

Management of Infections in the Pediatric Oncological Patient

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Infection in cancer patients

- **History:**
 - **Gram- negative enteric bacteria were predominant flora in infected patients in the 1960s and 1970s**
 - **Gram- positive bacteria emerged since late 1970s**
 - **Reasons for this shift:**
 - **Not entirely known**
 - **Extended use of broad- spectrum antibiotics**
 - **Increase in number of CVLs**

Infection in cancer patients

- **History:**
 - **Viridans streptococci infection:**
 - **Inhabitants of the GI tract, oropharynx and female genital tract**
 - **Increased rate of infection with extended use of CVLs**
 - **Patients receiving TMP/ SMX and Cipro alone also developed S. viridans infection**
 - **Associated with the use of Ara- C in AML patients**
 - **Cefuroxime/ cefepime recommended for viridans strept. prophylaxis (ANC > 500), Vanc added if prior infection**

Impaired Host Immune Defense in Oncological Patients

- **Malignancy**
- **Disruption of natural barriers**
 - **Procedures (venipuncture, CVLs, BMAs)**
 - **Mucositis**
- **Alteration of endogenous flora**
 - **Exposure to medical settings and nosocomial microorganisms**

Impaired Host Immune Defense in Oncological Patients

- **Decrease nutrition and metabolic imbalance**
- **Extended use of antibiotics**
- **Chemotherapy**
 - **defects in cellular/ humoral immunity**
 - **defects in neutrophil number/ function**
 - **NEUTROPENIA (ANC < 500/ μ L)**
 - **DECREASED SPECIFIC FUNCTION**

Viral Infections

- **Respiratory viruses**
 - **Influenza, Parainfluenza, RSV, Adeno, Rhino**
- **Herpesviruses**
 - **CMV (pneumonia, enteritis, BMT infection)**
 - **HSV (retinitis, encephalitis)**
 - **HHV- 6/ HHV- 7 (pneumonia, encephalitis)**
 - **EBV (mononucleosis, infectious LPD)**
 - **VZV (pneumonia, meningoencephalitis, nephritis)**

Fungal infections

- **Non- neutropenic patients:**
 - *H. capsulatum, C. immitis*
 - *C. neoformans, B. dermatiditis*
- **Neutropenic patients**
 - **Candida spp.**
 - **Aspergillus spp.**

Clinical syndromes

- **Fever and neutropenia**
- **Infectious diarrhea (*C. difficile*, Rotavirus)**
- **Typhlitis and colitis**
- **Respiratory tract infections**
- **Oral infections**
- **Skin/ soft tissue infections**
- **Others (UTI, deep abscess, conjunctivitis)**

Respiratory infections

- **Etiology of pneumonia**
 - **Bacterial:** *S. pneumoniae*, viridans streptococci, Staphylococcus, Pseudomonas, enteric gram- negative spp, Legionella, Listeria, Nocardia, Mycobacterium, etc
 - **Viral:** CMV, VZV, HSV, HHV- 6, RSV, adeno, influenza and parainfluenza
 - **Fungal:** Aspergillus, Mucor, Candida, Histoplasma, Blastomyces
 - **Parasitic:** *P. carinii*, *T. gondii*, *C. parvum*

Respiratory infections

- **Influence of host immune status:**
 - **Newly- diagnosed patients: CAP germs**
 - **Patients after intensive induction and low ANC: gram- negative bacteria and fungi**
 - **Patients with oral/ endotracheal ulceration or obstruction and low ANC: oral and enteric flora, Pseudomonas and fungi**
 - **Hypogammaglobulinemia: S. pneumoniae, H. influenzae and P. carinii**
 - **Low cell immunity: Fungus, viruses, Mycobacterium, Strongyloides**

Respiratory infections

- **Pattern of lung infiltrate on Xray:**
 - **Lobar/ segmental infiltrate - bacterial infection:**
 - Gram- positive : *S. aureus*, *S. pneumoniae*
 - Gram- negative : *Klebsiella*, *Enterobacter*, *Serratia*
 - **Nodules with rapid growth/ cavitation - Fungal infection:**
 - *Candida*, *Aspergillus*, *Mucor*
 - *Blastomyces*, *Cryptococcus*, *Coccidioides*
 - **Diffuse infiltrate: *P. carinii* or viruses**

Respiratory infections

- **Definitive diagnosis:**
 - **Lab studies:**
 - **Sputum culture/ examination**
 - **Blood cultures**
 - **Immunology studies (Ag identification)**
 - **Biopsy studies:**
 - **Endotracheal tube aspirate / flexible endoscopy**
 - **Transthoracic needle biopsy**
 - **Open lung biopsy**

Respiratory infections

- **Treatment:**
 - **Start early with empiric therapy**
 - **Cover both G+ and G- species infection: Vanc, aminoglycosides, cephalosporines and carbapenemes**
 - **Provide TMP/ SMX coverage in case of *P. carinii***
 - **Adequate length of therapy:**
 - **2 weeks for bacterial infection**
 - **3 weeks for *P. carinii*, followed by prophylaxis**
 - **4- 6 weeks for fungal infection (normal XRay!)**

Gastro- intestinal infections (diarrhea)

- **Diarrhea can have multiple etiologies**
- **Phase I diagnosis:**
 - **Standard stool cultures: Salmonella, Shigella, *E. coli***
 - **Other cultures: Yersinia, Vibrio, Rotavirus, *C. diff* toxins**
 - **Microscopic exam: Giardia, Cripto, Cyclospora**
- **Phase II diagnosis:**
 - **Microscopic examination: MAI**
 - **UGI endoscopy with biopsy**
 - **Colonoscopy with biopsy**

Gastro- intestinal infections (diarrhea)

- **Treatment of diarrhea:**
 - **Treat fluid imbalance:**
 - **Replace fluid losses by i.v. route**
 - **Return to oral feeding ASAP**
 - **Specific therapy:**
 - **Give supportive therapy in case there is no etiologic agent**
 - **Treat with appropriate antibiotics if possible**
 - **Do not give anti- diarrheal agent to immunosuppressed patients (fever, bloody diarrhea)**

Typhlitis/ colitis

- **Definition:**
 - **Intestinal wall thickening to > 0.30 cm by CT/ US**
 - **Suggestive clinical findings (pain, fever, low ANC)**
 - **Right colon involved in 72% of cases**
 - **Mortality up to 50%**
- **Anatomy:**
 - **Swollen and ulcerated intestinal mucosa**
- **Treatment**
 - **Abx coverage, rarely needs surgery**

Mucositis

- **Definition:**
 - Rupture of the epithelial mucosa with bacterial/fungal invasion
 - Viral reactivation can occur
 - Starts 4- 7 days after initiation of chemotherapy
- **Anatomy:**
 - Swollen and ulcerated perirectal soft tissue
- **Treatment:**
 - Supportive, adequate Abx coverage

Perirectal cellulitis

- **Definition:**
 - Inflammation of the perirectal mucosae
 - Pain is the main symptom
 - Favored by prolonged/ severe neutropenia
- **Anatomy:**
 - Swollen and ulcerated epithelial mucosa
- **Treatment**
 - Sitz bath and soft diet
 - Adequate Abx coverage

Fever and neutropenia (F/ N)

- **History:**
 - **Known as major admission criteria in oncological institutions**
 - **Risk of death by sepsis associated with low ANC level since 1960s**
 - **Oxacillin/ gentamicin first used as treatment, followed by clindamycin and chloramphenicol**
 - **Corticosteroids used sometimes to treat refractory fever**

Fever and neutropenia (F/ N)

- **History:**

- **Standard approach to F/ N patients introduced in USA in early 1980s**
- **Vanc/ Amikacin/ Ticarcillin proposed as first- line empiric treatment for F/ N**
- **Amphotericin B and Flucytosin added in case of persistent fever > 10 days**
- **Vancomycin use debated because of increased costs/ toxicity**

Fever and neutropenia (F/ N)

- **History:**
 - **Pre- printed order sheets for F/ N patients accepted as part of the standard care plan**
 - **IDSA published the first guidelines on F/ N in 1990**
 - **Interest seen in diversifying the range of tests/ studies used to diagnose conditions with F/ N**
 - **Research prompted on the role of endotoxemia in septic shock**

Fever and neutropenia (F/ N)

- **Present:**
 - **IDSA guidelines on F/ N released again in 1997 and 2002, respectively**
 - **Quinolones not approved for pediatric use and also predisposed to viridans strept. infection**
 - **Third oral large- spectrum cephalosporines introduced in the management of F/ N episodes**
 - **Multiple radiological studies used as screening tests for F/ N patients**

Fever and neutropenia (F/ N)

Cefixime Study Design

Initiate IV therapy for febrile neutropenia
(vancomycin plus tobramycin/ticarcillin or ceftazidime)

After 48 - 72 hr,
randomize

Continue IV therapy

Change to oral cefixime

If febrile after day 4, change
to ceftazidime monotherapy

If febrile after day 7,
add amphotericin B

If febrile after day 7,
add amphotericin B

Fever and neutropenia (F/ N)

Cefixime Study Results

(Shenep et al: *Clin Infect Dis* 32:36-43, 2001)

433 febrile episodes in 308 neutropenic children eligible

233 episodes not enrolled

200 episodes in 156 children randomized

100 continued IV therapy

73 successes, 27 failures
including 5 withdrawals

100 changed to cefixime

72 successes, 28 failures
including 5 withdrawals

Fever and neutropenia F/ N- low risk prediction rule, Klaase *et al*, JCO 2000

Table 1. Characteristics of the Derivative and Validation Sets

	Derivative Set (227 episodes)		Validation Set (136 episodes)	
	No. of Episodes	%	No. of Episodes	%
Age, years				
Median		6.8		7.6
Range		0.5-17		1-18
Male patients	111	49	82	60
Tumor type				
ALL	77	34	40	29
Brain tumor	35	15	12	9
AML	27	12	19	14
NHL	25	11	20	15
Soft tissue sarcoma	16	7	28	21
Other	47	21	17	12
Bone marrow disease	22	10	13	10
Leukemia	18	8	11	8
Other	4	2	2	1
G-CSF therapy	59	26	50	37
Localized bacterial infection	37	16	15	11
Central venous line				
None	33	14	26	19
Implanted reservoir	138	61	71	52
External line	56	25	39	29
Peak temperature, median, SD, °C		38.9, 0.58		39.1, 0.56
Complete blood count, median, SD, × 10 ⁹ /L				
ANC		0.04, 0.17		0.04, 0.18
Lymphocyte count		0.3, 0.57		0.3, 0.55
Monocyte count		0.04, 0.31		0.04, 0.3
Platelet count		61, 99		59, 101
Admission ANC ≥ 0.5 × 10 ⁹ /L	8	3	8	6
Bacteremia	28	12	19	14
Significant bacterial infection	43	19	27	20

Fever and neutropenia F/ N- low risk prediction rule, Klaase *et al*, JCO 2000

Table 2. Univariate Correlation of the Predictive Variables for Significant Bacterial Infection in the Derivative Set

Variable	Significant Bacterial Infection (43 episodes)		Other Cases (184 episodes)		P*
	No. of Episodes	%	No. of Episodes	%	
Mean age, years		7.4		7.4	.972†
Male patients	24	56	87	47	.314
AML/NHL	15	35	37	20	.038
Bone marrow disease	9	21	7	12	.002
Complete blood count					
ANC $\leq 1 \times 10^9/L$	30	70	118	65	.512
Lymphocyte count $\leq 0.7 \times 10^9/L$	33	77	136	75	.783
Monocyte count $< 0.1 \times 10^9/L$	36	84	107	59	.002
Platelet count $\leq 75 \times 10^9/L$	29	67	103	56	.170
Central venous line					.038
Implanted reservoir	22	51	116	63	
External line	17	40	39	21	
General appearance unwell on initial examination	17	40	40	22	.017
Localized bacterial infection	4	9	33	18	.168
G-CSF therapy	12	28	46	25	.694
Peak temperature $> 39^\circ C$	23	53	64	35	.023

*Pearson χ^2 test used for all variables except for age.

†Student's *t* test.

Fever and neutropenia F/ N- low risk prediction rule, Klaase *et al*, JCO 2000

Table 3. Reliability of the Exclusion, Prediction, and Outcome Variables

	Reliability*	P
Exclusion variable		
Comorbidity	0.53	.003
Prediction variables		
Expectation of prolonged neutropenia (> 7 days)†	0.05	.739
General appearance unwell on initial examination	0.69	< .001
Localized bacterial infection	0.18	.314
Monocyte count, WBC count 0.2 to 0.5 × 10 ⁹ /L	0.75	< .001
Peak temperature	0.91	< .001
Outcome variable		
Interstitial infiltrate or lobar consolidation on CXR	0.64	< .001

*The kappa statistic was used for binary variables and Spearman's rho was used for continuous variables.

†Used in previous studies as a prediction variable.²²

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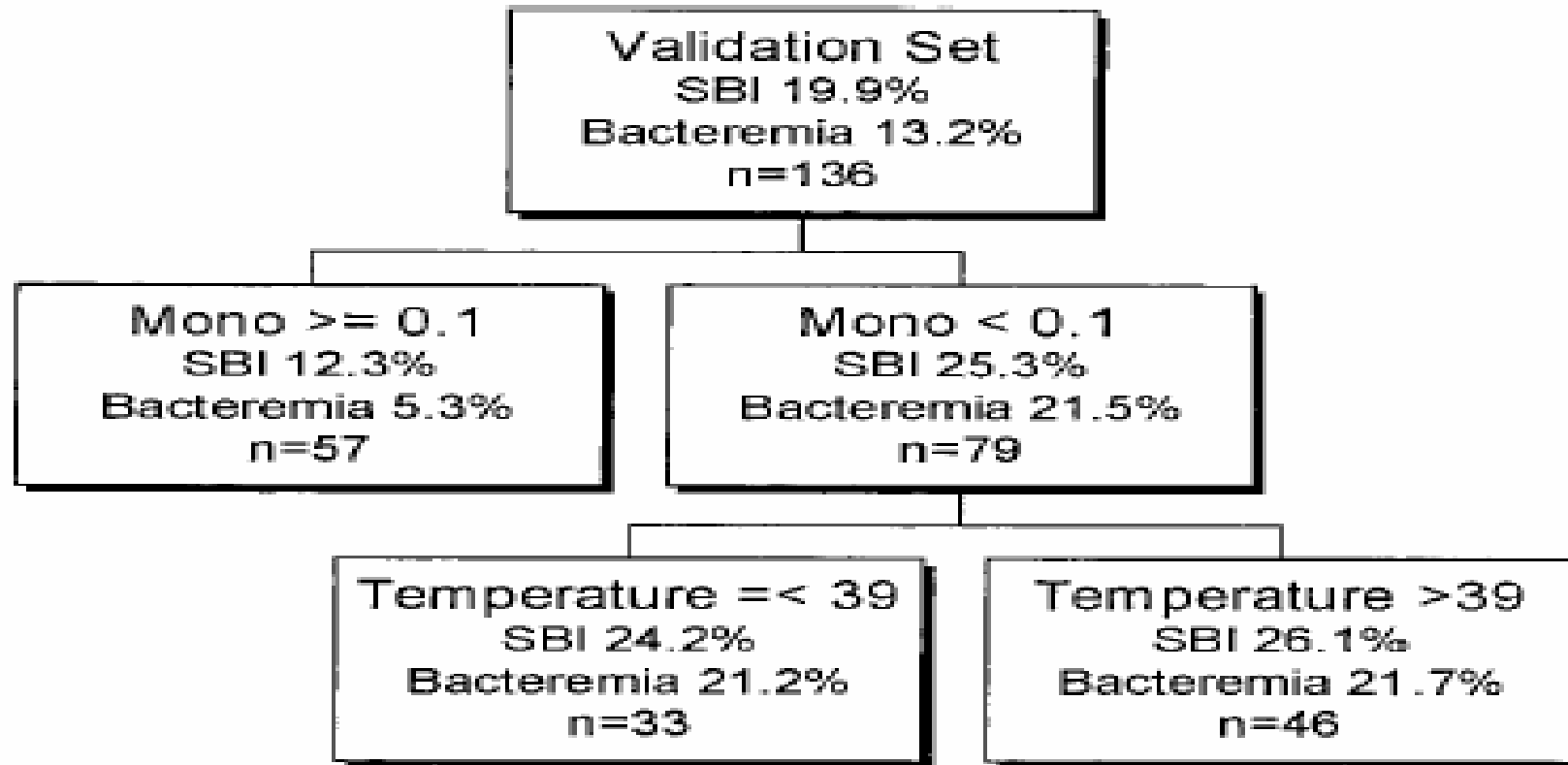


Fig 2. Diagram shows the significant bacterial infection and bacteremia in the validation set according to risk stratification generated from the derivative set. SBI, significant bacterial infection; Mono, monocyte count ($\times 10^9/L$).

Sepsis management

- **Septic episodes may run with pain, hemolysis and shock (*B. cereus* sepsis!)**
- **Fever may be absent**
- **Initial management with ICU admission:**
 - **CVL placement, IV fluids resuscitation**
 - **antibiotics (Cefepime and Vancomycin)**
 - **respiratory assistance**

Bacterial prophylaxis

- **To consider:**
 - **Toxicity of prophylactic regimens**
 - **Emergence of antimicrobial resistance**
 - **Risk of fungal overgrowth**
 - **Shifts in clinical flora**
 - **High treatment costs**

CONCLUSIONS

- **Infections in pediatric oncological patients represent a major therapeutic challenge**
- **Progress was achieved by using a standard approach to high- risk patients**
- **Antibiotic prophylaxis/ treatment remains a crucial component of the clinical management**
- **Further advance should consider specific features for different classes of patients**