Multiple Myeloma –what is new ?

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Background:

- Multiple myeloma is a malignancy of plasma cells .
- Accounts for aproximately:1% of all cancer & 10% of all haematologic malignancies.
- Slightly more common in men
- Twice more common in blacks than in white
- Median age of presentation : about 65 years

Risk factors

- Age>60.
- Exposure to pesticides (DDT)
- Radiation
- Wood,leather,metal sheet & nuclear industry worker .
- Kaposis sarcoma herpes virus

Clinical manifestations

- Bone disease –main cause of morbidity
  - -bone pain
  - -osteoporosis
  - -osteolytic lesion
  - -pathologic fracture

Clinical manifestations contd….

- Others-
  - ✓ Anemia
  - ✓ Hypercalcemia
  - ✓ Renal failure
  - ✓ Increased risk of infection

Mechanism of disease

- Plasma cell proliferation→ anaemia, bone marrow suppression, infection risk
- Osteoclast → bony lesions, fracture, vertebral collapse, spinal cord compression

Mechanism of disease cont..

- Paraprotein, hypercalcemia → renal failure
- Hypercalcaemia→ polyurea, thirst, drowsiness, coma

Progression

- Asymtomatic-pre-malignant stage

Monoclonal gamopathy of undetermined significance(MGUS)

- Present in

-3% in people over 50 years of age

-progresses to MM-1% per year

SMM

- Smoldering multiple myeloma

  progresses to MM

  10% per year - 5 years

  3% per year-5years & 1.5 peryear thereafter

Diagnosis

- For diagnosis:

  both criteria must be met:

1. Clonal bone marrow plasma cells >10% or biopsy proven bony or extra medullary plasmacytoma

Diagnosis Contd….

2. Any one or more of the following myeloma defining events(MDE):

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

Diagnosis Contd..CRAB:

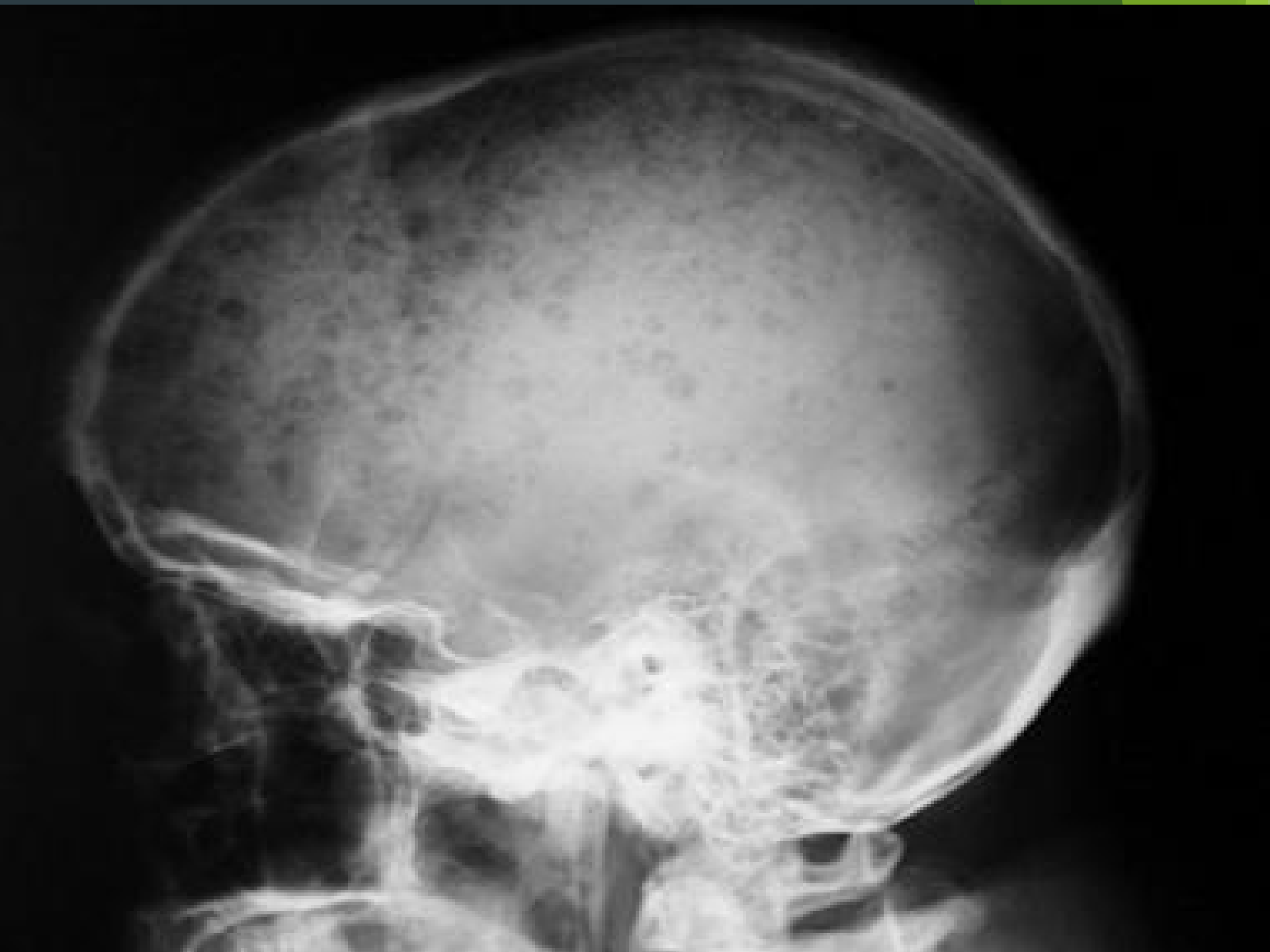
- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L(>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 Imol/L (>2 mg/dL)

CRAB: contd…..

- Anemia: hemoglobin >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL
- Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), PET-CT

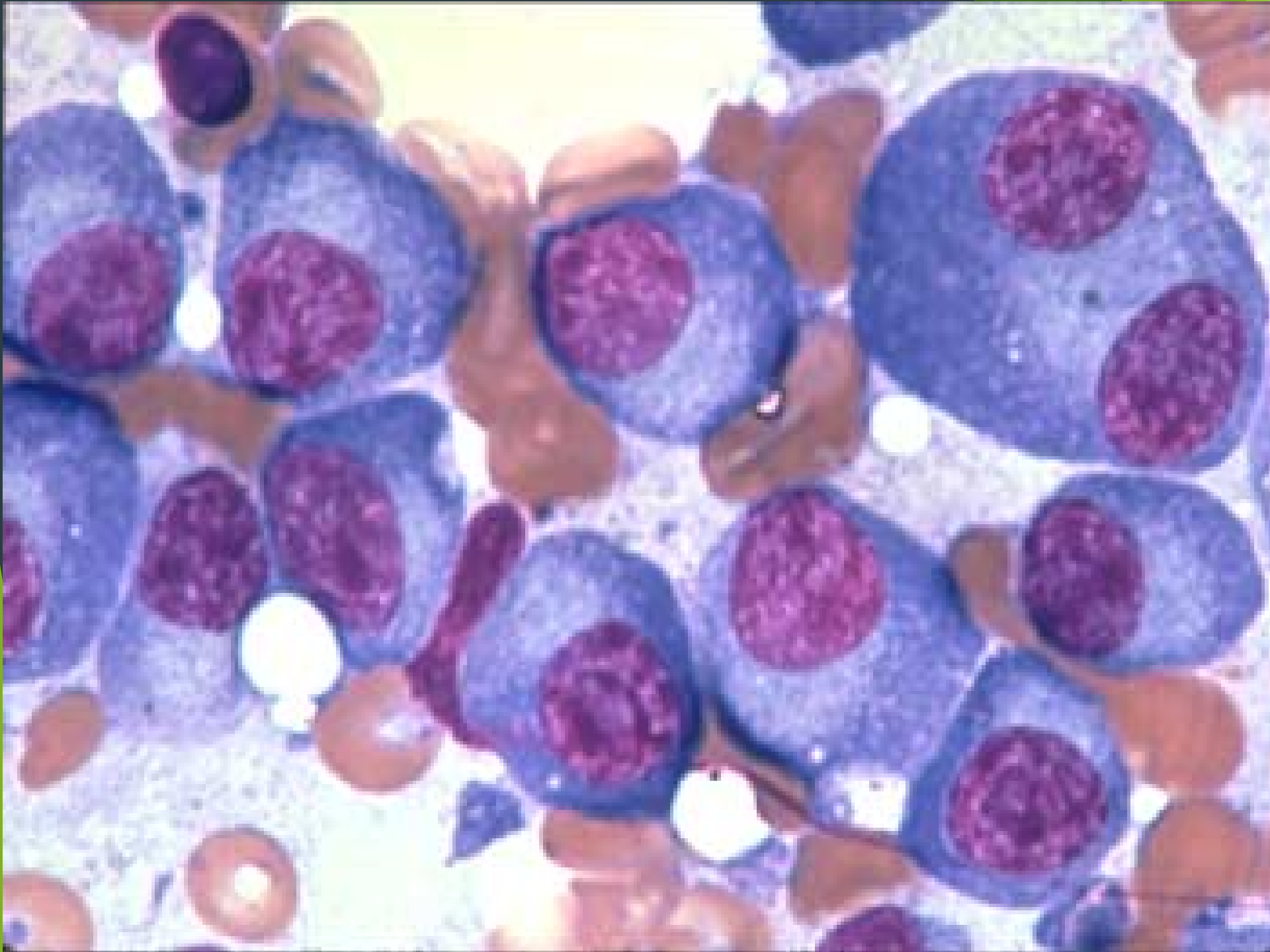
Bone lesion

- Unlike other malignancies that metastasize to bone,
- the osteolytic bone lesions in multiple myeloma exhibit no new bone formation.



Biomarker

- Clonal bone marrow plasma cell percentage 60%
- Involved: uninvolved serum free light chain (FLC) ratio 100 (involved free light chain level must be 100 mg/L)
- 1>focal lesions on MRI(at least 5mm in size)



Bone marrow studies

- Conventional
- Fluorescent in situ hybridization(FISH)
- Probes designed to detect t(11;14),t(4;14),t(6;14),t(14;16),t(14;20),
- trisomies,& del(17p)
- Conventional karyotyping

To assess treatment response

- Patient should be tested for the presence of
- M proteins using a combination of serum protein electrophoresis(SPEP)
- serum immunofixation (SIFE)
- the serum free light chain(FLC) assay.

Molecular basis

- Although multiple myeloma is still considered a single diseases,
- it is in reality a collection a of several different cytogenetically distinct plasma cell malignancies.

Staging of Myeloma

Durie-Salmon system

clinical stage of disease (stage I, II, or III) is based

- levels of M protein,
- number of lytic bone lesions,
- hemoglobin values and
- serum calcium levels.

Stages are further divided (A/B) according to renal function

International Staging System (ISS)

new, simpler, more cost-effective

- beta 2-micro globulin (β_2-M) and
- albumin

Stage	Durie-Salmon Criteria	ISS Criteria
I	· Hb >10 g/dL · S. Ca^{++} ≤12 mg/dL · x-ray, normal bone stru. or solitary bone plasmacytoma · Low M-component production rate — (IgG <5 g/dL; IgA <3 g/dL) · Bence Jones protein <4 g/24 h	β_2-M < 3.5 mg/dL and albumin ≥3.5 g/dL
II*	Neither stage I nor stage III	Neither stage I nor stage III
III	·Hb <8.5 g/dL ·S. Ca^{++} >12 mg/dL ·Advanced lytic bone lesions ·High M-component production rate — (IgG>7 g/dL; IgA>5 g/dL) ·Bence Jones protein >12 g/24 h	β_2-M ≥ 5.5 mg/dL

*Stage II = β_2-M <3.5 or β_2-M 3.5 – 5.5 mg/dL, and albumin <3.5 g/dL

sub classification **A)** S. Creat.<2.0 mg/dl &
B) S. Creat.>2.0 mg/dl

Risk Stratification for Multiple Myeloma

Risk group	**Percentage of newly diagnosed patients with the abnormality**
Standard Risk trisomies t(11:14) t(6;14)	75%
Intermediate Risk t(4;14) Gain(1q)	10%
High Risk t(14:16) t(14;20) del(17p)	15%

Major treatment regimens in multiple myeloma

- Melphalan- Prednisone(MP)
- Thalidomide- Dexamethone(TD)
- Pomalidomide- Dexamethasone(Pom/Dex)
- Bortezomib- Dex(VD)s
- Melphan-Prednisdne- Thalidomide(MPT)
- Bortezomib-Melphalan- Prednisone(VMP)

Major Treatment Regimens in Multiple Myeloma

- Bortezomib-Thalidomide-dexamethasone(VTD)
- Bortezomib-cyclophosphamide dexamethasone(VCD)
- Bortezomib-lenalidomide-dexamethasone(VRD)

Major Treatment Regimens in MM cont…

- Carfilzomib- linalidomide-dexamethasone(KRD)
- Carfilzomib- cyclophosphamide-dexamethasone(CCyD)
- Daratumab
- Elotuzumab- lenalidomide-dexamethasone
- Panobinostat- bortezomib

Bortezomib

- A novel first-in class proteasome inhibitor
- Effects- antimyeloma effects by
- Disruption of cell cycle
- Induction of apoptosis
- Alteration of bone marrow microenvironment
- Inhibition of nuclear factor kappa B(NFkB)

Older Treatment

- Melphalan plus prednisone

Newer Treatment

- High dose chemotherapy +auotologous stem cell transplantation(HDT-ASCT)

- Novel agents:
  - Bortezomib
  - Linalidomide
  - Thalidomide plus Corticosteroids

HDT-ASCT

- Higher rate of complete response(CR)
- Prolong progression free survival(PFS) and
- overall survival(OS) is better

Bad prognosis if…

- Raised B2-microglobulin >4.
- Low serum albumin <3g/dl.
- Cytogenetics –**ch13 deletion, hypodiploidy, T(4:14)**
- Raised LDH, CRP, Cr.
- Low platelet <150 and Hb<100.
- Bone marrow plasma cell percentage ≥ 50%
- Age >70.

Goals of MM Therapy

- Goals of treatment
  - Address pain relief & other disease symptoms
  - Control disease activity
    - prevent further organ damage
  - Debulk tumor and use internal fixation augmented with methacrylate
  - Joint arthoplasty
  - Prolong overall survival
  - Preserve normal performance

Other treatment / Supportive care

- Radiotherapy
- Surgery
- Bone care – bisphosphonates
- Transfusions
- Growth factors
- Treatment and prevention of infections
- Monitoring, management and prevention of s/e

Thanks