Studying the relationship between procalcitonin and CRP with prognosis of children admitted with fever and neutropenia at oncology ward

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INFECTIOUS COMPLICATIONS in CANCER PATIENTS

- Oncologic treatment affects both innate immunity, such as skin and mucosal barriers, as well as adaptive immunity, such as pathogen-specific B- and T-cell response.
- Factors leading to infection susceptibility include:
  - Underlying disease: hematologic malignancy, advanced-stage lymphoma, progressive disease and patients undergoing hematopoietic stem cell transplant (HSCT) being at highest risk.
  - Type of therapy: dose-intensive therapies such as high-dose cytarabine, AML induction, and HSCT.

INFECTIOUS COMPLICATIONS in CANCER PATIENTS

- Degree and duration of neutropenia with profound neutropenia defined as absolute neutrophil count (ANC) <100 /mm3 and prolonged neutropenia defined as lasting >7 days.
- Disruption of normal skin and mucosal barriers.
- Malnutrition.
- Defects in humoral immunity leading to risk of encapsulated bacteremia.
- Defects in cellular immunity (either at baseline or secondary to therapy) leading to susceptibility to viral, fungal, and some bacterial infections (especially those replicating intracellularly).
- Colonizing microbial flora.
- Foreign bodies; for example, CVCs and ventriculoperitoneal (VP) shunts.

MANAGEMENT OF INFECTIOUS COMPLICATIONS

- Critical and emergent assessment will direct the initial risk stratification and subsequent diagnostic evaluations.

Important initial questions and examinations include:

- Height of fever: fever >39.0C has been noted as an independent risk factor for serious bacterial infection.
- Presence of rigors or chills with central line flushing.
- Recent chemotherapy or radiation therapy (RT).
- Current medications (i.e., antimicrobial prophylaxis).
- Possible infectious exposures at home or school or with recent travel.
- Prior history of documented infections.
- Thorough physical examination with particular consideration for oral and perirectal mucosa, CVC access site, skin, and sites of any invasive procedure.

Febrile Neutropenia

- Febrile Neutropenia (FN) is defined by the following criteria:

  A single oral temperature ≥38.3C (101.0F) or an oral temperature ≥38.0C (100.4F) sustained for >1 h or that occurs twice within a 24-h period.

  An ANC <500/mm3 or ANC <1000 /mm3 expected to decrease to <500 /mm3 over the subsequent 48 h.
- Families should be advised against taking rectal temperatures.
- Recent consumption of hot or cold beverages should not alter management if the patient has had a documented oral temperature taken.
- Alternate routes for fever measurement, including axillary, otic, and temporal, should discouraged but all should be managed in the same manner if there is a documented fever.

Initial FN evaluation should include the following:

- Complete blood count with differential.
- Complete metabolic panel.
- Blood cultures from each lumen of the CVC or peripheral cultures if without a CVC (≥1 ml of blood).
- Clean-catch bacterial urine cultures (urine catheterization should not be done, especially in the neutropenic patient).
- Gram stain and culture from suspicious skin, oropharyngeal, or CVC sites.

Additional measures that may be considered but are not routinely recommended include:

- Peripheral blood cultures in addition to central cultures can be considered as a means to determine bacteremia versus CVC infection based on the differential time to positivity.
- Coagulation studies in the patient with bleeding.
- Chest radiography is not routinely recommended and should only be done in the patient with respiratory compromise, symptoms of pulmonary infection, or auscultatory signs.
- Patients with sinus tenderness should have computed tomography (CT) of the sinuses.

Additional measures that may be considered but are not routinely recommended include:

- Patients with esophagitis should be considered for endogastroduodenoscopy with biopsy and culture to rule out viral and fungal causes.
- Patients with diarrhea should have a stool sample sent for culture, rotavirus, and Clostridium difficile testing.
- Lumbar puncture is rarely indicated but if the patient has central nervous system (CNS) signs a head CT should be performed first to rule out mass lesions or hemorrhagic stroke which may lead to increased intracranial pressure.
- Shunt fluid examination from implanted devices such as VP shunts or Ommaya reservoirs is rarely indicated.

CRP and Procalcitonin

- Clinicians are searching for a marker which may add to exclusion or diagnosis of relevant infection underlying neutropenic fever.
- The rise of such a parameter should ideally precede the date of significant microbiologic findings or justify additional intensive search for a focus of infection even in patients without pyrexia.
- However, the literature concerning the significance of CRP, proinflammatory cytokines and soluble adhesion molecules in the clinical evaluation of neutropenic fever is surprisingly small.
- In the case of procalcitonin, available data look very preliminary.
- Furthermore, in case of CRP, it appears that the widespread view that its determination may add substantially to the clinical evaluation of neutropenic fever is not well founded by most clinical trials listed here.
- Most of the studies available demonstrate several limitations such as poor design and small size of the study population.

Serum and plasma parameters in clinical evaluation of neutropenic fever.
Südhoff T[1], Giagounidis A, Karthaus M.

CRP and Procalcitonin

- In septic critically ill cancer patients CRP concentrations are more elevated in those with neutropenia.
- However, the CRP course seems to be independent from the presence or absence of neutropenia.

C-reactive protein in critically ill cancer patients with sepsis: influence of neutropenia.

Póvoa P[1], Souza-Dantas VC, Soares M, Salluh JF.

- There remains a paucity of robust and reproducible data on the use of biomarkers in prediction of serious infection in children with FN.
- Available evidence suggests PCT has better discriminatory ability than CRP and that the role of serial biomarkers warrants further study.

An updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment of fever during neutropenia in children with cancer.

Haeusler GM[1], Carlesse F, Phillips RS.

CRP and Procalcitonin

- The PCT value is certainly helpful in guiding the physicians in clinical decisions and thus the better approach towards the management of **p**ediatric oncology patients with FN.

To Determine the Role of Procalcitonin in Febrile Neutropenic Episodes of Children Undergoing Treatment for Childhood Cancers

Purkayastha K, Seth R, Amitabh S, Xess I, Kapil A and Sreenivas V

- Elevated PCT levels are predictive of bacteremia.
- Using serial PCT levels within 24 hours allowed a better prediction of bacteremia than the PCT level at admission.

Serial procalcitonin levels to detect bacteremia in febrile neutropenia.

Reitman AJ, Pisk RM, Gates JV 3rd, Ozeran JD

CRP and Procalcitonin

- Serial measurement of PCT levels on a daily basis seems to be helpful for early prediction of severe bacterial infections, monitoring febrile episodes regarding response to antibiotic therapy, and early detection of complications in the infectious process.

Procalcitonin as an early marker of bacterial infection in neutropenic febrile children with acute lymphoblastic leukemia.

Hatzistilianou M[1], Rekliti A, Athanassiadou F, Catriu D

- PCT, when measured periodically, is a more useful diagnostic inflammation parameter in pediatric neutropenic-fever patients than CRP, both in estimating the severity of the infection and, the duration and origin of the fever. Hence, PCT might be helpful when deciding on initial therapy modification.

Role of procalcitonin and CRP in differentiating a stable from a deteriorating clinical course in pediatric febrile neutropenia.

Secmeer G[1], Devrim I, Kara A, Ceyhan M, Cengiz B, Kutluk T, Buyukpamukcu M, Yetgin S, Tuncer M, Uludag AK, Tezer H, Yildirim I.

STUDY DESIGN

- Objective:

  Studying the relationship between procalcitonin and CRP with prognosis of children admitted with fever and neutropenia at oncology ward

Materials and Methods

- 31 episodes of febrile neutropenia were enrolled.
- Admission labs: CBC, Electrolytes, B/C, U/A, U/C, CRP, Procalcitonin
- CXR (If clinically indicated)
- Variables: Duration of fever, Duration of hospitalization, Mortality

RESULTS

Age, Sex, …

- Mean age was 85.45 ± 54.64 mo (min 9 mo, max 178 mo)
- 16 male (51.6%) and 15 female (48.4%)
- 6 (19.4%) patients with defined focus of infection and 25 (80.6%) patients with undefined focus
- No POS B/C
- No mortality

Underlying Diseases

Underlying dis	No	%
AML	5	16.1
ALL	16	56.1
Hodgkin’s lymphoma	1	3.2
Lymphoblastic lymphoma	1	3.2
Burkitt’s lymphoma	2	6.5
Osteosarcoma	2	6.5
Ewing’s sarcoma	2	6.5
Neuroblastoma	1	3.2
Optic glioma	1	3.2
Total	31	100

Mean and SD of Duration of fever and Duration of hospitalization

Variable	Mean	SD	Min	Max
Duration of fever (day)	7.82	6.29	1	32
Duration of hospitalization (day)	11.52	10.87	3	53

Mean and SD of Biomarkers

Variable	Mean	SD	Min	Max
WBC /mm3	739.03	602.27	100	2400
ANC /mm3	351.78	338.28	30	756
CRP mg/dL	52.01	23.49	2	78

Procalcitonin Levels

Procalcitonon (ng/mL)	No. of Patients	% of Patients
< 0.5	12	38.7
0.5 - 2	8	25.8
2 - 10	6	19.4
≥ 10	5	16.1

Procalcitonin level and Duration of fever

Procalcitonin level (ng/mL)	No.	Duration of fever Mean± SD	P value
< 0.5	12	3 ± 1.6	
0.5 - 2	8	4.13 ± 2.7	
2 - 10	6	3.38 ± 2.64	
≥ 10	5	20.6 ± 11.10	< 0.001

Procalcitonin level and Duration of Hospitalization

Procalcitonin level (ng/mL)	No.	Duration of Hospitalization Mean ± SD	P value
< 0.5	12	6.67 ± 2.27	
0.5 – 2	8	8 ± 3.46	
2 – 10	6	7.5 ± 4.23	
≥ 10	5	29.6 ± 18.04	< 0.001

CRP level and Duration of fever

CRP level	No.	Duration of fever	P value
<10	3	3 ± 0.58	
>10	28	8.16 ± 6.64	0.45

CRP level and Duration of Hospitalization

CRP level	No.	Duration of hospitalization Mean ± SD	P value
<10	3	6.33±1.16	
>10	28	11.48±11.36	0.46

Discussion

- Recent studies have focused on the use of procalcitonin as a bacterial infection biomarker.
- Researches have shown that the levels of procalcitonin increase in children with sepsis and bacterial infection.
- An increase in procalcitonin levels may initially be diagnostic more than CRP.
- Numerous studies have shown the high sensitivity and specificity of procolitonin as a diagnostic marker for bacteremia.
- Therefore, the advantage of procalcitonin is early diagnosis, early choice of treatment and early recovery.
- CRP is an acute phase protein produced by hepatocytes and increases in response to systemic inflammation caused by infectious and non-infectious diseases.
- In many cases, increased leukocytes have also been reported as a nonspecific marker of systemic infection and tissue damage.

Discussion

- In the study of Giamarelos et al., the level of procalcitonin in the bacteremia group was 8.23 ng/ml, which was increased with the progression of the disease.
- One of the strengths of this study was the increase in procalcitonin levels in patients with bacteremia and severe sepsis, which provides a new perspective for the use of procalcitonin as a diagnostic tool for the severity of the disease and the need for antibiotic regimens.

Discussion

- Our study showed that children with high procalitonin levels experienced a longer duration of fever and hospitalization than those with lower levels of procalitonin, and this difference was statistically significant.
- Our study may be the first study to identify high procalitonin levels as a marker for long-term fever and hospitalization.
- The results of our study also showed that patients with severe sepsis had higher levels of procalcitonin than other patients, which was significant in procalcitonin but did not show a significant difference in CRP, which is consistent with the findings of Giamarelos et al.

Conclusion

- Procalcitonin might be an adjunctive biomarker in identifying severity of disease, duration of antimicrobial therapy and choosing the appropriate antibiotic for cancer patients with fever and neutropenia.
- Procalcitonin guided algorithms may limit the duration of antibiotic usage, reduce their adverse events and prevent the emergence of antimicrobial resistance.

Thank you