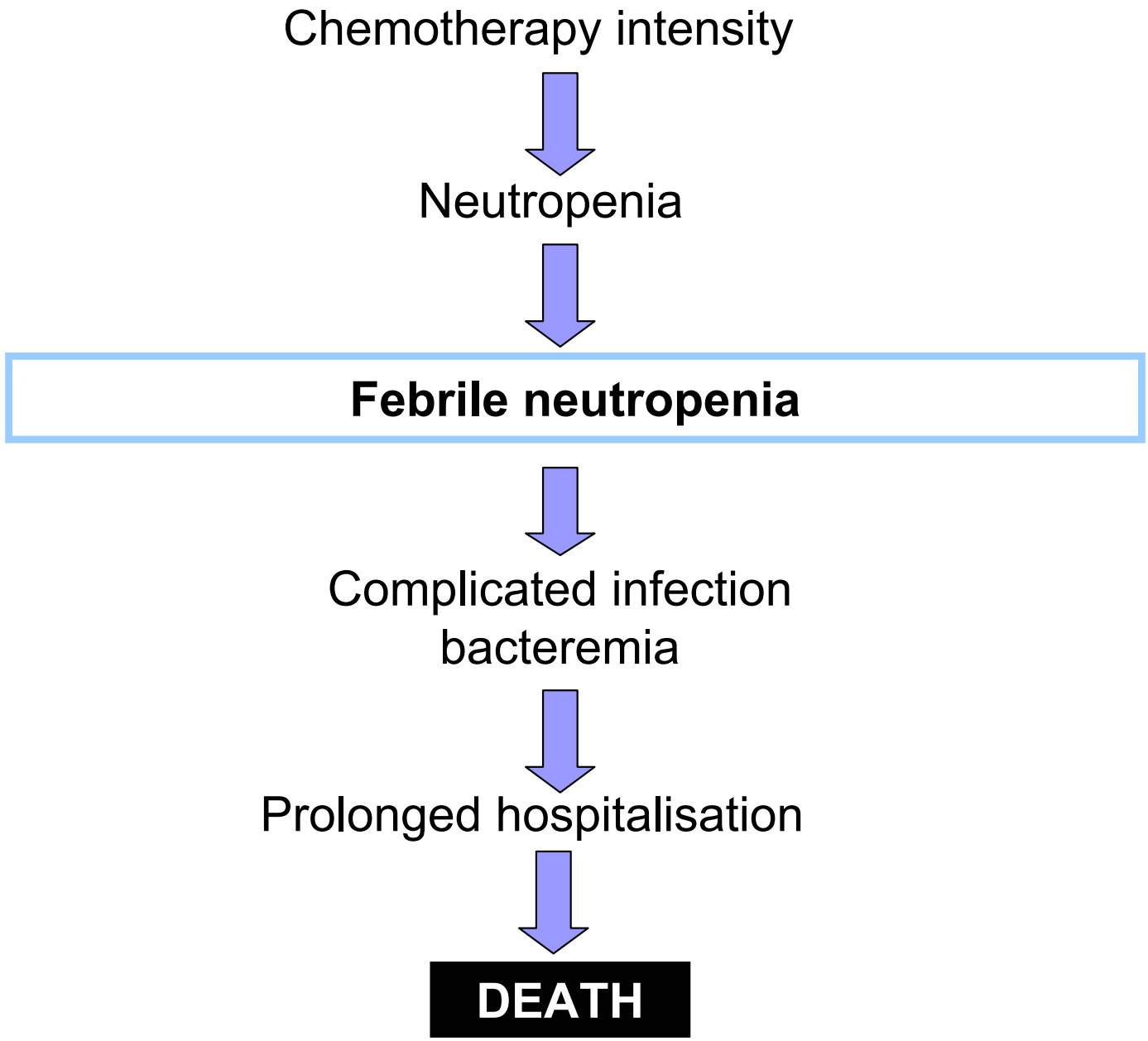
G-CSF

Hartmut Link

Febrile neutropenia (FN)

- Single oral temperature of ≥ 38.3 °C or
- A temperature of ≥ 38.0 C for ≥ 1 h
- Neutropenia is defined as a neutrophil count of <500 cells/µl or
- <1000 neutrophils/µl predicted to fall below 500 neutrophils/µl

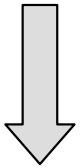
The course of neutropenia and its complications



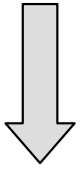
Potential short- and long-term effects of febrile neutropenia

Febrile Neutropenia

Short-term effects[1]

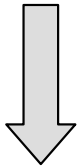


Infections

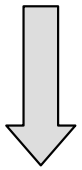


Hospitalisation

Long-term effects[2]



Dose reduction / Cycle delay

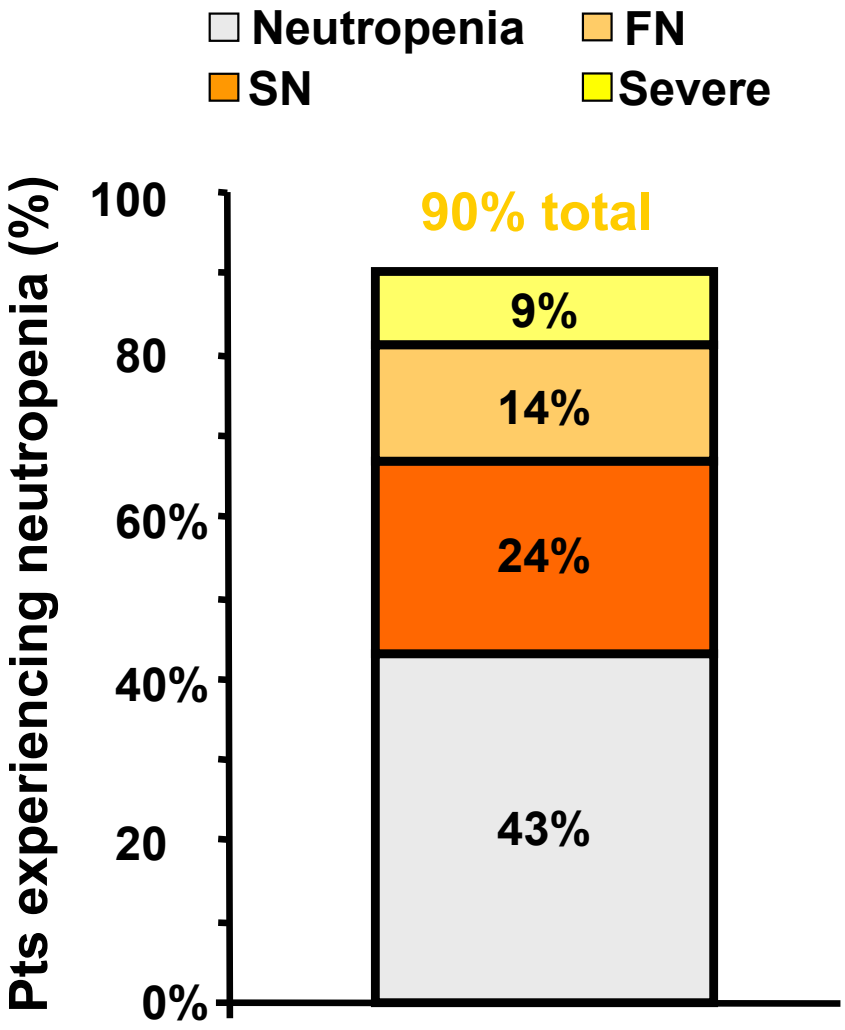


Reduced clinical efficiency of chemotherapy[3]

[1]Kuderer NM, et al. *Proc Am Soc Clin Oncol* 2004;22: Abstract 6049
[2]Leonard RCF, et al. *Br J Cancer* 2003;89:2062-2068
[3]Bonadonna G, et al. *N Engl J Med* 1995;332:901-906

Incidence of chemotherapy-induced neutropenia in cancer patients

- Myelosuppression a major dose-limiting toxic effect of cancer chemotherapy
- Prospective, nationwide study of 2302 cancer patients
  - Patients enrolled before beginning chemotherapy
  - Mean 3 cycles completed
- Neutropenic outcomes
  - **Neutropenia: ANC nadir < 10^9/L**
  - **Severe neutropenia (SN): ANC nadir < 0.5 x 10^9/L**
  - **Febrile neutropenia (FN): fever or infection, ANC nadir < 10^9/L**
  - **Severe FN: fever or infection, ANC nadir of 0.5 x 10^9/L**



Crawford J, et al. ASH 2004. Abstract 2210.

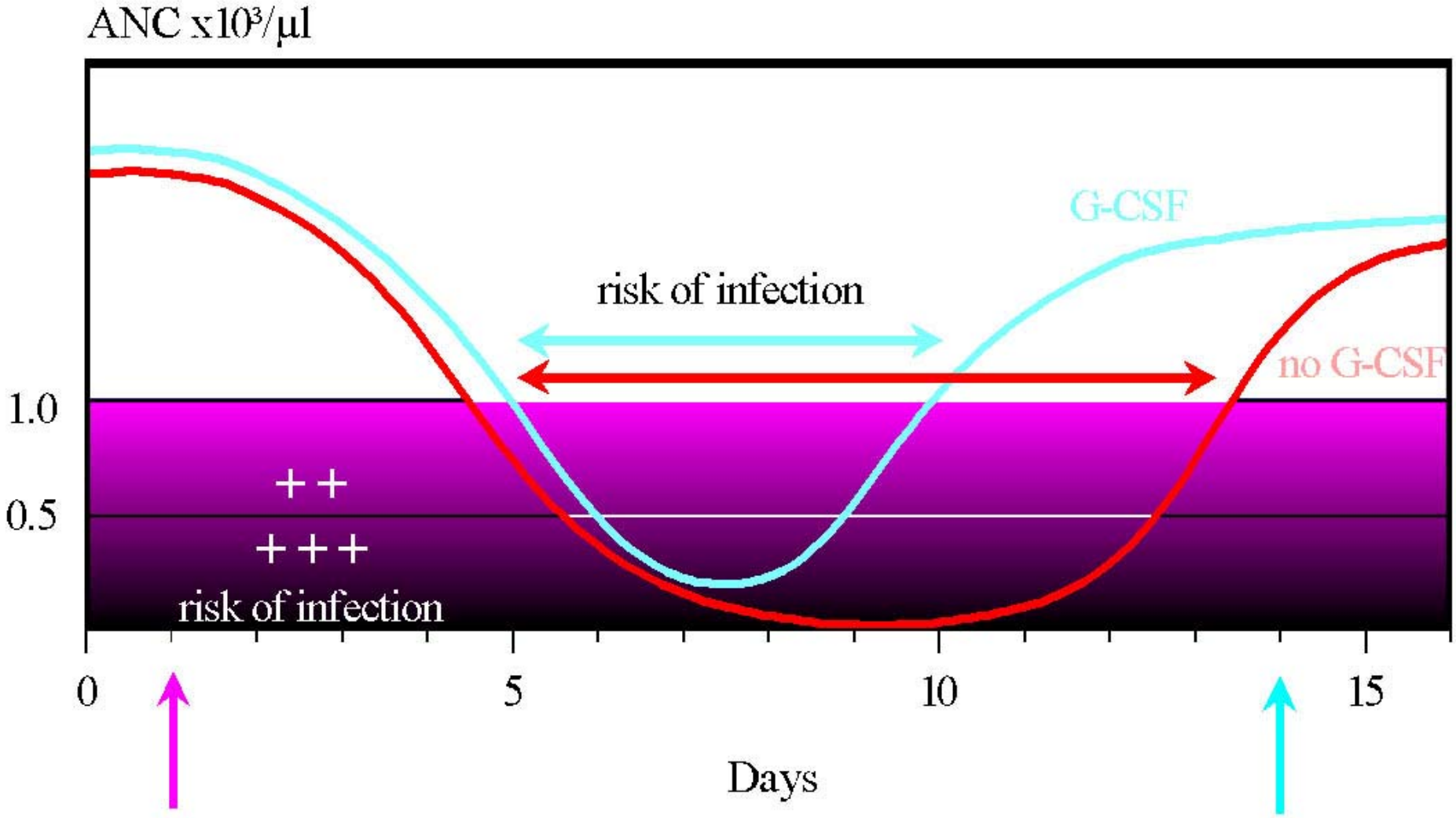
Risk factors for inpatient mortality of febrile neutropenia

Gram-negative sepsis	3.48	Gram-positive sepsis	2.29
Invasive candidiasis	2.55	Hypotension	2.12
Lung disease	2.94	Pulmonary embolism	1.94
Cerebrovascular disease	3.26	Heart disease	1.58
		Leukemia	1.48
Renal disease	3.16	Lung cancer	1.18
Liver disease	2.89	Age ≥65 years	1.12
Pneumonia	2.23		

Kuderer NM, (2006) Cancer. 106:2258–2266

Rationale for the use of G-CSF

Relationship between neutropenia and risk of infections



Prevention of Chemotherapy-Induced Febrile Neutropenia by Prophylactic Antibiotics Plus or Minus Granulocyte Colony-Stimulating Factor in Small-Cell Lung Cancer: A Dutch Randomized Phase III Study

Johanna N. Timmer-Bonte et al.
Journal of Clinical Oncology, 23, 2005: pp. 7974-7984

Prevention of Chemotherapy-Induced Febrile Neutropenia by Prophylactic Antibiotics Plus or Minus Granulocyte Colony-Stimulating Factor in Small-Cell Lung Cancer

1st cycle	Antibiotics n = 85	Antibiotics + G-CSF n = 90	
Febrile Neutropenia, Patients	20 (24%)	9 (10%)	p=0.01
Nadir of neutrophils	120/µl	430/µl	p<0.01
Days with neutropenia < 500/µl	7	4	p=0.01

Johanna N. Timmer-Bonte et al.
Journal of Clinical Oncology, 23, 2005: pp. 7974-7984

Relative risk for febrile neutropenia, early mortality, and infection-related mortality

	Febrile Neutropenia		Early Mortality		Infection-Related Mortality	
	RR	95% CI	**RR**	95% CI	**RR**	95% CI
Lymphoma	**0.71**	0.59 - 0.85	**0.69**	0.40 - 1.17	**0.58**	0.28 - 1.23
Solid Tumors	**0.44**	0.30 -0.65	**0.44**	0.30 - 0.65	**0.53**	0.28 – 1.02

With G-CSF prophylaxis
significant reduction in febrile neutropenia compared to controls

Kuderer, N. M. et al. J Clin Oncol; 25:3158-3167 2007

Results

- Administration of G-CSF results in a 50% risk reduction of developing febrile neutropenia.

- Prophylactic use of G-CSF in patients undergoing chemotherapy reduces the risk of febrile neutropenia and infections.

Guidelines

ASCO	American Society of Clinical Oncology
EORTC	European Society of Research and Treatment of Cancer
NCCN	National Comprehensive Cancer Network

Aapro MS et al. Eur J Cancer 42: 2433-53, 2006
Smith TJ et al. *J Clin Oncol* 2006;24:3187-3205
NCCN. Myeloid growth factors v1.2008; http://www.nccn.org. Last accessed Sept.30, 2008

ASORS

2006 Updated Recommendation

The 2006 Update Committee agreed unanimously that reduction in febrile neutropenia was an important clinical outcome that justified use of CSF, regardless of impact on other factors, when the risk of FN was about 20% and no other equally effective regimen that did not require CSF was available.

Please Note: The rate of FN risk has changed from 40% to 20%.

Primary Prophylactic CSF Administration (First and Subsequent-Cycle Use)

- Recommended for the prevention of FN in patients who have a high risk of FN based on:
  - Age
  - Medical history
  - Disease characteristics
  - Myelotoxicity of the chemotherapy regimen
- Required and recommended for "dose dense" regimens
- Clinical trial data support the use of CSF when the risk of FN is in the range of 20% or higher

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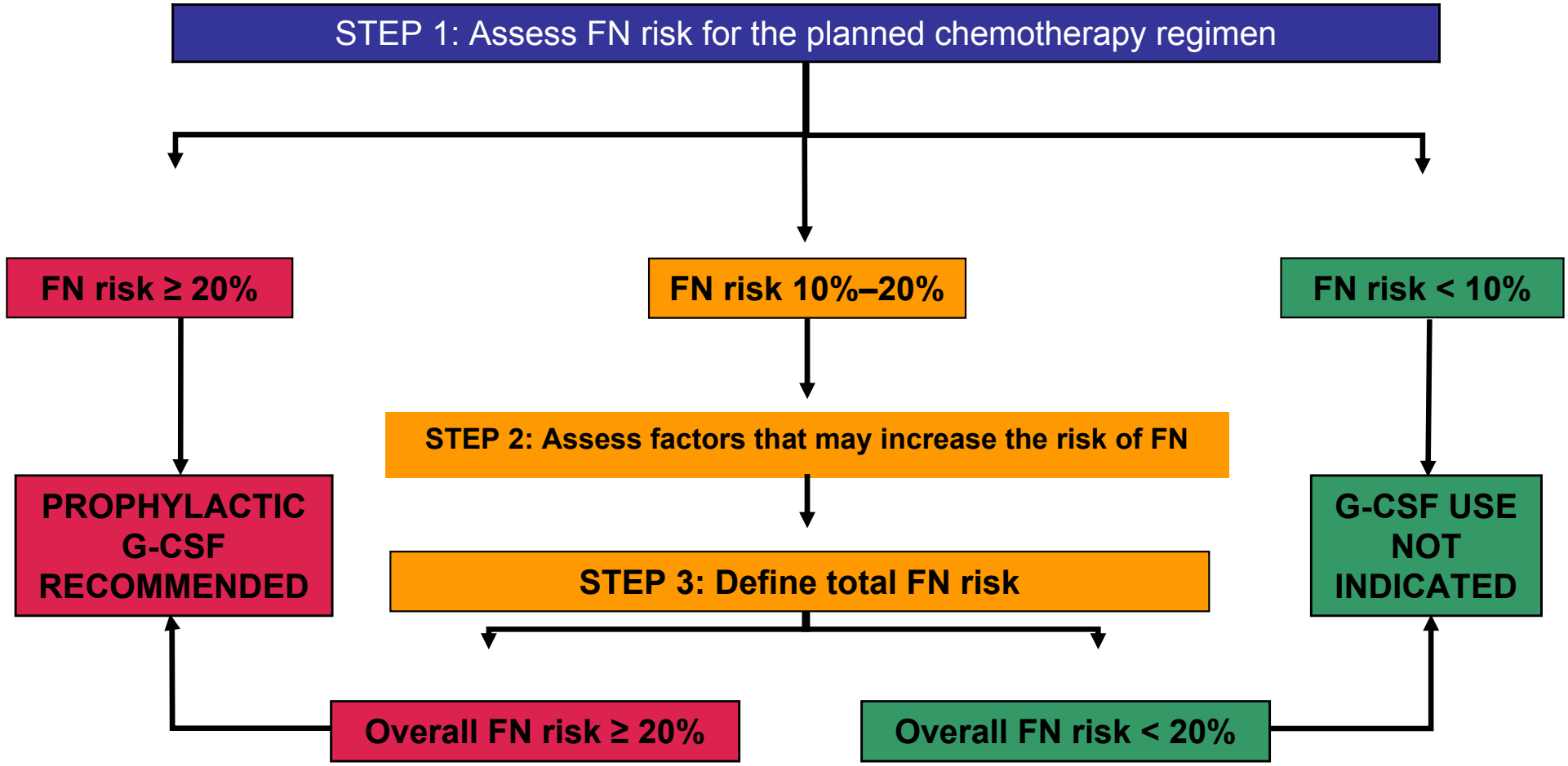
Primary Prophylactic CSF Administration (First and Subsequent-Cycle Use) (cont'd): Special Circumstances

- When the following clinical factors are present, primary prophylaxis with CSF is often appropriate **even with regimens with FN rates of <20%** :
  - Age >65 years
  - Poor performance status
  - Previous FN
  - Poor nutritional status
  - Open wounds or active infections
  - More advanced cancer
  - Extensive prior treatment, including large XRT ports
  - Administration of combined chemoradiotherapy
  - Cytopenias due to bone marrow involvement by tumor
  - Other serious comorbidities

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment



Age ≥ 65 years No antibiotic prophylaxis Advanced disease Previous episode of FN	Serious co-morbidities Poor performance status Open wounds or active infections	Poor nutritional status Female gender Combined chemoradiotherapy	Cytopenias due to tumour bone marrow involvement Haemoglobin < 12g/dL

Aapro MS et al. Eur J Cancer 42: 2433-53, 2006, Smith TJ, et al. *J Clin Oncol.* 2006;24:3187-3205

Chemotherapy-associated risk of febrile neutropenia in lung cancer

Disease	Chemotherapy regimen	FN-Category
SCLC	ACE	>20%
SCLC	Topotecan	>20%
SCLC	ICE	>20%
NSCLC	Etoposide / Cisplatin	>20%
NSCLC	Docetaxel / Carboplatin	>20%
SCLC	Etoposide / Carboplatin	10-20%
NSCLC	Paclitaxel / Cisplatin	10-20%
NSCLC	Gemcitabine / Docetaxel	10-20%
NSCLC	Vinorelbine / Cisplatin	10-20%

NCCN Practice Guidelines 1.2008; Aapro, M. Eur.J.Cancer,42,2006, 2433-2453

Resource use and costs associated with routine management of febrile neutropenia/leukopenia (FN/FL) in German hospitals

- Mean length of inpatient stay (SD): 8.9 (5.9) days
- Mean treatment cost per FN/FL with hospitalisation (± SD):
  - 3,950 (± 4,961) € , range 134 – 31,924 €
  - highest mean cost for patients with lymphoma: 4,808 €
- Hospital direct costs:
  - Hospital basic services and personnel 60%
  - Drugs: 19%
  - Diagnostics: 11%

Ihbe-Heffinger A et al. Blood. 2007;110(11):#3338 (Poster

Summary: Reasons for G-CSF therapy

- Reduction of febrile neutropenia
- Less mortality from febrile neutropenia
- Less morbidity from febrile neutropenia
- Maintain dose intensity of chemotherapy
- Cost-effectiveness
- Maintain quality of life during cancer therapy