SICKLE CELL PAIN

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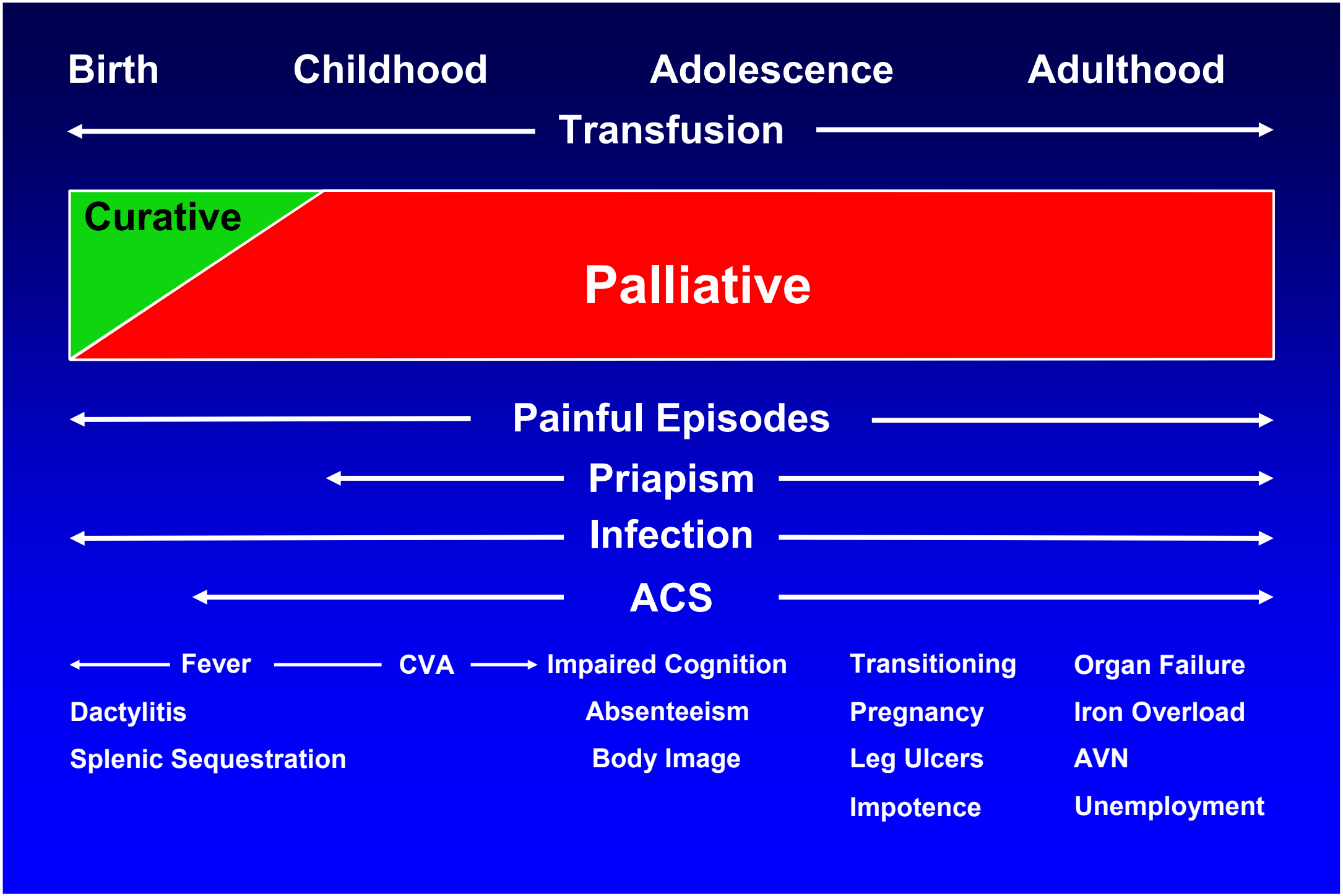
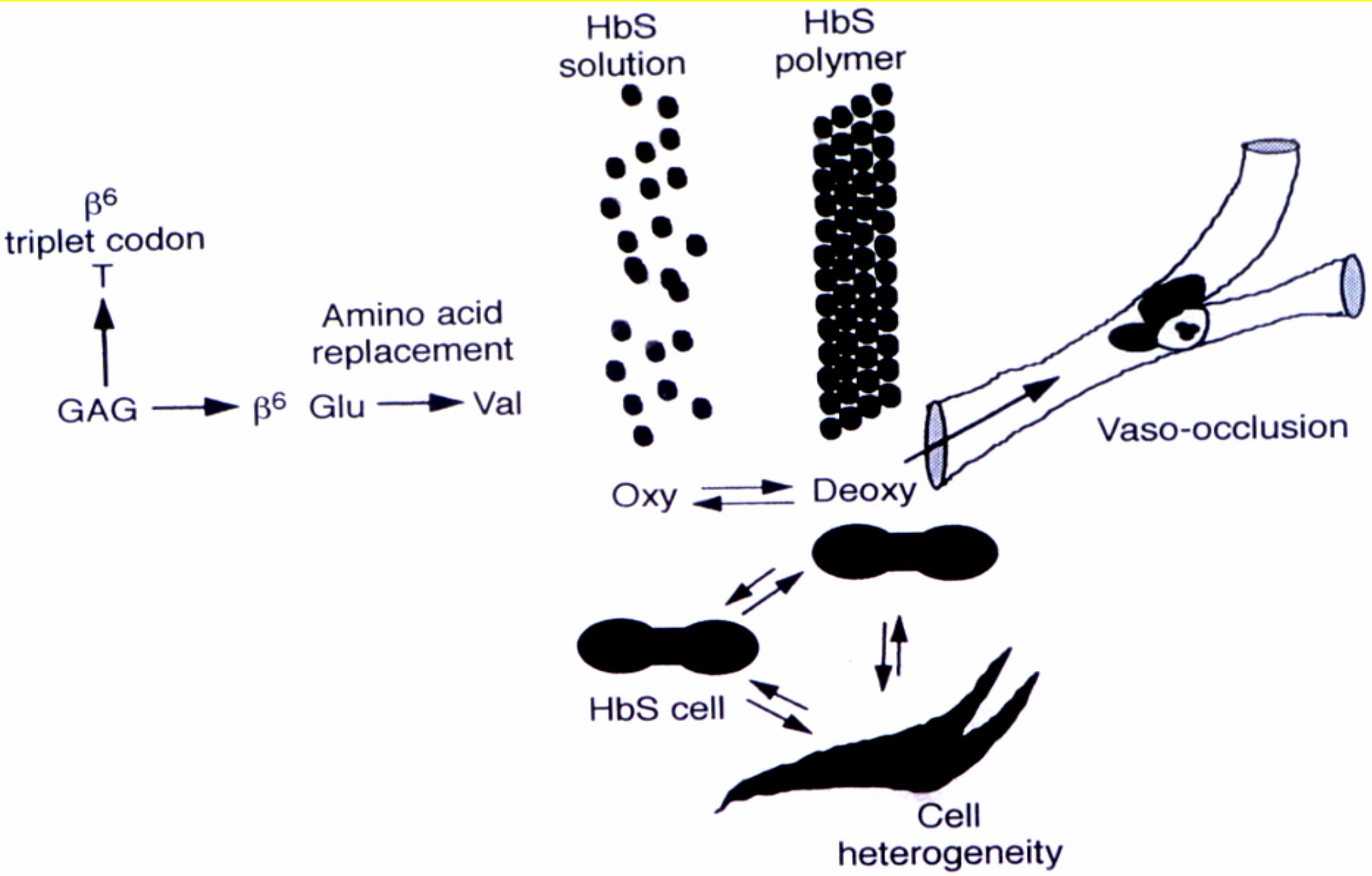
OBJECTIVES

- Review the Pathogenesis of Pain
- Describe Types of Sickle Cell Pain
- Present the Pharmacology of Pain Treatment
- Summarize Specific Approaches to pain Management
  - Outpatient Management
  - Management in the Emergency Room/Day Unit
  - Management in the Hospital

Sickle Cell Anemia
Morbidity Profile

- Anemia and its sequelae
- Pain Syndromes
- Organ Failure
  - *CVA, ACS, RF, etc.*
- Co-Morbidity


Birth
Childhood
Adolescence
Adulthood
Transfusion
Curative
Palliative
Painful Episodes
Priapism
Infection
ACS
Fever
CVA
Impaired Cognition
Transitioning
Organ Failure
Dactylitis
Absenteeism
Pregnancy
Iron Overload
Splenic Sequestration
Body Image
Leg Ulcers
AVN
Impotence
Unemployment


HbS
solution
HbS
polymer
β6
triplet codon
T
Amino acid
replacement
GAG
β6 Glu
Val
Vaso-occlusion
Oxy
Deoxy
HbS cell
Cell
heterogeneity

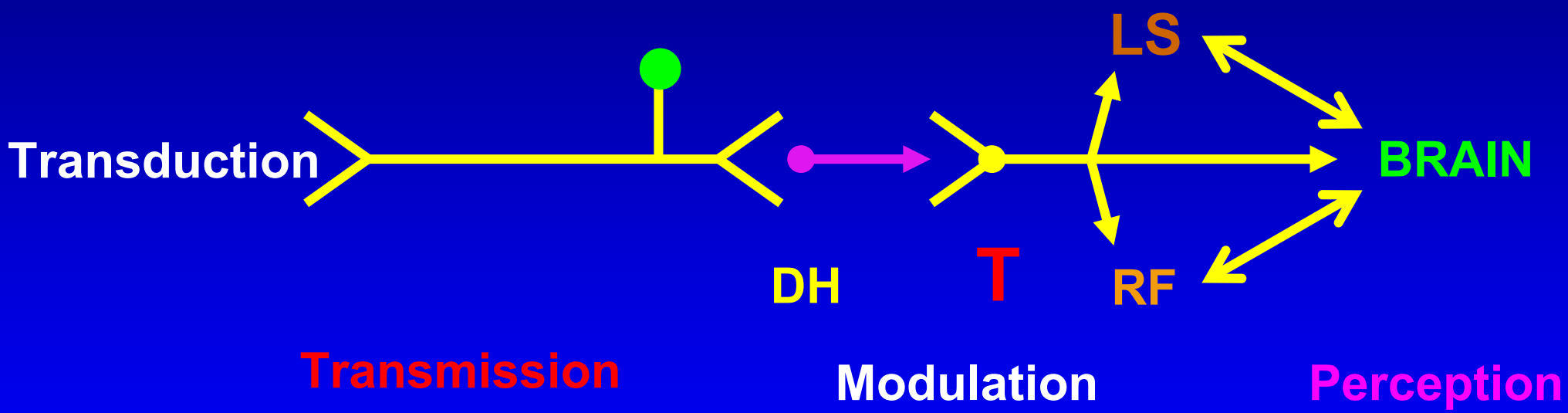
Sickle Cell Anemia
Pathogenesis

- Deoxygenation
- Polymerization
- Vaso-occlusion
  - Nociception (Tissue Damage)

Pain Pathogenesis

- Tissue Damage
- Transduction
  - Inflammatory mediators
  - Generation of pain impulse
- Transmission
- Modulation
- Perception

Molecular Mechanism of Pain



Sickle Cell Pain

Types & Pathogenesis

- Acute Pain
- Chronic Pain
- Neuropathic Pain
- Mixed

Sickle Cell Pain
Progressive Disease

Episodic — Chronic

Relapsing Remitting — Progressive

Sickle Cell Chronic Pain

- Pain with objective signs
  - » Avascular (aseptic) necrosis/Osteonecrosis
  - » Leg ulcers
  - » Chronic osteomyelitis
- Pain without objective signs
  - » “central sensitization”

Central Sensitization

Pain stimulates itself

This lowers the pain threshold

As a result ambient events cause pain

Psychobiology of Chronic Pain

Pain
Emotional Distress
Behavioral Dysfunction

Neuropathic Pain
Symptoms

- **Burning**
- **Tingling**
- **Shooting**
- **Lanci*nating***
- **ELECTRICAL**
- **Numb**
- **Paroxysmal**
- **Spontaneous**

Prerequisites *of* Effective *Pain Management*

- ***Know*** & ***believe*** the patient
- ***Know*** the ***disease***
- ***Know*** the ***pharmacology*** of analgesics
- ***Consider Alternative/Complementary RX***
- ***Consider Non-pharmacological RX***
- Education
- Legislation

Approaches to Pain Management

- Non-pharmacological
- Pharmacological
- Interventional
- Surgical

Non-Pharmacologic Management of Pain

- TENS
- Vibration
- Massage
- Heat or ice packs
- Menthol cream rub
- Therapeutic exercise
- Music
- Relaxation
- Diversion
- Meditation
- Self-Hypnosis
- Accupressure
- Accupuncture
- Biofeedback

Pharmacologic Management of Pain

1 - Non-opioids
2 - Opioids
3 - Adjuvants
4 - Complementary & Alternative Meds

*O*pioid **A**nalgesics

- μ **Agonists**
- **Mixed agonists/antagonists**
- **Partial agonists**
- **Antagonists**

Opioid Analgesics
μ Agonists

- Codeine
- Hydrocodone
- Oxycodone IR, CR
- Morphine IR, CR
- Hydromorphone
- Meperidine
- Fentanyl
- Oxymorphone
- Methadone (LA)
- Levorphanol (LA)

Opioid Analgesics

- **Partial Agonists**
  - Buprenorphine (Buprenex, Subutex)
  - Buprenorphine / Naloxone (Suboxone)
- **Mixed Agonists / Antagonists**
  - Pentazocine (Talwin, Talwin NX)
  - Nalbuphine (Nubain)
  - Butorphanol (Stadol, Stadol NS)

*O*pioid **A**nalgesics

μ Antagonists

- Naloxone *(Narcan)*
- Nalmefene *(Revex)*
- Naltrexone *(Revia)*

Opioids for Mild-Moderate Pain

Codeine	***(Tylenol 3, Tylenol 4)***
Oxycodone IR	***(Percocet, Percodan, Roxicet)***
Hydrocodone	***(Vicodin, Lorcet, Lortab)***

Opioids for Severe Pain

Equianalgesic Dosing

	parenteral	*po*
Morphine	10 mg	30 mg
Oxycodone (Oxycontin)	NA	30 mg
Hydromorphone (Dilaudid)	1.5 mg	7.5 mg
Levorphanol (Levodromoran)	2 mg	4 mg
Methadone	10 mg	20 mg
Fentanyl (Duragesic)	0.1 mg	NA
Meperidine	75 mg	300 mg
Oxymorphone	1.0 mg	5.0 mg

Methods of Administration of Opioids

Traditional / previously described methods

- PO, IM, IV, SC
- PCA, Nasal
- Transdermal, Transmucosal
- Epidural

Christensen et al – J P Hem/Onc 1996
Shaiova & Wallenstein – JNMA 2004
Yaster et al – Pediatrics 1994

Methods of Administration of Opioids

New recently described methods

- Iontophoresis with pt controlled delivery system
- Nebulization
- Implantable intrathecal delivery system; dose 1/100 of IV
- Topical

Koo et al – Am J Health Sys Pharm 2005
Ballas et al – Am JH 2004; Blood 2002
Smith et al – AJH 2005
Ballas et al – Blood (Suppl) 2004

Opioid Analgesics
Types of Formulations

Immediate Release

- For titration
- Acute pain
- Breakthrough pain

Controlled Release

- Maintenance treatment
- Chronic pain

Metabolism of Codeine

Morphine

- Naturally occurring μ agonist opioid
- Hydrophilic
- Three formulations: IR, CR, SR
- Histaminergic
- Gold standard for CA pain
- Assosciated with ACS ?

Morphine

- **Metabolites: M3G, M6G**
- **M6G: 4 times more potent**
  - ***Accumulates in renal failure***
  - ***Has long half-life***
  - ***Is a potent analgesic***

Prevalent Symptoms due to Morphine Metabolite Toxicity

Opioid receptor (*morphine-6-glucuronide*)	Non-*opioid* receptor (*morphine-3 glucuronide*)
Drowsiness	Impaired cognitive function
Nausea and emesis	Myoclonus, seizures
Coma	Hyperalgesia
Respiratory depression	---

Pharmacokinetics of Morphine

- Wide variability in patients with and without SCD
- Increased clearance during painful crises
- Increased clearance in children before puberty
- Increased clearance may be related to anemia, renal or hepatic blood flow

Dampier et al 1995

Faura et al 1996

Methadone

- Potent μ-opioid agonist
- Long half-life
- Short duration of analgesia (*4-6h*)
- Racemic mixture L&D isomers
  - *L-isomer: μ agonist + NMDA antagonist*
  - *D-isomer: NMDA antagonist*
- Inhibits re-uptake of serotonin & NE
- Least expensive opioid

Methadone

- Provides pain relief for 4-6 hrs
- Maintains significant serum level and suppresses heroin/opioid craving for 24hrs
- Methadone related death rose by 390% between 1995 and 2004
- The rise in all poisoning deaths rose only 54% in the same period

Most Commonly Prescribed Drugs with Potential for QT Prolongation

- Clarithromycin
- Erythromycin
- Levofloxacin
- Fluoxetine
- Amitriptyline
- Sertraline
- Salmeterol
- Sumatriptan
- Venlafaxine
- Indapamide
- Doxepin
- Tamoxifen
- Imipramine
- Risperidone

Fentanyl

- Approved formulations
  - Oral transmucosal fentanyl citrate
  - Fentanyl effervescent buccal tablet
  - Transdermal fentanyl
  - Parenteral fentanyl

Oxymorphone

- Numorphan IM, SC, Supp
- IR, CR oral formulations (Opana, ER)

Adjuvants

- Antihistamines
- Anti-depressants
- Anti-convulsants
- Benzodiazepines
- Phenothiazines
- GABA-B Agonist (***Baclofen***)
- α-2 Agonist (***Clonidine***)

Antidepressants and Priapism

Trazadone/Desyrel	+4
SSRI's	+2
TCA	+1
Wellbutrin (Bupropion)	0
Serzone/Nefazodone	0
Remeron (Mirtazapine)	0

Opioid Therapy of Sickle Cell Pain

Side Effects

- Nausea
- Allergy
- Myoclonus
- Sedation
- Respiratory Failure
- Vomiting
- Constipation
- Seizure
- Mental Changes

Common Terms (Cont.)

Addiction: Pattern of compulsive drug use characterized by continued craving for an opioid and the need to use the opioid for effects other than pain relief

Physical Dependence: Physiologic phenomenon characterized by the development of withdrawal syndrome following abrupt discontinuation of therapy

Tolerance: Increasing amount of an opioid is required to produce the same effect as was produced with previous lesser dose

Pseudoaddiction

- Drug-seeking behavior due to poor response to opioids or to low dose of opioids
- Patients may be falsely labeled as addicts and be under-treated for pain when opioids are indicated
- Such behavior is corrected by adequate pain relief including adequate prescribing of opioids

Sickle Cell Pain

Management Places

- Clinic
- Emergency Room
- Day Unit
- Hospital

Sickle Cell Pain
Management in Clinic

- Baseline Data include:
  - History and Physical Exam
  - Past History / Family History
  - Known Complications
  - Medications
  - Comprehensive Lab Data

Sickle Cell Pain

Management in Clinic

- Collection of Baseline Data
- Treatment plan in the ER, Day Unit, Hospital
- Prescribe analgesics if needed
- Education

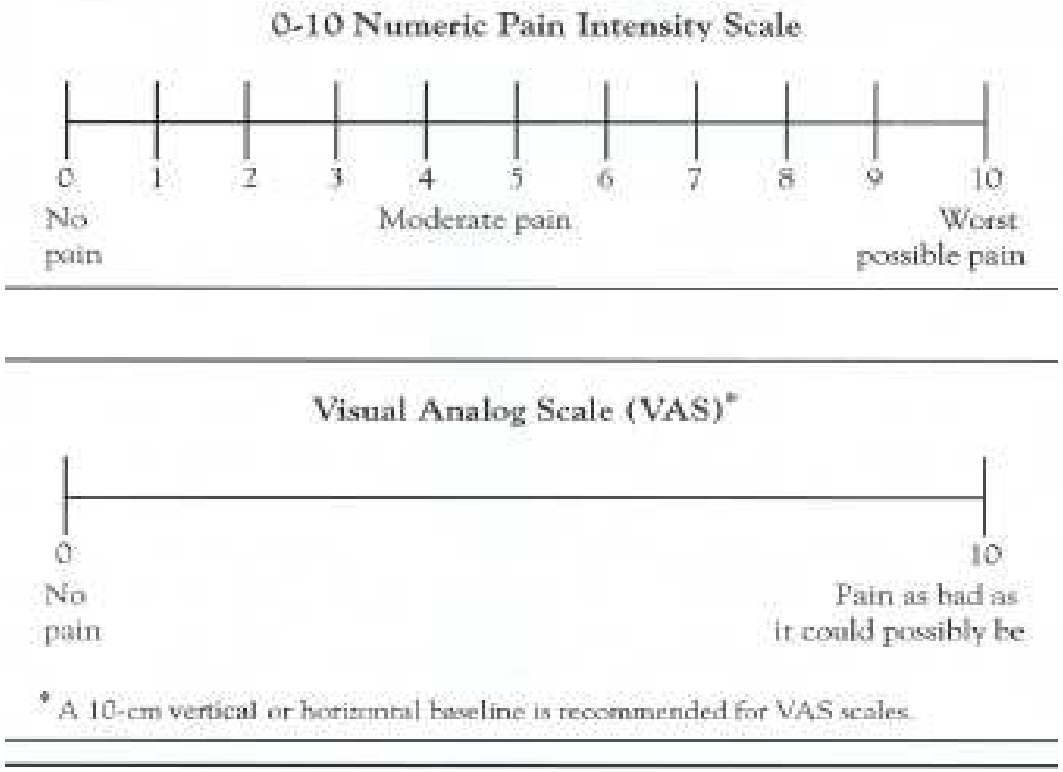
Sickle Cell Pain

Management in Emergency Room

- Assessment
- Individualize Treatment
  - Refer to treatment plan
- Give analgesics IV every two hours for a total of 3 doses
- Give Adjuvants
- If the pain is resolved, discharge
- If pain persists, admit to hospital
- Treat underlying cause if found

Pain Assessment

Figure 2. Examples of Pain Scales



Pain Assessment Goals

- **Quantify & Observe**
  - Pain intensity
  - Relief
  - Modify factors
  - Location
- Trigger
- Mood
- Sedation
- Outcome

Sickle Cell Pain

Management in the Day Unit

- Assessment
- Individualize Treatment
  - Refer to treatment plan
- Give analgesic bolus IV, evaluate every 30 min and give maintenance
- Give Adjuvants
- Discharge within 6 hours

Types of Painful Episodes of Hospitalized Patients with SS

- Isolated acute painful episode
- Acute painful crisis superimposed on a chronic pain syndrome
- Complicated acute painful episodes (example: acute pain & ACS, etc…)
- Neuropathic pain may coexist with any of the above

Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Believe the patient.
- Determine the patient's therapeutic goal
- Conduct thorough clinical assessment.
- Select the appropriate opioid analgesic, its dose, and frequency of administration based on previous experience.

Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Administer opioid analgesics parenterally (preferably IV) on a regular basis usually every 2 hours in adults (maintenance dose).
- Give non-opioid analgesics and adjuvants in combination with opioid analgesics. NSAIDs are contraindicated in the presence of impaired renal and/or hepatic function and history of gastropathy or asthma
- Monitor sedation and vital signs with special attention to the respiratory rate.

Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Assess pain severity every 30 minutes.
- Give rescue doses (25-50% of maintenance dose) for breakthrough pain every 30 minutes if adequate pain relief is not achieved.
- If three or more rescue doses are needed in 24 hours or less increase the maintenance dose by 25-50% and follow the same procedure of assessment and dose adjustment.

Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- Decrease or skip maintenance dose in the presence of severe sedation or if RR <10/min.
- After 2-3 days of therapy decrease the maintenance dose by 25% every 24 hours and replace with an oral opioid in divided doses on a regular basis.

Treatment of Acute Sickle Cell Pain in the Hospital

Fixed Schedule of Parenteral Analgesia with Rescue Doses

- After **24-48 hours** the oral opioid may be given as needed. If pain relapses escalate the dose into its previous level of administration.
- **Patients may be discharged if they are pain free with no co-morbid condition or if pain is adequately controlled with oral analgesics.**
- Design a discharge plan with follow up as an outpatient.

Management of Painful Crisis in the Hospital

- Key Steps
  - Fixed Schedule
  - PCA Issues
    - Titration to relief
    - Basal dose
    - Lock out dose / Interval
    - Weaning
    - Switching to Orals

Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Believe the patient.
- Determine the patient's therapeutic goal.
- Administer IV boluses of either morphine (2.5-10mg) or hydromorphone (0.5-2mg) every 10-15 min. Meperidine (10-25mg) is used only in patients who are truly intolerant of morphine or hydromorphone.

Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Reassess the patient's perception of pain 10 min after each bolus. Continue to administer intravenous boluses every 10-15 min until either the pain scale is decreased 50%, the pain is relieved, or the patient is sedated. The total loading dose of opioid should be recorded to document the demand dose.
- Start pain controlled analgesia (PCA) by using 50% of the demand dose of opioid that was used in loading the patient to be delivered with a 6 min lockout interval. Reassess the patient's perception of pain every 4-8hrs.

Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Encourage the patient to control their own pain by reinforcing the quantity of opioid that they can deliver as needed and the equivalent potency when converting from meperidine to morphine or hydromorphone.

Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- Determine the hourly use of opioid during the day and give 66% of the hourly dose as a continuous infusion at night to ensure rest.
- On day 2 or 3 of hospitalization replace by an equivalent oral dose of opioid analgesic on a fixed schedule around the clock and decrease the PCA dose by 25% every 24 hours.

Treatment of Acute Sickle Cell Pain in the Hospital

Suggested Scheme for PCA in Treatment of Acute Sickle Cell Pain

- After 24-48 hours, the PCA can be discontinued. Oral breakthrough doses can be administered between fixed doses of oral analgesics.
- Patients may be ready for discharge if they are pain free or if their pain is adequately controlled with oral analgesics.
- Taper the opioid after discharge over the following 1-2 weeks to prevent symptoms of the abstinence syndrome.
- Resume control of chronic pain utilizing the 3 Step Analgesia Ladder if indicated.

Management of Acute Pain Superimposed on Clinical Pain

- Keep meds for chronic pain as taken
  - May D/C short acting opioids
- Follow steps for episodic acute pain
- Extra caution

Management of Painful Crisis in the Hospital

- Key Steps
  - Prevention of withdrawal
  - Discharge planning
  - Follow-up

Prevention of Withdrawal Syndrome

Methadone

Clonidine