects can be quickly reversed with opioid antagonists. NSAIDs, on the other hand, have considerable systemic adverse effects that may not be readily obvious. NSAIDs decrease the levels of prostaglandins and prostacyclin, prostanoids that are essential in modulating the vascular tone of smooth muscle and renal blood flow. Thus, NSAIDs may worsen the clinical picture of acute chest syndrome as a result of vasocontrictive effects.

Preliminary reports on the use of nitric oxide (NO), a vasodilator, in patients with sickle cell disease support a possible role of this agent in the management of acute chest syndrome in the future.[133] Other vasodilators such as prostacyclin and calcium channel antagonists have not been reported in the management of acute chest syndrome. Another recent investigational approach to treat acute chest syndrome includes the use of purified poloxamer 188, which is a non-ionic surfactant. It is hypothesised that this agent reduces blood viscosity, prevents adhesion of RBCs to vascular endothelium and improves microvascular blood flow.[134,135]

Because acute chest syndrome is relatively frequent in patients with sickle cell anaemia, and in view of the need to monitor arterial blood gases in its management, it is important to establish baseline blood gases and pulmonary function tests for all patients. These determinations will be of value in evaluating patients who present with acute onset of pulmonary signs and symptoms.

Genitourinary Complications

Sickle cell anaemia is associated with numerous renal complications that span a spectrum from hyposthenuria to end-stage renal failure (table XV).[136-139]

Table XV. Renal complications of sickle cell anaemia

Haemodynamic changes
Increased ERPF and GFR in childhood
Decreased ERPF and GFR in adults
Glomerular abnormalities
Focal and segmental glomerulosclerosis
Proteinuria and nephrotic syndrome
Chronic renal failure
Acute renal failure
in multiple organ failure syndrome
drug-induced
Abnormalities of proximal tubule function
Increased reabsorption of PO_4 and β2-microglobulin
Increased excretion of uric acid and creatinine
Decreased excretion of uric acid with age
Abnormalities of distal tubule function
Hyposthenuria
Defective urinary acidification
Renal tubular acidosis
Hyperkalaemia
Papillary necrosis
Haematuria

ERPF = effective renal plasma flow; **GFR** = glomerular filtration rate.

UTI is usually caused by *E. coli* and is more common in females than in males. The increased frequency of UTI in sickle cell anaemia may relate to renal infarction or to immunodeficiency. The hypoxic, acidotic and hypertonic environment of the renal medulla causes sickling of the RBC in the vasa recta and leads to infarction of the renal medulla, hyposthenuria and haematuria (gross or microscopic). Inability to acidify the urine after an acid load can also occur. These renal tubular defects (haematuria, hyposthenuria) occur not only in patients homozygous for the sickle gene, but also in patients who are heterozygous (for example, AS, SC, SD and SO).

Management of haematuria in a patient with sickle cell anaemia follows conservative guidelines. Strict bed rest alone results in spontaneous remission in most patients. In a few instances, gross haematuria may be severe enough to warrant blood transfusion or exchange transfusion. Nephrectomy should be avoided. The use of aminocaproic acid and desmopressin may be effective in controlling haematuria. Renal medullary carci-

noma should be ruled out in all patients with gross haematuria.

Potassium excretion is also impaired and episodes of hyperchloraemic acidosis have been reported. *In vitro* haemolysis of collected blood samples kept in the lab at room temperature for some time before analysis may explain the spurious hyperkalaemia in some patients with sickle cell anaemia. Occasionally, hyperkalaemia is reported in association with Type 4 renal tubular acidosis, but renal insufficiency is present in the majority of these patients. Papillary necrosis may be more common in Hb SC disease.[140] Hyperuricaemia in patients with sickle cell anaemia is the result of both increased bone marrow activity with consequent enhanced urate production secondary to purine metabolism and an acquired decreased renal tubular clearance of urate. Gout has been described in a few patients. Allopurinol may be indicated to lower serum urate levels.

Nephrotic syndrome, with or without hypertension, occurs frequently. Microscopic haematuria, proteinuria, hypertension and the nephrotic syndrome are markers of incipient end-stage renal failure. Proteinuria occurs in 25% of patients with sickle cell anaemia and elevated serum creatinine levels in approximately 7%. Proteinuria causes congestion of tubular endothelium as a result of tubular uptake of protein. Congestion induces growth factors which, in turn, lead to proliferation of fibroblasts that culminate in renal fibrosis and renal failure. The pathological lesion is usually glomerular enlargement and peripheral focal segmental glomerulosclerosis. Treatment with enalapril (an angiotensin-converting enzyme inhibitor) seems to reduce the degree of proteinuria in patients with sickle cell anaemia suggesting that capillary hypertension may be a pathogenic factor in sickle cell nephropathy. Once chronic renal failure sets in, patients require long-term haemodialysis and are candidates for kidney transplantation.[9,10,71]

Priapism occurs when sickle cells congest the copora and prevent emptying of blood from the penis. It can result from tricorporal involvement (both of the corpora cavernosa and the corpus spongiosum) or bicorporal involvement (both corpora cavernosa). The latter is more common, especially in children, and is not regularly associated with impotence. There are two major clinical presentations of priapism: acute and chronic.[141] The acute presentation is characterised by a prolonged painful erection that persists beyond several hours, responds poorly to exchange transfusion and frequently requires surgical intervention. Acute priapism may be followed by complete or partial impotence. The chronic form of priapism is characterised by repetitive, reversible, painful erections called 'stuttering' priapism. It usually occurs after intercourse or it may awaken patients early in the morning. Stuttering priapism responds well to diazepam or pseudoephedrine. Patients who become impotent may benefit from psychological counselling and the insertion of penile implants. A practical and relatively simple approach to manage outpatients with priapism has been recently reported.[127] Specifically, aspiration of the corpora cavernosa followed by irrigation with a dilute epinephrine solution was effective in producing detumescence in most patients. Patients who do not respond to this approach are potential candidates for exchange transfusion and/or surgery.[142]

Leg Ulcers

Leg ulceration is a painful and sometimes disabling complication of sickle cell anaemia that occurs in 5 to 10% of adult patients. Severe pain may necessitate the use of opioid analgesics. Leg ulcers are more common in males and older patients, and less common in patients with α-gene deletion, high total Hb level or high levels of Hb F.[57] Leg ulcers seem to be more common in patients who are also carriers of the CAR β-gene cluster haplotype.[143]

Treatment of leg ulcers includes wound care using wet to dry dressings soaked in saline or Burrow's solution. With good localised treatment, many ulcers heal within a few months. Leg ulcers that persist beyond 6 months may require blood transfusion or skin grafting, although results of the latter treatment have been disappointing. Because leg ulcers may recur after minimal trauma, protec-

tive legging with non-elastic (special velcro) lower-extremity orthoses with ankle straps, to be worn during working hours, appears to be an effective preventive measure.[144]

Principles of management of leg ulcers include education, protection, infection control, debridement and compression bandages. Efficacy of blood transfusion/exchange transfusion, hyperbaric oxygen and skin grafting is anecdotal in nature. Osteomyelitis may complicate chronic leg ulcers, especially those associated with deep wounds, and it is advisable to rule out this complication with a bone scan or magnetic resonance imaging (MRI), with gadolinium as needed. To date, there has been no controlled trial of the treatment of sickle cell leg ulcers to identify the best approach to management.

The relationship between leg ulcers in patients with sickle cell anaemia and hydroxyurea is not clear. Early reports[145] showed that hydroxyurea seems to have a salutary effect on leg ulcers. Recent reports[146] indicated that hydroxyurea used in the treatment of myeloproliferative disorders is associated with increased incidence of leg ulcers. To date, there is no evidence whether hydroxyurea is beneficial or harmful in the management of leg ulcers in patients with sickle cell anaemia. Ferster and colleagues[147] recently reported their experience with a group of 93 children and young adults with sickle cell disease treated with hydroxyurea for a median follow-up of 3.5 years. Leg ulcers did not complicate the clinical picture of these patients.

Recent advances in the management of leg ulcers include the topical application of a platelet-derived growth factor prepared either autologously or by recombinant technology, and the use of cultured skin grafts. The use of newly described semipermeable polymeric membrane dressing may promote healing.[148] To date, there are no data about these new modalities in the management of leg ulcers in patients with sickle cell anaemia.

Avascular Necrosis

Avascular necrosis (also called ischaemic necrosis or osteonecrosis) is the most commonly observed complication of sickle cell disease in adults. Although it tends to be most severe and disabling in the hip area, it is a generalised bone disorder in that the femoral and humeral heads as well as the vertebral bodies may be equally affected. The limited terminal arterial blood supply and the paucity of collateral circulation make these three areas especially vulnerable to sickling and subsequent bone damage. Patients with sickle cell anaemia and α-gene deletion have a higher incidence of avascular necrosis because the relatively high hematocrit increases blood viscosity and thus, enhances microvasculopathy in the aforementioned anatomic sites.[55,56] The MCV and serum aspartate aminotransferase (AST) levels are negatively correlated with avascular necrosis.[56]

Medical treatment of avascular necrosis is symptomatic and includes providing non-opioid and/or opioid analgesics for pain relief, as well as minimal weight bearing. Advanced forms of the disease require total bone replacement. Core decompression (figure 4) in the management of avascular necrosis appears to be effective if done in the early stages of avascular necrosis.[149] Results of hip arthroplasty in patients with sickle cell anaemia are not as encouraging as results of arthroplasty performed for an arthritic hip.[150] Placement of an internal prosthesis may be difficult owing to the presence of hard sclerotic bone in patients with sickle cell anaemia. Other problems associated with hip arthroplasty in these patients include an increased incidence of infection,[151,152] a failure rate of about 50% and a high morbidity due to loosening of both cemented and uncemented prosthesis. Recent techniques of arthroplasty may improve the life expectancy of hip prostheses.

Hepatobiliary System

Chronic hyperbilirubinaemia, cholelithiasis and gall bladder disease are common in patients with sickle cell anaemia. At least two-thirds of patients with sickle cell anaemia have hepatomegaly and 75% have cholelithiasis. About 90% of patients with cholelithiasis undergo cholecystectomy either prophylactically or after an episode of acute calculus cholecystitis. Most cholecystectomies are currently performed by laparoscopy, a much simpler

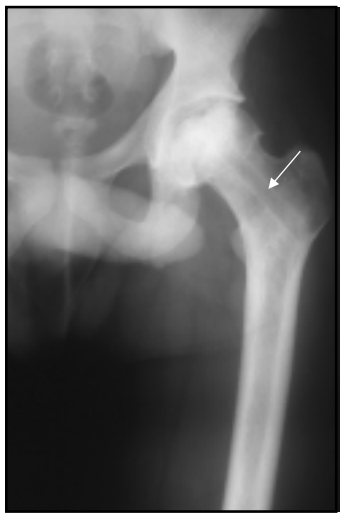

Fig. 4. Radiograph of the hip of a patient with sickle cell anaemia showing Ficat Stage III avascular necrosis with extensive subchondral sclerosis and collapse of the femoral head. The arrow shows the site of prior surgical decompression.

procedure than laparotomy, and are associated with less morbidity.[153,154]

A genetic basis for the hyperbilirubinaemia pertains to mutations in UDP-glucoronyl transferase 1 (UGT 1A), the enzyme that catalyses bilirubin glucoronidation. It seems that genetic polymorphism of the UGT 1A enzyme affects the metabolism of bilirubin. The bilirubin level as well as gallstone formation appear to be significantly higher in patients with the 7/7 genotype compared with the 6/6 genotypes of the enzyme.[155] Similar findings were reported in patients with Hb E-thalassemia.[156]

Hepatic crisis (also called sickle cell intrahepatic cholestasis) is manifested by the sudden onset of right upper quadrant pain, progressive hepatomegaly, increasing bilirubin levels (mostly indirect), and prolongation of prothrombin and partial thromboplastin times.[157] The levels of liver enzymes [γ-glutamyl transpeptidase (γGT) and alanine amino transferase(ALT)] are also increased but not to those levels seen in acute viral hepatitis. Hepatic crises vary in severity from minor episodes to severe life-threatening situations. Total blood exchange is a recommended form of therapy. Blood exchange is indicated if the total bilirubin level increases progressively to values greater than 50 g/L. At that level, the prothrombin time values are usually prolonged. Blood exchanged should be total in nature, that is, remove whole blood and replace it with red cells and fresh frozen plasma in order to correct the coagulation abnormality.

2.2 Specific Treatment

It is the hope of patients with sickle cell disease and their families that there will be, in the near future, therapy that will either cure or markedly alter the natural history of this disease. With better understanding of the pathology of sickle cell disease and co-ordination of multiple therapies that attack different pathological mechanisms of the disease, this goal seems likely. Table XVI lists current approaches that have the potential to ameliorate or cure sickle cell disease. Although the long term safety and efficacy of these novel therapies have not been well studied, there is good potential for them to reach phase III clinical trials in the near future.

2.2.1 Curative Treatment

Transplantation

Allogeneric bone marrow transplantation (BMT) as a treatment for sickle cell anaemia was first used in Europe for patients from Africa on the assumption that the risks of disease in their countries of origin justified the hazards of transplantation.[71] These patients did well and since then additional

Table XVI. Methods of primary molecular and cellular therapy in patients with sickle cell anaemia

Induction of fetal haemoglobin
Cellular rehydration
Anti-adhesion therapy
Nitric oxide and its precursors
Transplantation
Gene therapy
Other approaches

patients have undergone transplantation in Europe and the US.[71,158]

Children and adolescents younger than 16 years of age who have severe complications (stroke, recurrent acute chest syndrome or refractory pain) and have an HLA-matched donor available were the best candidates for transplantation. About 1% of patients with sickle cell anaemia met these requirements. About 100 patients with sickle cell anaemia have undergone BMT compared with more than 800 patients with β-thalassemia. More than 90% of the patients with sickle cell anaemia survived, 70 to 85% had event-free survival and 15% graft rejection. Neurological complications (seizures or intracranial bleeding) were common in the first transplant recipients. Careful control of blood counts, blood pressure and anticonvulsant-drug prophylaxis may forestall these complications. Follow-up is still short and the full extent of toxicity is unknown. Whether transplantation can reverse established organ damage is also not known, but early reports from Europe suggest some improvement in chronic lung, bone and CNS disease.[71] Data from the US, however, showed that BMT does not reverse the progression of neurological events.

Successful umbilical cord blood transplantation from related and unrelated donors in children with sickle cell anaemia seems to be possible.[159-161] A recent report of two patients with high risk sickle cell disease, publicised by the news media, achieved cure by using unrelated umbilical cord blood cell transplantation (UCBCT).[160] Both patients were reported to be alive with donor haematopoietic engraftment and without new manifestations of sickle cell disease at 21.1 and 3.3 months, respectively, after UCBCT.

Gene Therapy

Gene therapy, in simple terms, is the introduction of new genes into healthy or abnormal cells either *in vitro* or *in vivo*. Gene therapy in sickle cell anaemia is limited at present to investigational laboratory procedures and the use of transgenic mouse models to determine the most effective and safest method of altering the genetic information in haematopoietic stem cells. Research in this area has advanced at a faster rate than previously expected and gene therapy may be available for trial in selected patients with sickle cell disease in the near future.[162]

2.2.2 Preventive Treatment

The goal of preventive therapy is to ameliorate the clinical picture of sickle cell disease in general, and to decrease the frequency and severity of acute painful episodes in particular. For many years the major goal of primary therapy for sickle cell disease was to identify an antisickling agent that would prevent or reverse the polymerisation of sickle Hb in RBCs. Although the search for beneficial antisickling compounds continues, the promising approach to prevent the polymerisation of sickle Hb has been the use of compounds that increase the production of Hb F. The status of these attempts is as follows.

Molecular Therapy

Induction of Hb F: high levels of Hb F have a beneficial effect in patients with sickle cell anaemia. Platt et al.[54] has shown that there is a significant inverse correlation between the frequency of painful crises and Hb F levels greater than 4%, i.e. the higher Hb F, the milder the disease. Hb F interferes with the polymerisation of sickle Hb and, the higher (and the more pancellular) it is, the lower the intracellular concentration of sickle Hb. However, there are exceptions to this rule in that there are patients with high Hb F levels and severe disease and *vice versa*.

Agents that have been shown to increase the level of Hb F in humans are listed in table XVII. Among these, currently hydroxyurea as monotherapy seems to be the least toxic and most effective.[2-4] Moreover, the only drug studied for efficacy in a relatively large scale, placebo-controlled, randomised clinical trial is hydroxyurea.

Hydroxyurea: is a cell-cycle specific cytotoxic agent that inhibits ribonucleotide reductase. The molecular mechanism(s) by which hydroxyurea increases the production of Hb F is(are) unknown. Possible mechanisms include perturbations in cellular kinetics and/or recovery from cytotoxicity,

Table XVII. Agents that augment fetal haemoglobin production

Cell-cycle specific agents
Azacytidine
Cytosine arabinoside
Myleran
Hydroxyurea
Short chain fatty acids
Arginine butyrate - IV
Isobutyramide - PO
Phenylacetate - PO
Phenylbutyrate - PO
Valproic acid - PO
Recombinant human erythropoietin (rHuEPO)
Combination therapy
Hydroxyurea + rHuEPO
Other combinations

IV = intravenous; **PO** = oral.

recruitment of early erythroid progenitors and recruitment of primitive erythroid progenitors (BFU-E) that lead to production of Hb F-containing reticulocytes (F-reticulocytes). Long-term hydroxyurea therapy with the maximum tolerated dose (mean dose 21.3 ml/kg) with respect to myelosuppression, raises Hb F by as much as 15 to 20% (mean 14.9%, range 1.9 to 26.3%).

In the randomised, placebo-controlled, double-blind MSH study, among 299 adult patients with sickle cell anaemia with three or more painful crises per year, hydroxyurea resulted in a significant ($p < 0.001$) reduction in the incidence of painful crises, acute chest syndrome and transfusion requirement.[3,4] There was no difference between the placebo and hydroxyurea arms in the incidence of death, stroke and hepatic sequestration. Maximum tolerated doses of hydroxyurea were not required to reduce the incidence of painful episodes. Although an increase in Hb F seems to be the obvious and logical explanation for the salutary effects of hydroxyurea, other reasons for its beneficial effects include changes in RBC volume, cellular hydration, the cell membrane and a direct effect on endothelial cells

Adverse effects of hydroxyurea are listed in table XII. Toxic effects are dose- and time-dependent. Careful monitoring of blood counts every 2 weeks after starting hydroxyurea can prevent these. Later the frequency of monitoring of blood counts and blood chemistries can be decreased to once every 1 to 2 months once the patient is in a stable condition and receiving an acceptable maintenance dose. Anaemia is a rare toxic effect of hydroxyurea and, in fact in the MSH study, most patients who took hydroxyurea experienced an increase in their Hb levels. The idiosyncratic effects of hydroxyurea occur in some patients but not others. However, the incidence of these effects was similar between the placebo and hydroxyurea in the MSH study.[4] In animal studies, hydroxyurea had carcinogenic and teratogenic effects.[163-165] To date, however, no carcinogenic effect has been reported in patients with polycythemia vera and erythrocytosis due to congenital heart disease treated with hydroxyurea.[166,167]

The following limitations should be considered when using hydroxyurea to prevent painful crises in patients with sickle cell disease. Firstly, hydroxyurea was approved in the US by the Food and Drug Administration for the prevention of crises. Secondly, the long-term effects of hydroxyurea in patients with sickle cell disease are not known, and finally, some patients do not respond to hydroxyurea. Methods to identify these non-responders are being studied in order to improve the selection process for hydroxyurea therapy. In some patients combining hydroxyurea with other agents that augment Hb F production may be indicated.

Short chain fatty acids: the role of butyrate analogues as potential inducers of Hb F synthesis was based on the observation that infants who have high plasma levels of γ-aminobutyric acid (GABA) in the presence of maternal diabetes mellitus do not undergo the normal fetal-to-adult haemoglobin switch. This led to the discovery that butyric acid, sodium butyrate, and GABA inhibit the normal progress of haemoglobin switching in developing animal models and stimulate the production of Hb F in adult animals. Butyrate seems to exert its effect through sequences near the transcriptional

start site to induce the activity of the human γ-globin gene promoter.

A small Phase I/II study where three patients with sickle cell anaemia and three patients with β-thalassemia were treated with intravenous arginine butyrate showed significant and rapid increase in fetal globin synthesis to levels that can ameliorate the clinical picture of these disorders.[168] The demonstration of specific neuropathological lesions in baboons receiving extended infusions of arginine butyrate at 4-fold the human dose, however, raised safety concerns about the use of butyrate in humans.[169]

The prolonged use of arginine butyrate is limited because it has to be given intravenously and because it is rapidly metabolised by the liver. This generated efforts to find oral butyrate analogues for the induction of Hb F. Isobutyramide, a butyrate derivative, has been produced as an oral alternative and has been shown to increase Hb F production.[170] Sodium phenylbutyrate, an analogue of butyric acid, is an investigational drug currently undergoing investigation in a Phase III trial for the treatment of patients with inherited disorders of the urea cycle. Non-anaemic patients receiving sodium phenylbutyrate were found to have high levels of Hb F.[171]

Because butyric acid and its analogues are short chain fatty acids, other compounds that belong to this category were considered as potential inducers of Hb F. Non-anaemic patients receiving valproic acid for epilepsy had increased levels of Hb F.[172] With the exception of arginine butyrate, the analogues mentioned in this section (isobutyramide, phenylbutyrate, phenylacetate and valproic acid) are available in oral form.

Together, available data suggest that short chain fatty acids may play a role in the primary treatment of sickle cell disease by increasing Hb F production. However, their precise role, either alone or in combination with other agents, awaits controlled phase III clinical trials.

Erythropoietin: hematopoietic growth factors such as IL-3, colony-stimulating factor (CSF) and granulocyte-monocyte CSF can augment Hb F levels in erythroid cell cultures and in experimental animals.[173]However, none of these have been reported for this purpose in clinical trials. Recombinant human erythropoietin (rHuEPO) has been shown to increase Hb F levels in erythroid cell cultures, and in non-anaemic baboons and macaques. The molecular mechanism by which rHuEPO augments Hb F levels seems to be the result of recruitment of F positive progenitor cells, primarily CFU-E derived from an influx of the more primitive BFU-E compartment.[173] Clinical trials in which high doses of rHuEPO along with iron supplementation were given to patients with sickle cell anaemia showed an increase in the percentage of F-reticulocytes and Hb F.[174]

Extreme caution must be exercised in giving growth factors to patients with sickle cell anaemia. The administration of G-CSF to three patients with sickle cell disease caused severe pain and multiorgan failure with a fatal outcome in one.[175-177] The administration of erythropoietin to patients with sickle cell disease on a regular basis without transfusion will increase the production of sickle Hb and the Hb level to 10g% or higher that, together, are associated with increased blood viscosity which, in turn, may accelerate vaso-occlusion.

Cellular Therapy

Polymerisation of deoxy sickle Hb results in cellular dehydration which, in turn, increases the intracellular concentration of sickle Hb that leads to further polymerisation, thus, creating a vicious cycle. Major mechanisms by which water is lost from sickle cells include the Ca^{2+}-activated potassium channel (Gardos channel) and the KCl cotransport channel. Activation of these channels results in K^+ and water loss from sickle erythrocytes with consequent dehydration. A decrease in the intracellular concentration of sickle Hb, even small decreases, can slow the polymerisation of sickle Hb to a point where RBCs can exit from the capillaries (decreased transit time) before the sickle Hb polymerises (increased delay time for polymerisation). Hydroxyurea achieves this goal by decreasing the effective concentration of sickle Hb and diluting it with Hb F, which does not participate in

polymerisation. Another approach to inhibit polymerisation is to rehydrate sickle RBCs and restore their normal water content.[178,179]

Recently, a selective approach to specifically rehydrate sickle RBCs by inhibiting the Gardos pathway has been tried by using oral clotrimazole.[178] In five patients treated with 20 mg/kg/day of clotrimazole, the RBC Gardos channel was inhibited, cell K^+ content increased, RBCs were rehydrated, and a very modest increase in haemoglobin levels was noted. The effects of clotrimazole on cellular rehydration, however, were very modest compared with those seen in hydroxyurea. Nevertheless, the advent of clotrimazole offers a novel and different therapeutic approach for the treatment of sickle cell disease. It warrants a larger long-term clinical trial to determine its efficacy in the primary treatment of sickle cell disease. Furthermore, a combination of hydroxyurea and clotrimazole may ensue in an additive beneficial effect in ameliorating the clinical picture of sickle cell disease. Similar results were found by the use of oral magnesium,[179] which inhibits the KCl co-transport channel.

2.2.3 Other Novel Approaches to Therapy

These include NO,[133] anti-adhesion molecules,[47] the surfactant poloxamer-188,[134] levocarnitine,[180] arginine,[181] zileuton, a 5-lipoxygenase inhibitor,[182] green tea,[183,184] aged garlic,[183,184] and herbal extracts.[185] Some of these agents are being used on an investigational basis. There are anecdotal reports of success in a few patients using some of these agents. The efficacy of any of these agents, however, awaits proof by phase III double-blind, placebo-controlled trials.

3. Conclusions

In recent years, there have been considerable advances in understanding the pathogenesis of sickle cell anaemia. Although management of sickle cell anaemia continues to be primarily palliative in nature, there have been promising preventative and curative approaches to therapy. Pain management should be individualised and coupled with the proper utilisation of opioid and non-opioid analgesics in order to acheive adequate pain relief. Early recognition and treatment of organ failure minimises morbidity and improves outcome. The use of hydroxyurea decreases the morbidity and mortality of sickle cell disease. Cure is possible in selected children with bone marrow or cord blood transplantation. Future research seems to focus on refining the molecular and cellular approaches to therapy including gene therapy, and mechanisms that rehydrate sickle RBC and/or prevent their adhesion to vascular endothelium.

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