IMPLEMENTATION OF A RAPID RESPONSE FEVER PROTOCOL FOR IMMUNOCOMPROMISED PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

A Quality Improvement Initiative at the University of Colorado Hospital

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OBJECTIVES

• To discuss risk factors associated with fever and infection in the immunocompromised host
• To describe the significance of fever and infection in oncology patients
• To discuss initial strategies for fever management in oncology patients
• To discuss Rapid Response Fever Protocol implementation in immunocompromised patients
WHY DO WE CARE ABOUT FEVER???

- 80% of patients with a heme malignancy will develop FEVER
- 10-40% of solid tumor oncology patients will develop FEVER
- FEVER is a sign of INFECTION
- FEVER is a sign of SEPSIS
- FEVER may be the ONLY sign of INFECTION and impending SEPSIS
- SEPSIS may progress to SHOCK and DEATH
WHY DO WE CARE ABOUT SEPSIS???

- Sepsis is the 10th leading cause of death in the United States
- Mortality rate nearly 30% and >50% in cancer patients
- Leading cause of non-relapse mortality in patients with cancer
- 1 out of 10 admitted with neutropenic fever will die of SEPSIS
- FEVER may be the only sign of SEPSIS in oncology patients
- Serious infections cause delays in cancer treatment
- Serious infections impact quality of life, survival and cost
WHO IS AT RISK FOR SEPSIS???

- Immunocompromised patients
  - Innate
  - Adaptive/acquired
- Neutropenia
  - Chemotherapy
  - Medications
  - Bone marrow failure
- Immunosuppression
  - Chemotherapy
  - Targeted therapies/monoclonal antibodies
  - GVHD treatment
RISK FOR SEPSIS Cont’d…

- The very young (<1 yr)
- The old (>65 yr)
- Those with comorbidities
  - Diabetes
  - Lung disease
  - CHF
  - Psychological instability
  - Recent surgery/invasive/dental procedure
  - Lines and devices
  - Immobility/wounds
DISEASE AND TREATMENT CONSEQUENCES

• Breakdown of mucocutaneous barrier
  • Tumor invasion
  • Surgical intervention
  • Chemotherapy
  • TBI/localized XRT
  • Lines/tubes
  • GVHD

• Cellular destruction
  • Phagocytes
  • B/T-cells/Asplenia
  • Disease

• Neurologic/functional/nutritional impairment
CAUSES OF FEVER

- Variety of infections
- Medications
  - Antibiotics
  - Chemotherapy
  - Monoclonal Abs
  - ATG
- Malignancy
- Inflammatory conditions
  - GVHD
  - Connective tissue disorders
- Endocrine disorders
- Vaccines/blood products
INFECTIOUS CAUSES OF FEVER/SEPSIS

• Gram negative bacteria
  • Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, etc.
  • Account for 40-50% of septic shock
  • Typically more pathogenic

• Gram positive bacteria
  • Streptococcus pneumoniae, Staphlococcus aureus, enterococcus
  • Account for 5-10% of septic shock
  • Typically less pathogenic

• Yeast/Fungal organisms
  • Candida, Aspergillus, Zygomycetes

• Viral

• In 20% of septic shock, organism not identified
SIGNS AND SYMPTOMS OF INFECTION

- **Physical Exam/ROS**
  - **Vital Signs** - HR, RR, BP, O2
  - **General** - ill appearance, fever, chills
  - **CNS** - lethargy, headache, disorientation, somnolence
  - **HEENT** - sinus, oral lesions, thrush, esophogitis
  - **Cardiopulm** - murmurs, tachy, cough, sputum, SOB, abn lung sounds, tachypnea, hypotension, dec. SaO2
  - **Abdomen** - tenderness, distension, hypoactive BS, N/V/D
  - **GU** - urgency, freq, burning, hematuria, flank pain, dark urine, N/V, decreased urinary output
  - **Skin** - rash, wounds, erythema, drainage, IV’s, foleys, lines, etc.
FEBRILE NEUTROPENIA (FN)

• Definition
  • FEVER \( \geq 38^\circ\text{C} \) (oral) on 2 occasions 1 hour apart OR a single temperature of \( \geq 38.3^\circ\text{C} \)

  AND

  • ANC of <500cells/mm³ or an ANC expected to decrease to <500cells/mm³ during next 48 hrs.

• Oncologic EMERGENCY

• An analysis of >40,000 patients admitted with FN (1995-2000)
  • Mortality rate is nearly 10% among all cancer patients hospitalized with FN
  • Highest mortality 14.3% in leukemia
  • Mortality 21% in patients with >1 comorbidities
  • Average length of FN hospital stay (LOS) was 11.5 days
  • Average length of FN LOS for leukemia was 19.7 days

IDSA, 2010; Kuderer, et al. (2006)
FEBRILE NEUTROPENIA COST/LOS

- Kuderer analysis (n=55,276 encounters) - mean cost $19,110 ($1,661/day)
  - Mean leukemia FN cost $38,583 ($1,958/day)
- Caggiano analysis (n=22,060) - mean heme malignancy cost $20,400 ($1,594/day)
  - Mean leukemia FN cost $28,200 ($1,669/day)
- Shilling analysis (n=3,814) - mean hospitalization cost $18,042-$27,587 ($2,004-$2,189/day)
  - Mean cost for hematologic malignancies $52,579 ($2,590/day)

Kuderer, et al., 2006; Shilling, Parks, Deeter, 2011; Caggiano, et al., 2005
HOW DO WE PREVENT INFECTION???

- Minimize exposure
  - Hand hygiene (patients, caregivers, staff)
  - Masks
  - Avoid crowds and ill contacts
  - Food restrictions
  - HEPA filtration
  - Positive pressure
  - Environmental exposures (plants, flowers, soil, dust, etc.)
- Prophylactic/Empiric antibiotics
- Myeloid growth factors
The PROBLEM:
- HUGE antibiotic delays
- HUGE delays in supportive care
- HUGE delays in order entry procedures

WHERE?
- EVERYWHERE!!
- ED
- Clinics
- Infusion Centers
- Express Admit Units
- Inpatient Units
SYSTEM STRATEGIES FOR TIMELY INTERVENTIONS

- #1 Rapidly **identify** patients at risk for sepsis
- #2 Rapidly **triage** patients at risk for sepsis
- #3 Rapidly **treat** patients at risk for sepsis

Rapid Response Treatment Protocols
DOES TIMELINESS REALLY MATTER???

• Timeliness of interventions makes a difference!!
  • reduces morbidity
  • reduces mortality
  • reduces hospital LOS
  • reduces ICU interventions
  • reduces healthcare cost
EVIDENCE SUMMARY
“EARLY INTERVENTION”

• Rivers et al. Landmark Study (2001)
  • Lower 28 and 60 day mortality rates
  • Reduced hospital LOS
  • Lower healthcare associated costs

  Early goal-directed anti-sepsis interventions reduce mortality and associated cost

• Kumar, et al. (2006)
  • 7.6% decrease in survival for each hour delay in antibiotics
  • 82.7% survival when antibiotics within 30 minutes
  • 77.2% survival when given within 1 hour
  • 42% survival when delayed for >6 hours

Timeliness of antibiotics improves survival

Rivers et al. (2001); Kumar, et al.
EVIDENCE SUMMARY

“ANTIBIOTIC APPROPRIATENESS”

• Gaieski, et al. (2010)
  • Improved survival when appropriate antibiotics given within 1 hour vs. >1hr (mortality 19.5% vs. 33.2%, p=.02)
  • Improved survival when given within 1 hour of qualification for EGDT vs. >1hr from EGDT qualification (25% vs. 38.5%, p=.03)

Timeliness and appropriateness of antibiotics improves survival

• Kumar, et al. (2009)
  • Appropriate antibiotic therapy in 80.1% of cases
  • Overall survival 43.7%
  • Survival after appropriate and inappropriate initial antibiotic therapy 52% vs. 10.3%, p<.0001.

Inappropriate antibiotic therapy in sepsis adversely affects survival

Kumar, et al. (2009); Gaieski, et al. (2010)
EVIDENCE SUMMARY

“CLINICAL PRACTICE GUIDELINES”

- Surviving Sepsis Campaign
- National Comprehensive Cancer Network (NCCN) Guidelines
- Infectious Disease Society of America (IDSA) Guidelines
- American Society of Clinical Oncology (ASCO)
- National Collaborating Centre for Cancer (NCC-C; NICE)

CPG’s recommend prompt interventions to reduce morbidity and mortality related to infection

NCCN (2012); Flowers, et al. (2013); Freifeld, et al. (2010); Bullinaria, et al. (2010); NICE (2012)