Virtual Public Workshop:
Drug Development Considerations for Empiric Antibacterial Therapy in Febrile Neutropenic Patients

April 23, 2024

Hosted by: Center for Drug Evaluation and Research, Office of Infectious Diseases (OID) U.S. Food and Drug Administration

Introductory Remarks

Peter Kim, MD
Director, Division of Anti-Infectives,
Office of Infectious Diseases (OID)
Office of New Drugs (OND)
CDER, FDA

Drug Development Considerations for Empiric Antibacterial Therapy in Febrile Neutropenic Patients—Virtual Public Workshop

Introductory Remarks

Peter Kim, MD, MS
Director, Division of Anti-Infectives
Office of Infectious Diseases/OND/CDER/FDA
April 23, 2024

Workshop Objectives

- During today's workshop, we will bring together key stakeholders from academia, industry, a federal partner, and international regulators to have an open scientific discussion regarding:
  - The current state of development and need for antibacterial drugs for empiric therapy in febrile neutropenic patients
  - Trial design and operational challenges of clinical trials in febrile neutropenia (FN)
- Workshops are an opportunity for stakeholders to come together to discuss ideas regarding a scientific challenge. Workshops are not advisory to the Agency, and the Agency will not provide drug development advice.

Background

- Generally, FN is considered a medical emergency requiring early recognition and initiation of empiric systemic antibacterial therapy to avoid potential progression to sepsis and death.
  - Literature accounts of high mortality among FN patients prior to the use of empiric carbenicillin-based treatment.[1,2]
    - Of note, these were leukemia and cancer patients with *P. aeruginosa* bacteremia

[1]Schimpff, S., et al. (1971). Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *New England Journal of Medicine* **284,** 1061–7.
[2]Bodey, G.P., et al. (1971). Carbenicillin therapy for Pseudomonas infections. *Journal of the American Medical Association* **218,** 62-66.

Background - 2

- Cefepime and IV ciprofloxacin (in combination with piperacillin sodium) are the only FDA approved antibacterial drugs for empiric therapy for febrile neutropenic patients
- No new antibacterials have been approved for this indication in over a quarter of a century
- No oral antibacterial drugs have been approved for this indication
- There are scientific and practical challenges that affect feasibility of clinical trials in FN

Some of the Challenges

- Heterogeneity of the patient population
  - Characterization of FN episodes
    - Microbiologically documented, clinically documented, unexplained fever (suspected infxn vs. non-infectious)
  - How define primary analysis population?
  - Are there ways to enrich for patients most likely to have bacterial infxns (e.g., diagnostics, enrollment criteria)?
- Trial design considerations
  - Superiority vs. Non-Inferiority (NI)
    - If NI, need adequate justification of a margin

Some of the Challenges - 2

- Primary endpoint considerations
  - Clinically meaningful
    - Mortality vs. composite endpoint?
- Feasibility considerations related to sample size

Program Overview

- Session 1:
  - Historical perspective on empiric therapy for febrile neutropenia
  - Current treatment options
  - Diagnostic testing
  - Antibacterial management for neutropenic patients following a nuclear detonation incident
  - Industry perspective

Program Overview - 2

- Session 2:
  - Regulatory pathways and programs to expedite drug development
  - Regulatory considerations on clinical trial design
  - Statistical considerations
  - Perspectives from EMA and PMDA
- Moderated Panel Discussion

Panel Discussion Questions

1. Please discuss the greatest unmet needs for empiric treatment of febrile neutropenia.
   - Please comment on an ideal drug profile.
2. Discuss strategies for enrichment of the study population in patients most likely to have a bacterial etiology for their fever (e.g., clinical characteristics, diagnostics, etc.).
3. Regarding trial design considerations in febrile neutropenia:
   - Please discuss what would be an appropriate primary endpoint and when it should be assessed.
   - Please discuss the primary efficacy population.
   - Are there strategies to make trials more feasible?
4. We note that there are limited data on the use of new antibacterial drugs in neutropenic patients. If time allows and recognizing that this question is not directly related to empiric treatment of febrile neutropenia, please comment on the need, utility and feasibility of obtaining efficacy and safety data for new drugs in the treatment of neutropenic patients with defined systemic bacterial infections.

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We are looking forward to a robust discussion!

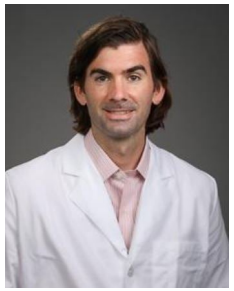
U.S. FOOD & DRUG ADMINISTRATION

Thank you!


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session 1: Background

Andrea Zimmer, MD-Moderator



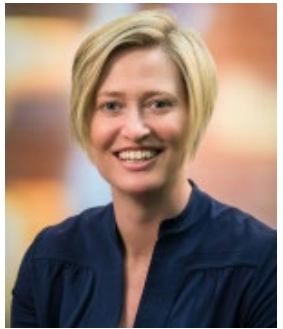
Robert Pease, MD—Co-Moderator

Randy Taplitz, MD

Anita Sheoran, PhD

Andrea Zimmer, MD

Douglas Girgenti, MD



Kimberly Hanson, MD

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HISTORICAL PERSPECTIVE ON PROPHYLAXIS AND EMPIRIC THERAPY OF FEBRILE NEUTROPENIA

RANDY TAPLITZ, M.D.
PROFESSOR AND CHAIR, DEPARTMENT OF MEDICINE
CITY OF HOPE NATIONAL MEDICAL CENTER

Timeline of Relationship of Leukemia Therapy and Infection over 60 years

Age of Discovery: 1948 1971

- Relationship between Cytotoxic chemotx, neutropenia, infection risk (Bodey Annals 1966)
- Empiric antibiotic therapy reduces GN mortality in FN (Schimpff NEJM 1971)

The Enlightenment:1980's

- Combination abx prevailed
- gentamicin role?
- vancomycin role?
- combination therapy equivalent to monotherapy with ceftazidime

Age of Antibiotic Glory: 1990's

- Ciprofloxacin (approved 1987)
- Pip/Tazo (approved 1993)
- Cefepime (approved 1996)
- G-CSF approved 1991
- Refinement of RISK ASSESSMENT and use of FQ prophylaxis

The RESISTANCE (aka "The Troubles" : early 2000's - present

- The rise of resistant bacteria in FN patient
- FQ resistance
- alpha strep
- GNR's

The Empire Strikes Back: 2010 present

- Newer antibiotics for resistant GN's

CASE

56-year-old man presented with two months of progressive fatigue; found to have WBC 83.5 with 65% blasts

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- 7+3 induction with cytarabine and daunorubicin, with **levofloxacin,** posaconazole and acyclovir as antimicrobial prophylaxis
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Scenario 1

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Scenario 2

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- Placed on ceftazidime-tazobactam, but with prolonged hypotension and multiorgan system failure was made DNR and passed away

Association of Neutropenia with Infection and How to Treat: The 60's-70's

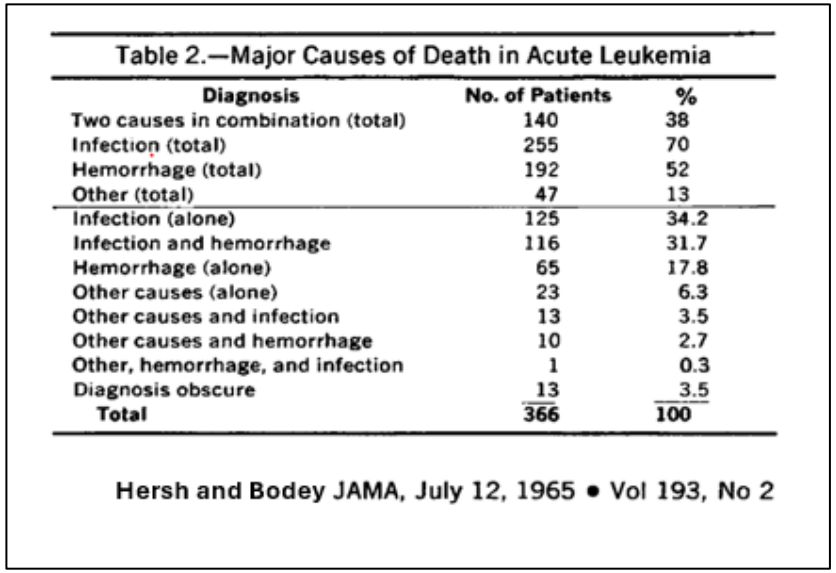


Table 2.—Major Causes of Death in Acute Leukemia

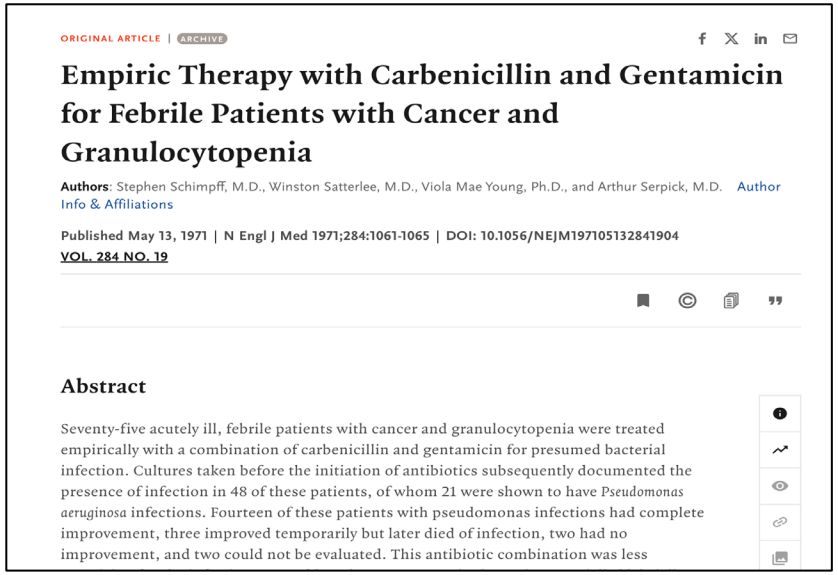
Diagnosis	No. of Patients	%
Two causes in combination (total)	140	38
Infection (total)	255	70
Hemorrhage (total)	192	52
Other (total)	47	13
Infection (alone)	125	34.2
Infection and hemorrhage	116	31.7
Hemorrhage (alone)	65	17.8
Other causes (alone)	23	6.3
Other causes and infection	13	3.5
Other causes and hemorrhage	10	2.7
Other, hemorrhage, and infection	1	0.3
Diagnosis obscure	13	3.5
Total	366	100

Hersh and Bodey JAMA, July 12, 1965 • Vol 193, No 2

Early 1960's, descriptions of infection as One of the major causes of death in Patients with acute leukemia

Quantitative Relationships Between Circulating Leukocytes and Infection in Patients with Acute Leukemia

Description of a quantitative relationship between the number of circulating leukocytes and infection in patients with acute leukemia (Bodey, Annals 1966)



ORIGINAL ARTICLE | ARCHIVE

Empiric Therapy with Carbenicillin and Gentamicin for Febrile Patients with Cancer and Granulocytopenia

Authors: Stephen Schimpff, M.D., Winston Satterlee, M.D., Viola Mae Young, Ph.D., and Arthur Serpick, M.D. Author Info & Affiliations

Published May 13, 1971 | N Engl J Med 1971;284:1061-1065 | DOI: 10.1056/NEJM197105132841904

VOL. 284 NO. 19

Abstract

Seventy-five acutely ill, febrile patients with cancer and granulocytopenia were treated empirically with a combination of carbenicillin and gentamicin for presumed bacterial infection. Cultures taken before the initiation of antibiotics subsequently documented the presence of infection in 48 of these patients, of whom 21 were shown to have *Pseudomonas aeruginosa* infections. Fourteen of these patients with pseudomonas infections had complete improvement, three improved temporarily but later died of infection, two had no improvement, and two could not be evaluated. This antibiotic combination was less

First prospective, randomized trials of empirical abx regimens for neutropenic patients (<1000 PMN/mm3) published in 1971/1972

Refinement of Empiric Therapy in the 1980s

- Consider in-vitro synergy, serum bactericidal activity, serum concentration of antibiotics; which antibiotics?
  (Klatersky, Arch Intern Med 1982; 142: 1984)

- Combination vs single antibiotic therapy
  - Ceftazidime alone versus combination therapy in cancer patients with febrile neutropenia *(Pizzo et al NEJM, 1986: 315:552)*
    - Regimens equally effective, with failure rates of 5 and 4%

- Subsequently **MANY** studies affirming that monotherapy can be safe and effective for FN during this period, though patients with prolonged neutropenia **OR** with documented infection are likely to need revision/additions

Risk Assessment and the Development of Newer Antibiotics in the 1990's

Risk Assessment tools developed:

- Talcott – risk prediction model that identified patients at high risk of acute medical complications based on criteria vs low risk and could be treated at home. A multicenter randomized trial confirmed outpatient treatment was safe. *(Talcott et al JCO 1992, vol 10, 2. pp316)*
- Subsequently **MASCC** *(klatersky et al, J Clin Oncol 18:3038-3051, 2000)* and **CISNE** *(Carmona-Bayones et al J Clin Oncol 33:465-471, 2015)* scores also developed and validated
- Risk assessments for modification of empiric antibiotics based on specific patient features (e.g., abdominal pain and anaerobic antibiotics)

Newer antibiotics and G-CSF developed/approved:

- Ciprofloxacin – drug approved 1987, oral, well absorbed, great gram-negative spectrum – studied in both treatment and prophylaxis
- G-CSF – approved 1991
- Zosyn – approved 1993, studied for FN treatment
- Cefepime – approved 1996, studied for FN treatment

A Few Words on Antibiotic Prophylaxis in Granulocytopenia and Leukemia

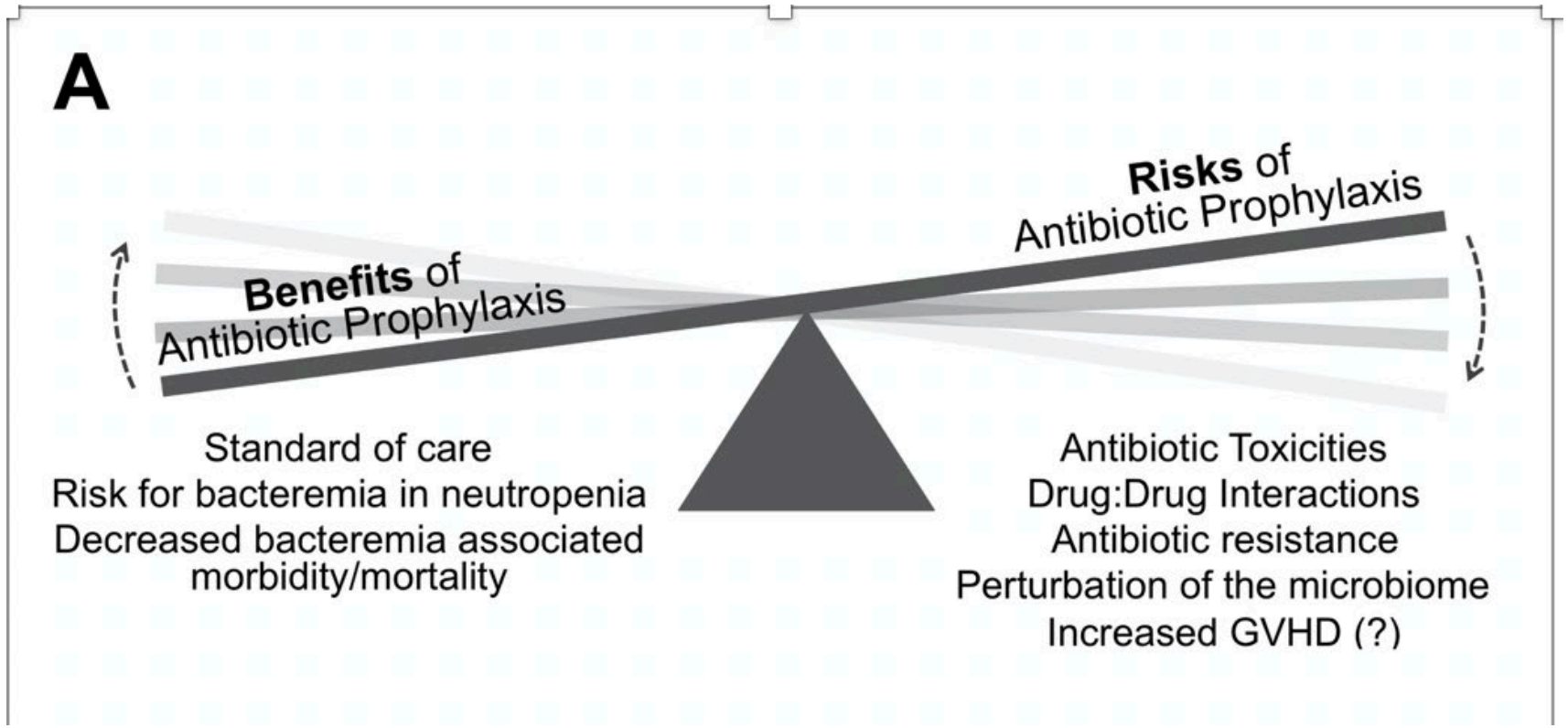
- 1960-70's - since endogenous gut flora associated with infection, studies of non-absorbable antibiotics
  - » Diverse outcomes and not well tolerated
- 1960's and 1970's
  - » TMP-SMX in preventing bacteremia and reducing days of fever
- **1980's and beyond**
  - **More commonly Fluoroquinolone prophylaxis**
    - **» 100's of studies; many mixed patient populations, mostly not randomized controlled; reduction in bacteremia and infection related outcomes, but not as clear for mortality**
- 1990's 2 meta-analyses
  - Reduced infection related outcomes, but not infection related mortality

- **Since 2000 three studies (randomized controlled, prospective observational and open label randomized as well as a number of meta-analyses) on fluoroquinolone prophylaxis**
  - **Generally well tolerated, but no clear mortality benefit**

Cruciani et al Clin Infect Dis. 1996;23(4):795–805 *; Engels et al* J Clin Oncol. 1998;16(3):1179–87; *Bucaneve, N Engl J Med 2005; 353:977-987, Reuter et al, Clinical Infectious Diseases*, Volume 40, Issue 8, 15 April 2005, Pages 1087–1093*Gafter-Gvili Cochrane Databalse Syst Rev 2012; 1. Mikulski et al Journal of Infection (2018) 76, 20-37; Alexander et al JAMA (2018) vol 320, 10995*

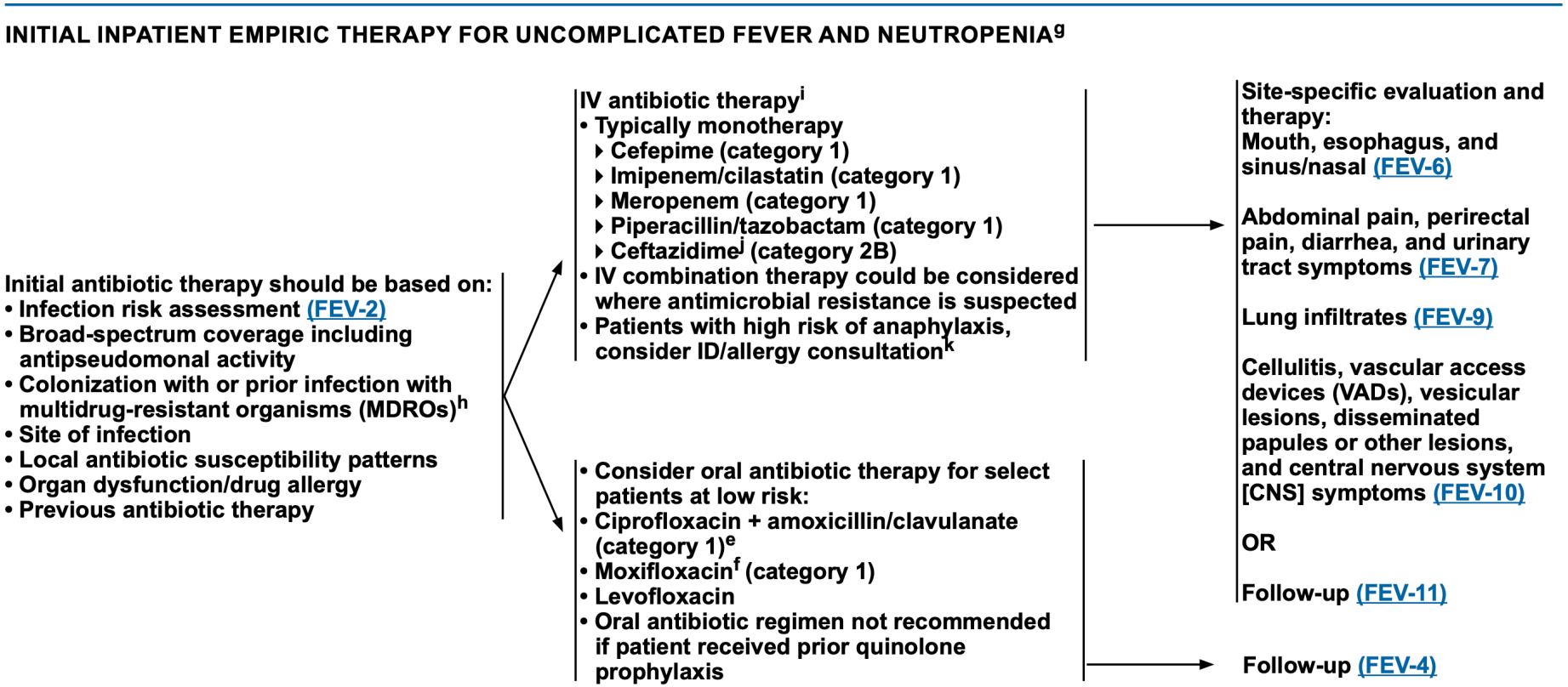
Gafter-Gvili Cochrane Databalse Syst Rev 2012; 1. Mikulski et al Journal of Infection (2018) 76, 20-37

Rethinking Antimicrobial Prophylaxis



Horton, Haste and Taplitz; Curr Hematol Malig Rep (2018) 13:59-67 DOI 10.1007/s11899-018-0435-0;
Jenq et al. Biol Blood Marrow Transplant. 2015;21(8): 1373–83 ; Peled et al. Blood. 2016;128(20):2395–402 ;
Taur et al Blood (2014) 124 (7): 1174–1182

Treatment of Febrile Neutropenia



NCCN guidelines, 2023

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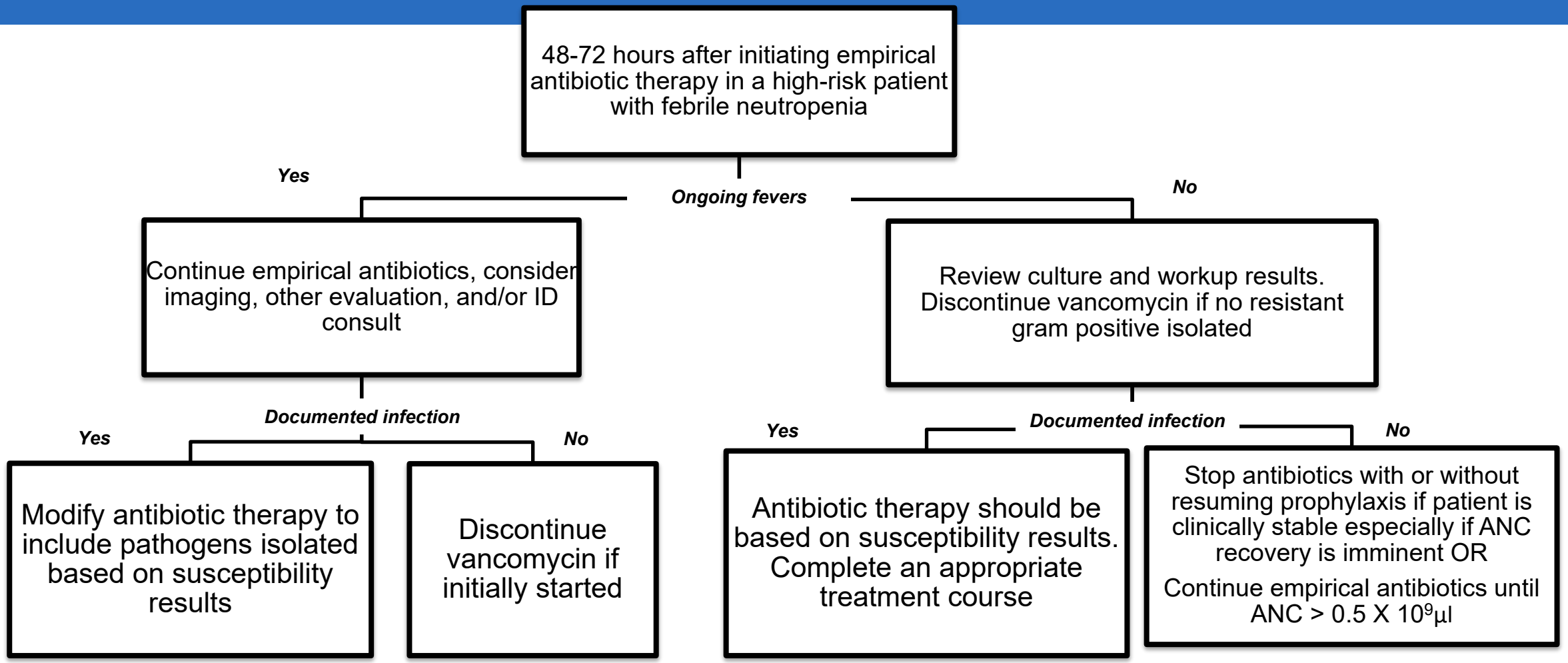
Deescalation
A Follow-up Approach to High-risk Patients with Febrile Neutropenia



adapted from Zimmer et al, J Oncol Pract 2019.15:19-24); Averbuch et al. *Haematologica*. 2013;98(12):1826-1835); Verlinden et al OFID vol 9 Mar 2022; Lopez-Cortez et al Lancet Infectious Dis 2024 24:375-85; (Freifeld et al. CID 2011:52 (15 February) de57);www.thelancet.com/infection Vol 24 April 2024

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Where we are today: The Rise of Multidrug Resistant Organisms

- In early days, bacteremias were dominated by Gram neg, then gram positives; recent studies reveal more equally distributed Gram negatives and gram positives, but a concerning increase in drug resistant pathogens including ESBL and carbapenem R organisms Zimmer et al, OFID 2022;9(7) and Mikulska et al, J Infect 2014; 68(4): 321

- Enterobacterales, mainly Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii resistant to carbapenems, have been increasingly implicated as pathogens of concern in cancer patients *Perdiouri et al; Microorganisms 2019, 7, 277*

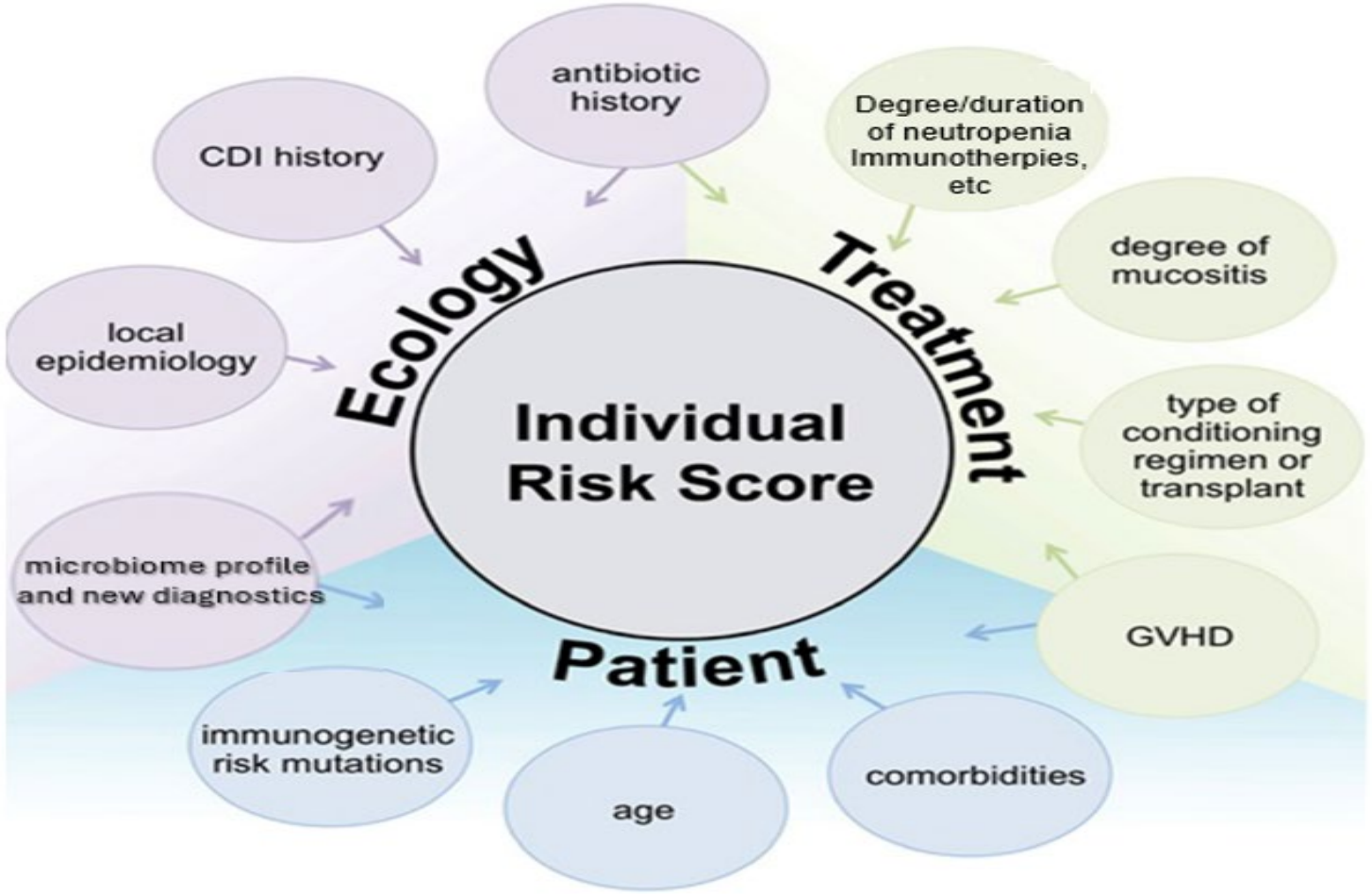
- Colonization with multi-drug-resistant organisms (MDRO) has been shown to lead to worse outcomes, including higher non-relapse mortality (NRM) of 25.4 versus 3% *averbach et al CID.2017*

- Infections with MDRO with limited treatment options are associated with increased morbidity, mortality, and healthcare costs. Several metagenomic and other studies have shown that decreased microbiota diversity with the use of broad-spectrum antibiotics is associated with increased GVHD as well as reduced overall survival *Taur et al Blood (2014) 124 (7): 1174–1182; Zhou et al (2022) Front Immunol 13:1045497*

Where we are today?

- Ever more complicated patients – “net state of immunosuppression/Immune activation” - it isn’t just about neutropenia!
- We still think in terms of:
    - Prophylaxis
    - Treatment
    - Deescalation or escalation
- The time has come to reconsider the paradigm for when/how/who we treat, and what anti-infectives we use.
- Newer anti-infective options are needed in this setting

Strategic Risk Score for Antibiotic Prophylaxis and Treatment



Adapted from: Horton, Haste, Taplitz; Curr HematolMalig Rep. 2018 Feb;13 (1); 59-67

Current Options for Empiric Treatment of Febrile Neutropenia

Andrea J. Zimmer, MD, FACP, FIDSA
Associate Professor
Medical Director, Oncology Infectious Diseases
Fred & Pamela Buffett Cancer Center

University of Nebraska Medical Center℠

Outline

Populations at risk for Febrile Neutropenia (FN)

Stratifying risk for morbidity and mortality during FN

Empiric therapy options for FN

- Outpatient
- Inpatient

Contemporary data on FN among U.S. cancer centers

Stratifying Risk for Chemotherapy-Associated Febrile Neutropenia and Infections

High risk	• Anticipated neutropenia > 10 days • Allogeneic HCT • Acute leukemia
Intermediate risk	• Anticipated neutropenia 7-10 days • Lymphoma, CLL • Multiple myeloma • Autologous HCT or CAR T cell therapy
Low risk	• Anticipated neutropenia < 7 days • Solid tumors

Baden JNCCN 2016

Predictors of Morbidity and Mortality in FN

Multinational Association for Supportive Care in Cancer **MASCC Risk Index Score***	
Characteristic	Weight
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No COPD	4
Solid tumor	4
No dehydration	3
Outpatient onset	3
Age ≤ 60 years	2

*MASCC ≥ 20 indicates low risk

Clinical Index of Stable Febrile Neutropenia **CISNE Score⁺**	
Characteristic	Points
ECOG PS > 2	2
Stress-induced hyperglycemia	2
COPD	1
Chronic CV disease	1
Mucositis grade > 2	1
Monocytes <200 u/L	1

⁺CISNE score of 0 indicates low risk

Jean Klastersky JCO 2000
Carmona-Bayonas JCO 2015

Management of Febrile Neutropenia

Triage patients with fever seeking emergency medical care within 6 weeks of receiving chemotherapy

Assume bacterial infection
Draw blood cultures and other bloodwork

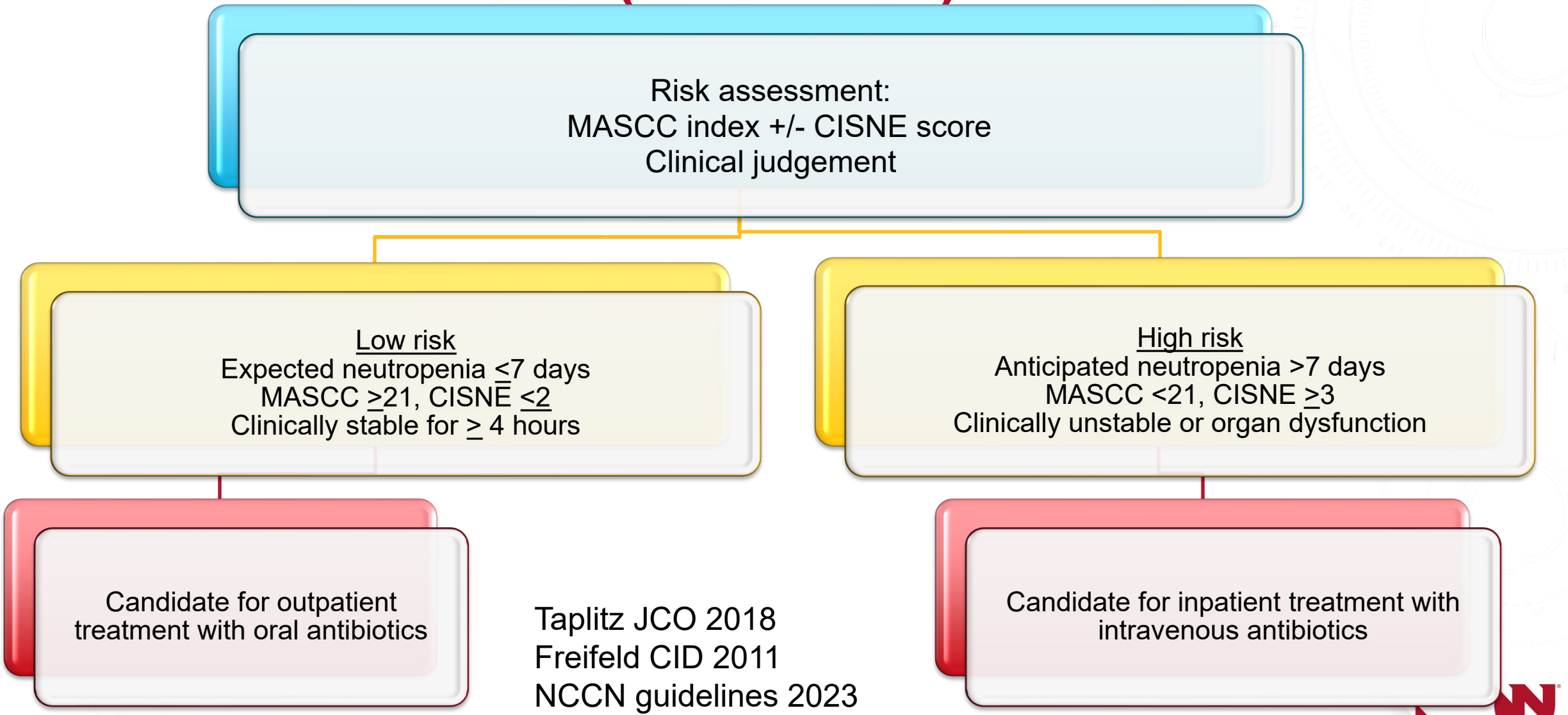
Assessment within 15 minutes of triage:
History, physical examination, and symptom-directed radiography and cultures (urine, sputum, etc)

Within one hour of triage:
Administer first dose of empirical antibiotic therapy*

*Empirical antibiotic selection should be guided by clinical signs/symptoms, prior culture data, and local antibiogram

Taplitz JCO 2018
Freifeld CID 2011
NCCN guidelines 2023

Management of Febrile Neutropenia (continued)



Taplitz JCO 2018
Freifeld CID 2011
NCCN guidelines 2023

United States Guideline Recommendations on Empiric Treatment of Febrile Neutropenia

Outpatient oral antibiotics

Fluoroquinolone
- Ciprofloxacin 750 mg po bid*
- Levofloxacin 750 mg po daily*

PLUS

Amoxicillin/clavulanate 875 mg bid OR 500 mg q 8*

Inpatient intravenous antibiotics

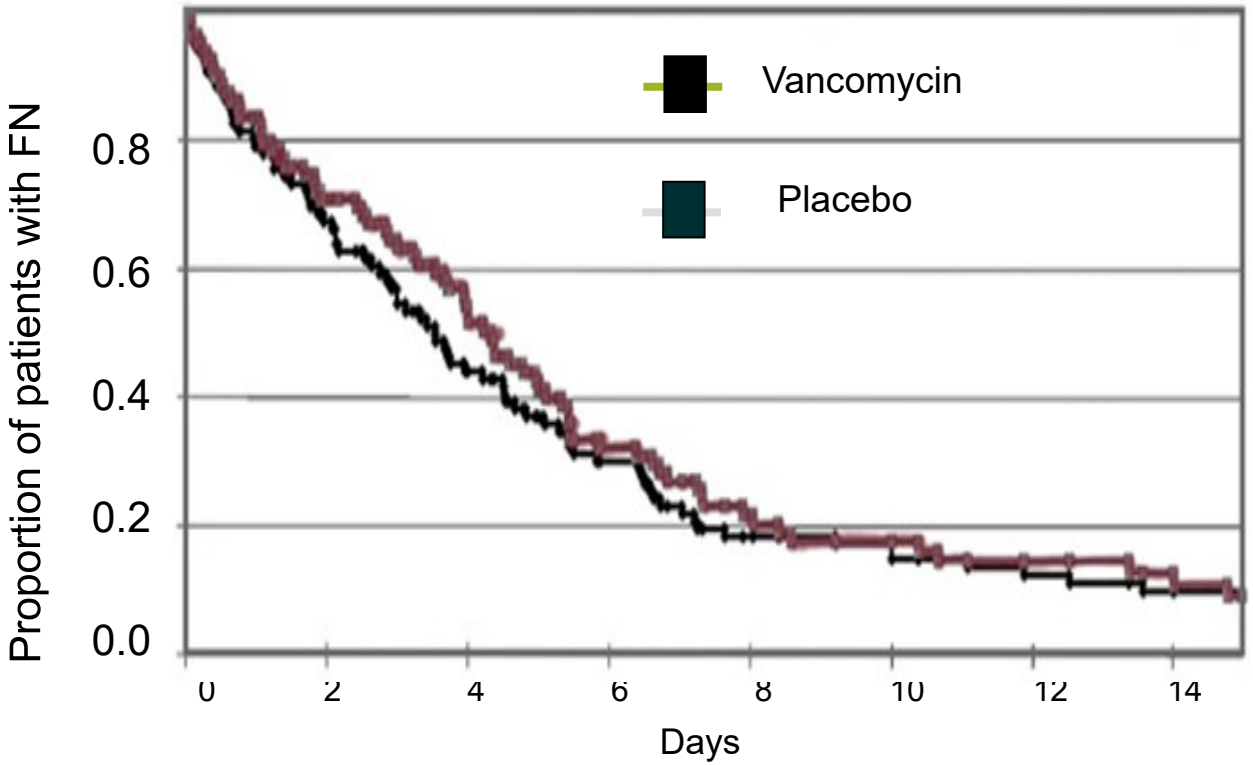
- Cefepime 2 g IV q 8 hours
- Ceftazidime 2 g IV q 8*
- Imipenem/cilastatin 500 mg IV q 6*
- Meropenem 1 g IV q 8 OR 500 mg IV q 6*
- Piperacillin/tazobactam 4.5 g IV q 6-8*

* Indicates off-label use

Taplitz JCO 2018
Freifeld CID 2011
NCCN guidelines 2023

Adding Vancomycin to Empiric Therapy for Febrile Neutropenia?

Time to defervescence in FN with IV Vancomycin vs Placebo



165 patients with FN at ≥ 48 hrs after piperacillin/tazobactam randomized to vancomycin vs placebo. No difference in duration of fevers or breakthrough infections, higher adverse events in vancomycin group

Indications for Vancomycin

- Suspected catheter-related infection
- Skin or soft-tissue infection
- Concern for MRSA pneumonia
- Hemodynamic instability

Cometta CID 2003
Taplitz JCO 2018
Freifeld CID 2011
NCCN guidelines 2023

Newer Therapies for Resistant Gram-negatives

Carbapenem resistant Enterobacterales (CRE)

- Ceftazidime-avibactam[a,b,c]
- Imipenem-cilastatin-relebactam[a]
- Meropenem-vaborbactam[a]
- Cefiderocol[b]

Multi-drug resistant *Pseudomonas aeruginosa*

- Ceftolozane-tazobactam
- Imipenem-cilastatin-relebactam
- Ceftazidime-avibactam
- Cefiderocol

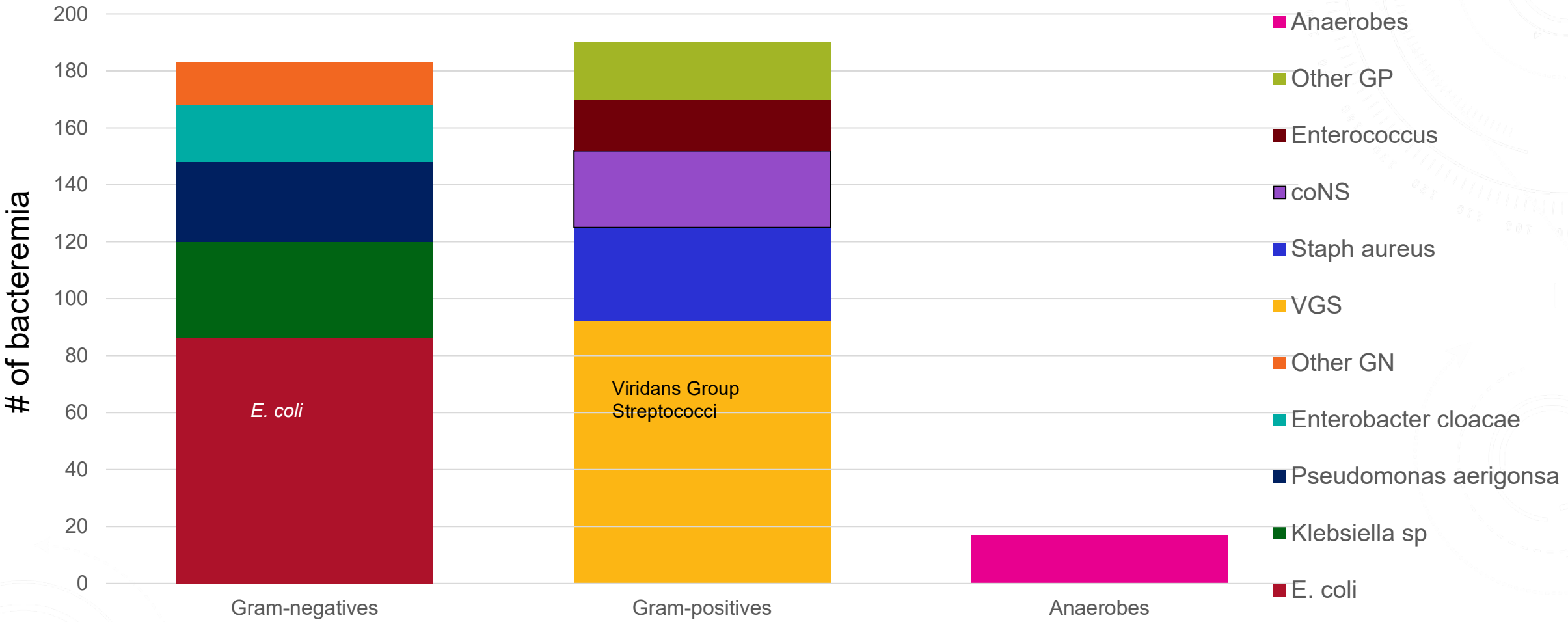
Other resistant Gram-negatives

- Carbapenem-resistant *Acinetobacter baumannii* (CRAB)[d]: Cefiderocol, sulbactam-durlobactam
- *Stenotrophomonas maltophilia*[d]: Cefiderocol, Ceftazidime-avibactam (plus aztreonam)

[a]KPC-producing infections, cefiderocol is an alternative
[b]NDM-producing infections aztreonam is used in combination with ceftaz-avibactam, combo may also be used for *Stenotrophomonas maltophilia*
[c]OXA-48-like-producing infection, cefiderocol is an alternative
[d]Combination therapy is recommended

Tamma CID 2023
Kaye Lancet Infect Dis 2023

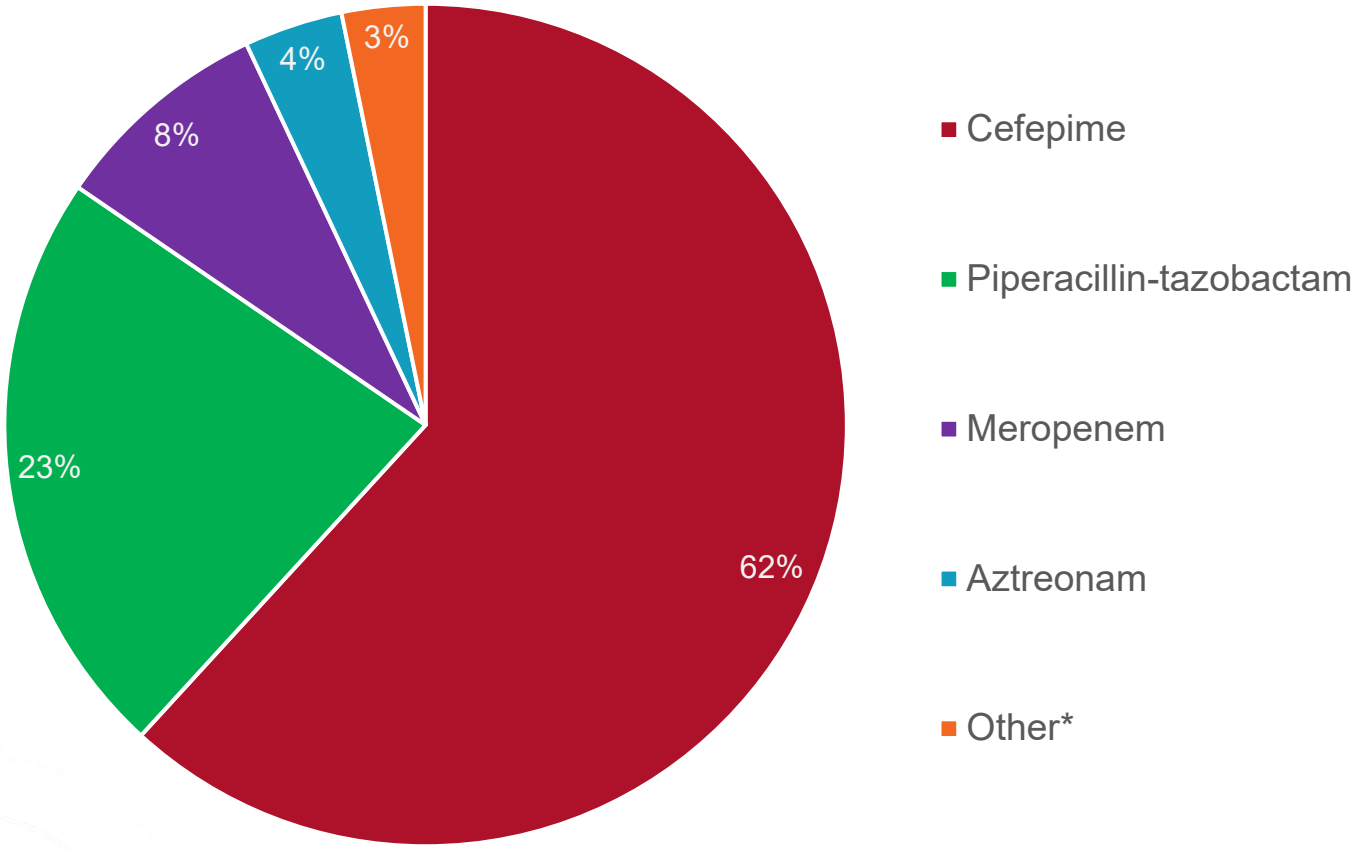
Causes of Bacteremia During High-Risk Febrile Neutropenia Across Sixteen U.S. Cancer Centers



Equal rates of Gram-negative and Gram-positive organisms among 343 patients with hematologic malignancies, FN, and bacteremia

Zimmer OFID 2022

Practice Patterns Among U.S. Cancer Centers: Initial Empiric Treatment of Febrile Neutropenia



*Ceftazidime (8), Ceftriaxone (2), Doripenem (1)

Additional GP coverage with systemic Vancomycin, Daptomycin or Linezolid was administered in 163/343 (48%).

Aminoglycosides were administered in combination with beta-lactams in 20/343 (6%) patients.

GN Susceptibility to Most Common Initial Empirical Antibiotics

	All Gram negatives # susceptible/ # tested (%)	Enterobacterales	Pseudomonas
Cefepime	150/178 (84)	123/145 (85)	**26/28 (93)**
Pip-tazo	145/164 (88)	118/135 (87)	**23/25 (92)**
Meropenem	**119/124 (96)**	**96/98 (98)**	19/22 (86)
Levofloxacin	85/173 (49)	65/139 (47)	19/27 (70)
Aminoglycosides	147/175 (84)	120/143 (84)	**27/28 (96)**

UNMC
Nebraska Medicine

Thank you for contributions or review of materials

- Alison Freifeld, MD
- Michael Satlin, MD
- Randy Taplitz, MD

Diagnostic Testing in Febrile Neutropenia

Kimberly Hanson MD, MHS

University of Utah and ARUP Laboratories

Overview

- Microbiologic testing at neutropenic fever onset
- Pathogen directed testing for bacteria
- Highlight recent diagnostic studies including participants with febrile neutropenia

Febrile Neutropenia (FN)

- Common complication of cytotoxic chemotherapy[1]
  - incidence varies based on tumor type/treatment modality and patient factors
    - 10-50% of solid tumors
    - 80% hematologic malignancies

- Clinical focus of infection suspected in 30-65%[2,3]
  - microbiologic confirmation by culture 40-50%[3,4]
    - bacterial infection generally more common than fungal or viral
      - First FN episode, prophylaxis, skin site[5], various pediatric prediction rules[6-7] associated with increased likelihood of bacterial infection

1. Klastersky et al. Clin Infect Dise 2004; 39: S32-S37; 2. Bachlitzanski et al. Microorg 2023; 11:2547; 3. Zimmer at al. J Onc Pract 2019; 15:19-24; 4. Raheja Cureus 15(8): e42843; 5. Tamai et al. Blood 2008; 112(11):4365; 6. Haeusler et al. / EClinicalMedicine 23 (2020): 100394

Microbiologic diagnosis

Optimize antimicrobial therapy

- potential to improve outcome and reduce hospital cost

Diagnostic challenges

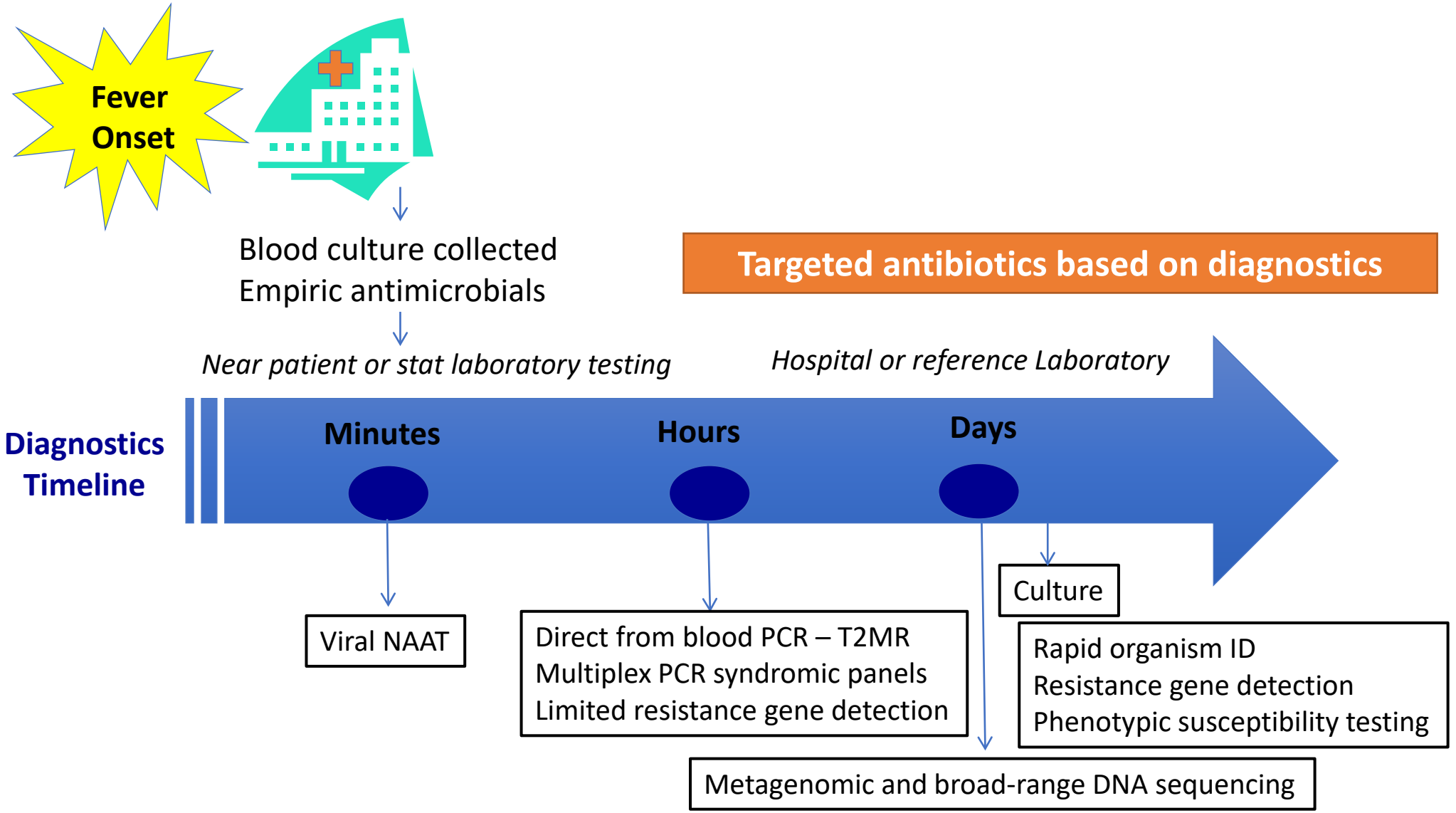
- symptoms non-specific and infectious differential diagnosis is broad
- increased risk for multi-drug resistant pathogens and co-occurring opportunists
- invasive testing may not be possible due to critical illness and/or coagulopathy

Diagnostic advances

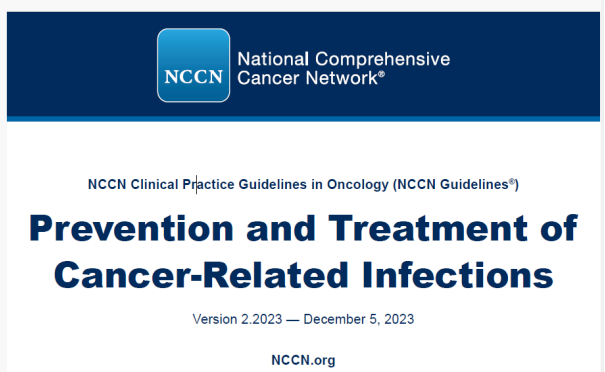
- culture independent methods including agnostic approaches
- rapid organism ID and antimicrobial resistance from blood positive culture bottles

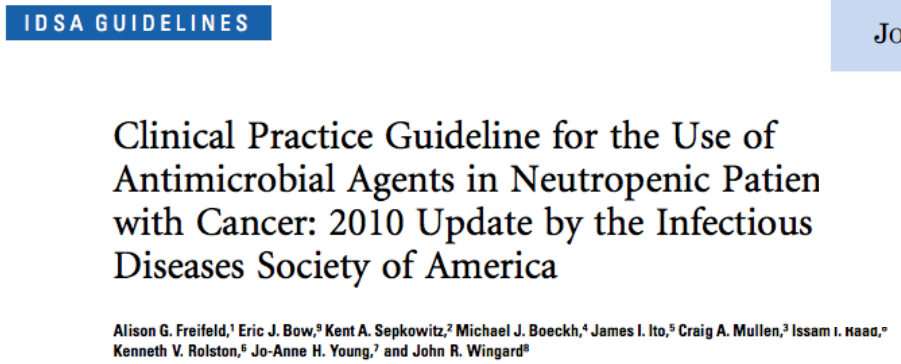
Current Diagnostic Landscape

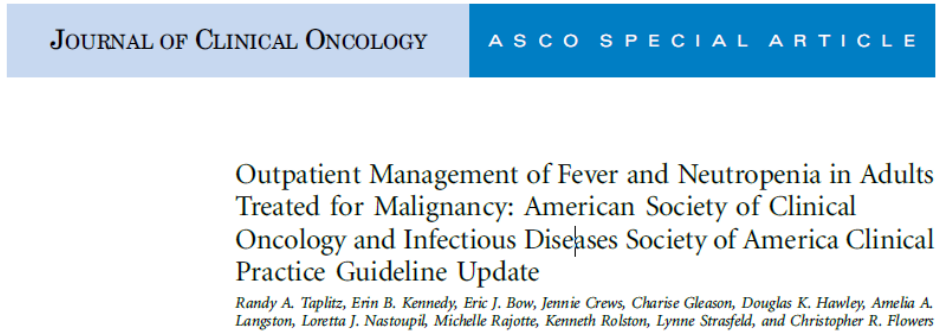
Hypothetical patient with neutropenic fever



Blood Culture







- Bacteremia detected in approximately 10-30% of FN episodes
  - Minimum two sets from different sites (detects 90% of blood stream infections in adults[1])
  - At least one from the central venous catheter if present
    - ➢ Drawing from all lumens decreases likelihood of missing a catheter associated infection[2]
  - Low yield of repeat blood cultures for persistent FN without accompanying hemodynamic change[3]
    - ➢ 1-2% positivity rate (new organism detected) after day 1

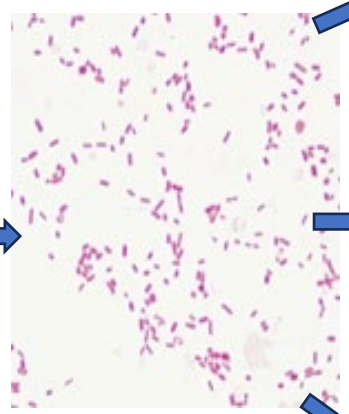
1. Lee et al. *J Clin Microbiol.* 2007;45(11):3546–3548; 2. Guembe et al. *Clin Infect Dis.* 2010;50(12):1575–1579; 3. *Robinson et al. OFID* 2022

Rapid organism identification (ID) with or without antibiotic resistance information

Days

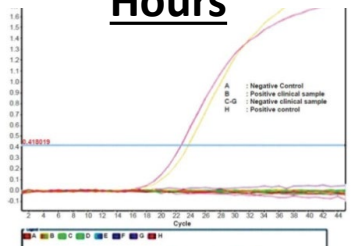
Blood Culture

Minutes

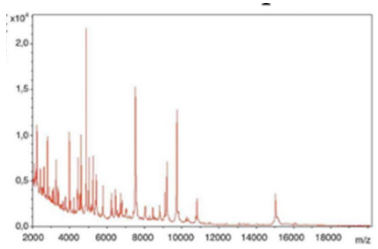


Gram Stain

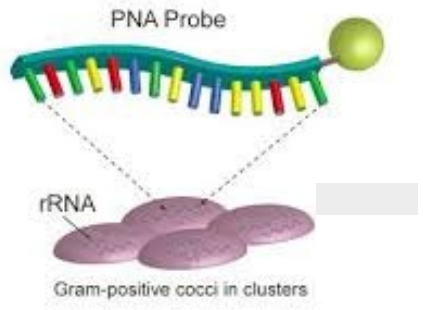
Hours



Multiplex PCR/Microarray



Mass Spectroscopy



PNA-FISH

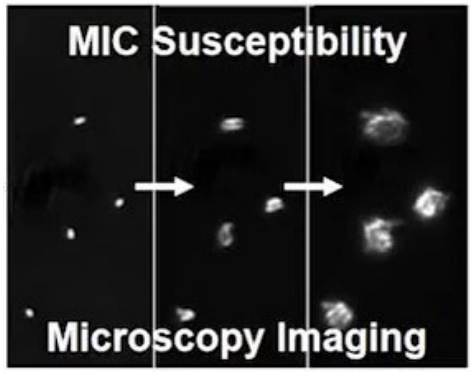
Hours

Detection of selected resistance genes

Zimmer et al. approx. 80 % ID by current panels

gram positive	gram-negative
MecA/MecC	CTX-M
Van A/B	KPC, NDM, IMP, VIM

Rapid phenotypic antibiotic susceptibility testing (AST)



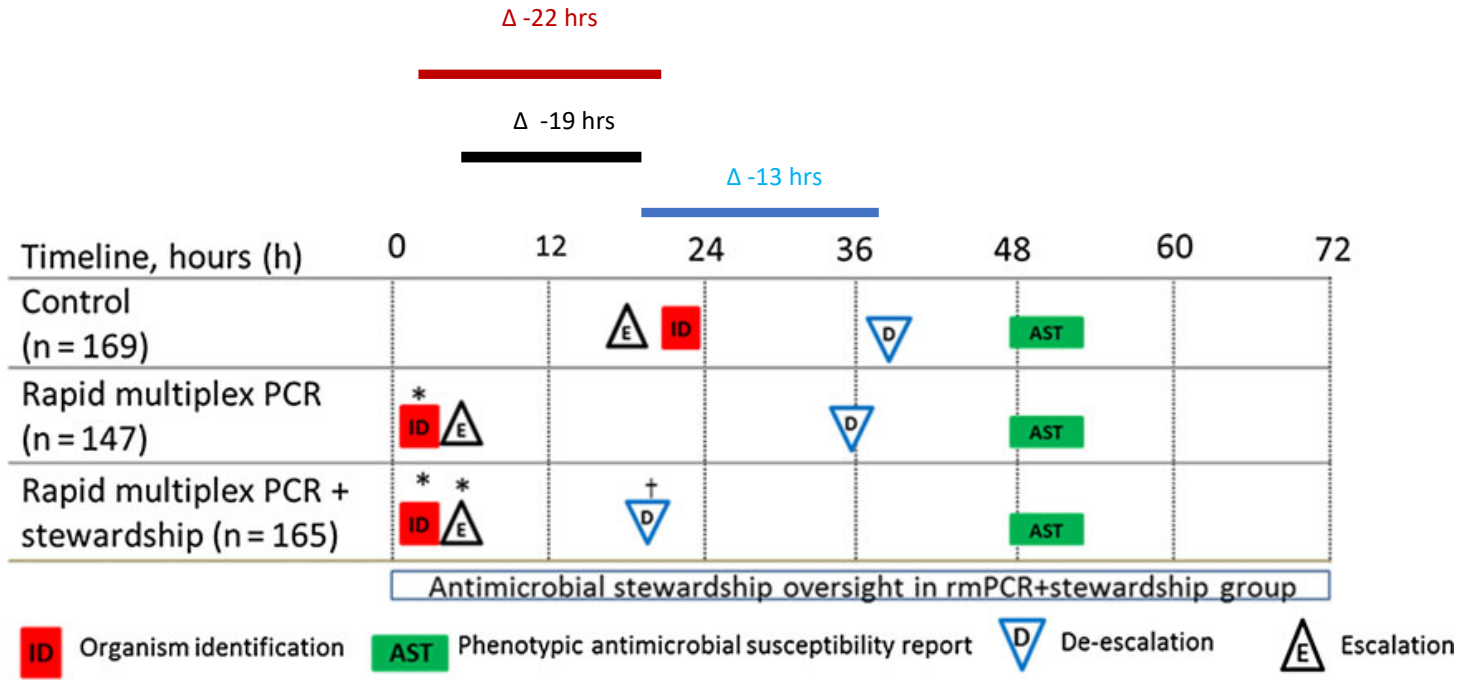
Example of Clinical Impact

*Randomized study of rapid molecular ID with limited resistance determinants (mec*A, *van* A/B and KPC) *from positive blood cultures (+BCx)*

Banerjee et al . CID 2015; 61(7):1071-80

3 Arm BCID Study

- 617 patients (12% FN)
  - standard work-up + reporting
  - PCR + enhanced reporting
  - PCR + enhanced reporting + stewardship



PCR arms less broad-spectrum use (-12 hrs)

De-escalation driven by Gram-positive organisms

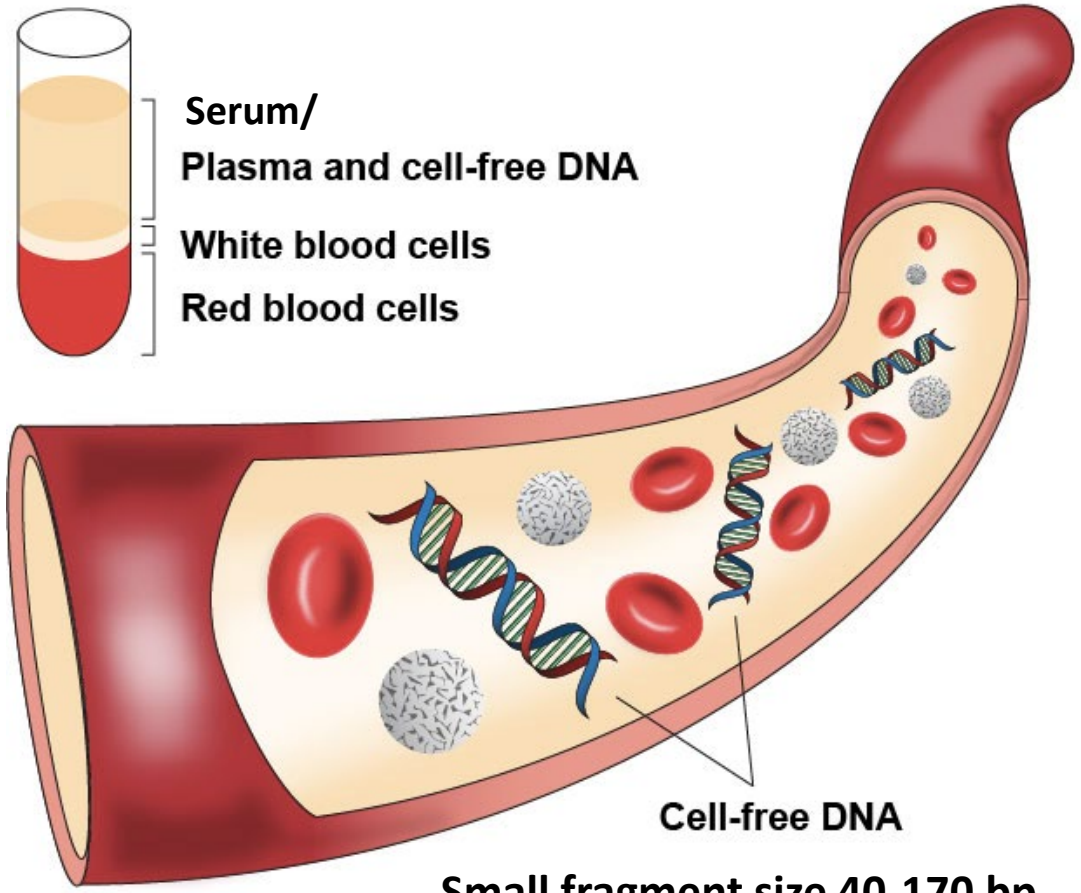
Microbial Cell Free DNA (mcfDNA)

- Enters the blood or other body fluid during cellular apoptosis or necrosis, translocation of commensals, or from localized invasive disease

- Detection by NGS or PCR
  - Targeted approaches may be more sensitive (microbial DNA 0.001%)
  - Unbiased (metagenomic) approaches detect more species

- Caveats
  - limited resistance information
  - low level mcfDNA detectable in plasma of healthy controls
  - persists longer than cultured organisms

Non-invasive sample type



Small fragment size 40-170 bp

mcfDNA sequencing in patients with FN

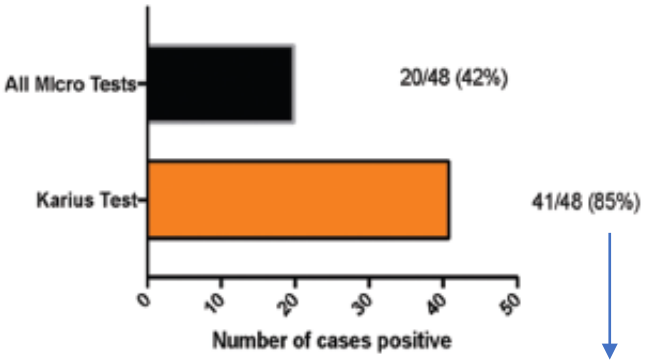
- Single center observational study of metagenomic send out test
  - 55 subjects with mcfDNA testing at fever onset and while febrile (up to 5 specimens)
  - compare DNA results to blood culture and clinical case adjudication by a panel
  - assessed agreement and potential impact on antimicrobial selection

mcfDNA agreement with blood culture and clinical diagnosis

Total (N = 55)	Blood Culture Positive	Blood Culture Negative	Clinical Diagnosis Positive[a]	Clinical Diagnosis Negative[b]
Karius test positive	9	31	41	0
Karius test negative	1[c]	14	7	7

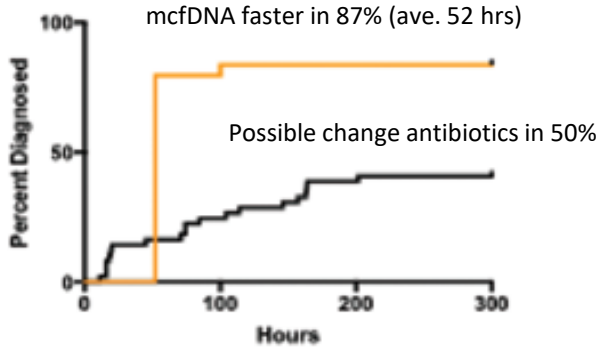
Few potential false negatives

Number of positive results in patients adjudicated to have infection



61% polymicrobial, often endogenous GI/oral flora

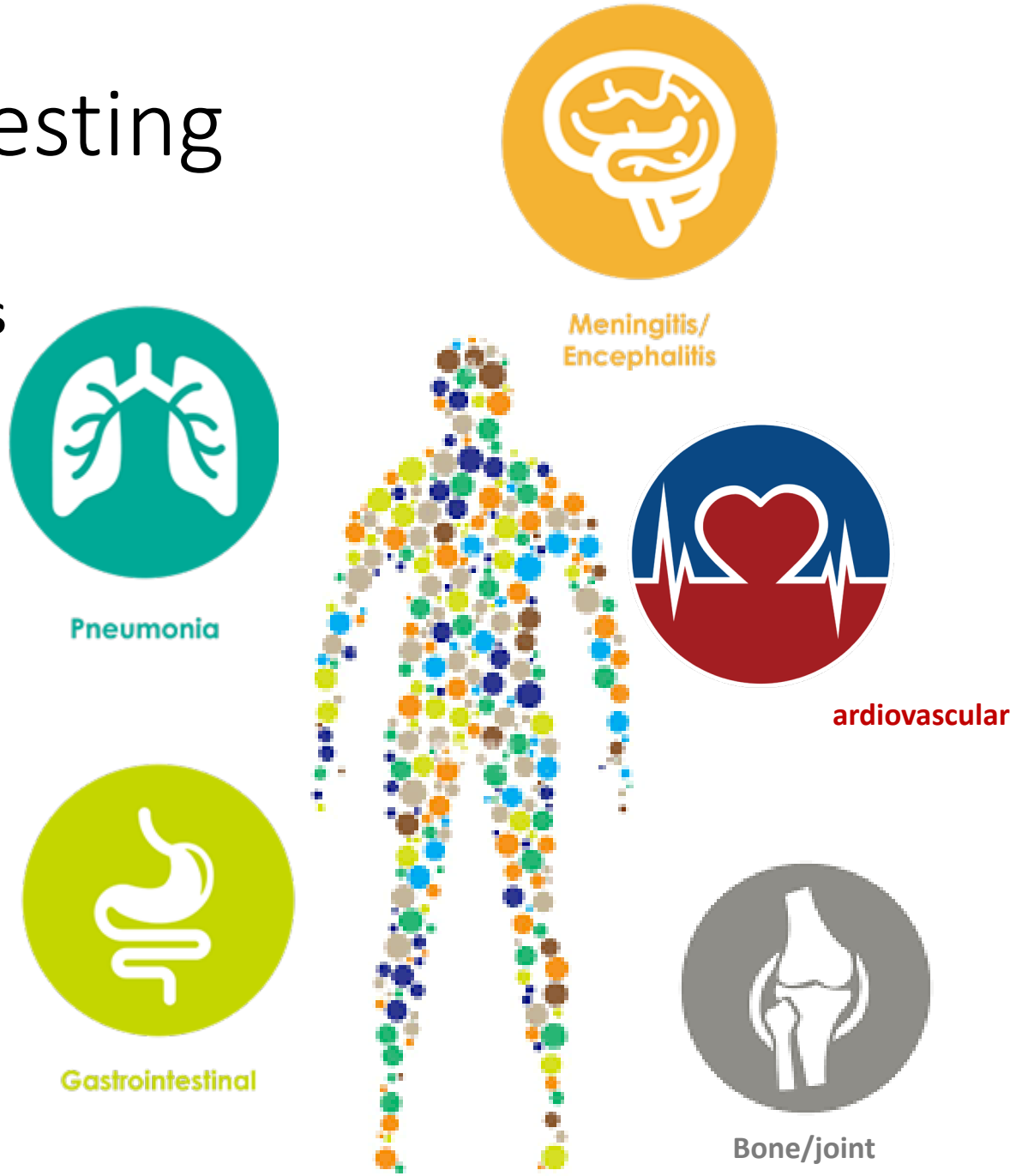
Time to organism identification



Benamu et al CID 2022; 74:1659

Syndromic Molecular Testing

- Various sample types, various methods
  - Targeted multiplex PCR panels
  - Broad range PCR with sequencing
  - Metagenomic NGS
- General comments
  - Higher positivity than culture
    - ➢ Inclusivity targeted panels may be limited
  - Negative predictive value uncertain

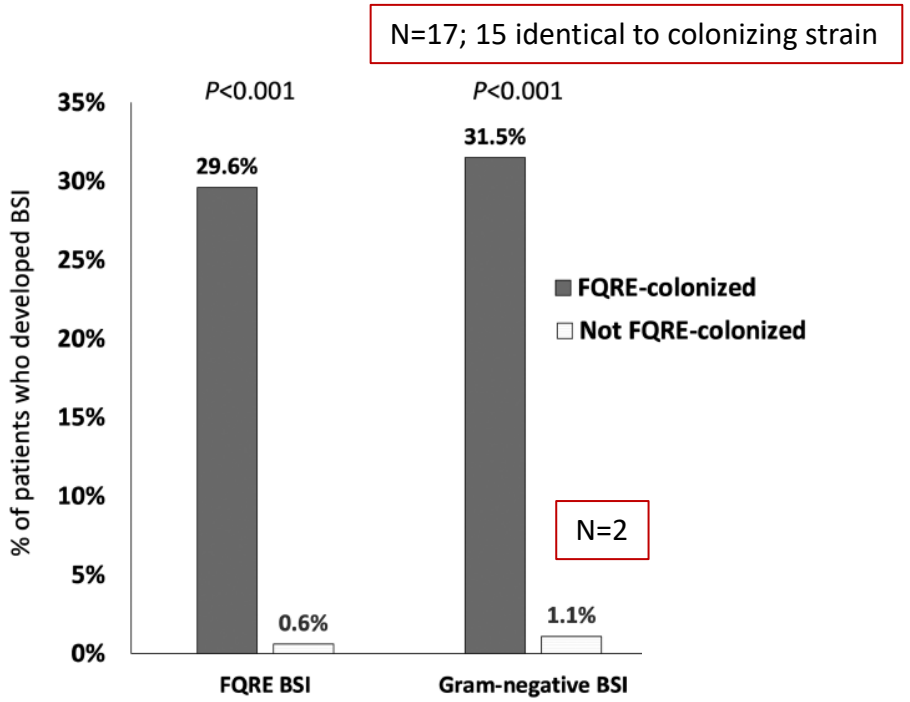


Colonization/microbiome

Fluoroquinolone resistant Enterobacteriaceae (FQRE)

- Single center observational
- 234 HSCT recipients received levofloxacin prophylaxis during neutropenia
  - Stool or rectal swab collected on admission and weekly until count recovery
    - ✓ Culture on selective MacConkey agar
    - ✓ Colonizing FQRE and subsequent BSI isolates underwent whole genome sequencing
    - ✓ Bacteremias tracked

Proportion of patients developing Gram- negative blood stream infection by colonization status



Satlin et al. CID 2021; 73(7):1257

Conclusions

- Blood culture remains an essential component of the FN work-up
  - rapid organism ID with AST/genotypic resistance from positive blood culture bottles now standard of care for more rapid antimicrobial adjustment

- Rapid culture independent syndromic tests
  - may also enable more rapid antibiotic modifications, especially when positive

- Colonization status may help inform optimal prophylaxis and/or risk for invasive infection

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ADMINISTRATION FOR STRATEGIC PREPAREDNESS AND RESPONSE

BARDA
BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY

Antibiotic Management for Neutropenic Patients Following a Nuclear Detonation Incident

Anita Sheoran, PhD

Health Scientist, Antimicrobials Program, Division of Chemical, Biological, Radiological, and Nuclear (CBRN) Countermeasures, Center of Biomedical Advanced Research and Development Authority (BARDA), Administration for Strategic Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS)

FDA Public Workshop: Drug Development Considerations for Drugs for Empiric Antibacterial Therapy in Febrile Neutropenic Patients; April 23, 2024

ASPR's mission:
Assist the country in **preparing for**, **responding to**, and **recovering from** public health emergencies and disasters.

The BARDA Model

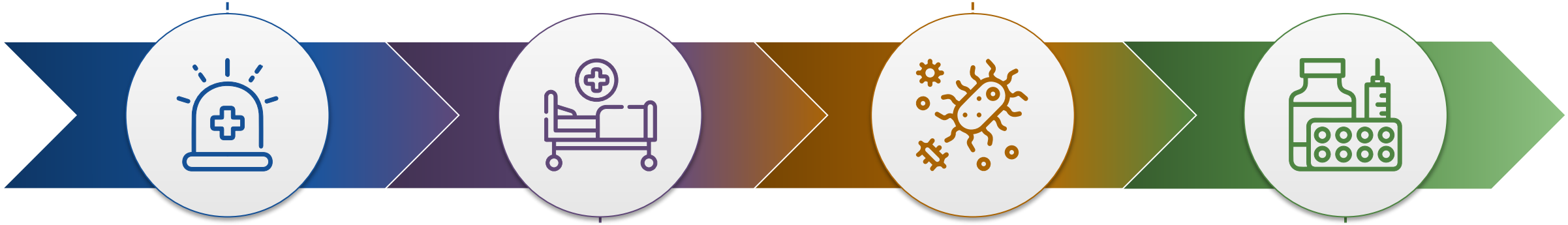
BARDA develops and makes available medical countermeasures (MCMs) by forming unique public-private partnerships to drive innovation off the bench to the patient to save lives.

- Flexible, nimble authorities
- Multi-year funding
- Cutting edge expertise
- Facilitate partnerships
- Promote innovation

Secondary Infections during Public Health Emergencies

PUBLIC HEALTH EMERGENCY
- CBRN Incident
- Pandemic Influenza
- Emerging Infectious Disease

SECONDARY INFECTIONS
- Drug-resistant bacteria and fungi present in healthcare settings
- Increased likelihood of patients developing secondary infections that cannot be treated with available antimicrobials

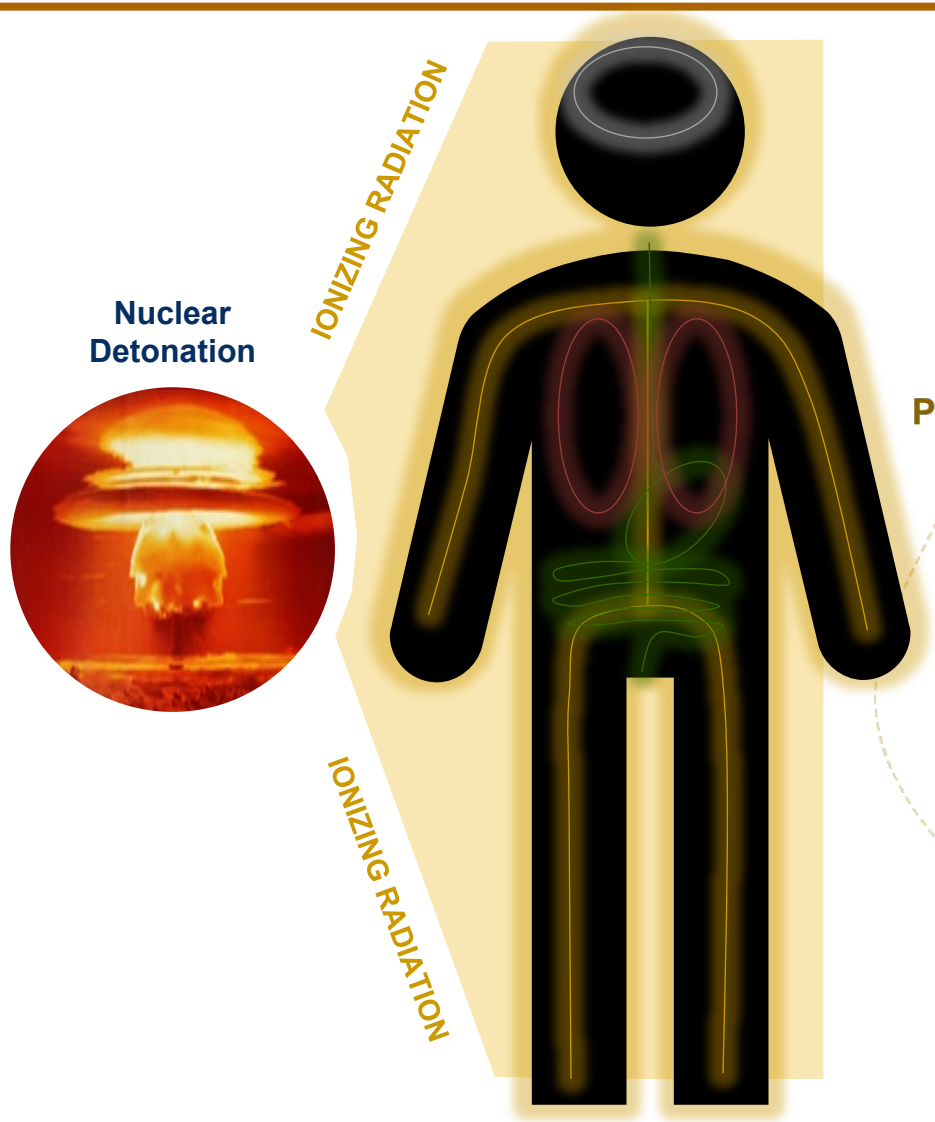


HOSPITALIZED PATIENTS
- More hospitalized patients
- Patients with prolonged hospital stays
- Additional patients requiring outpatient care

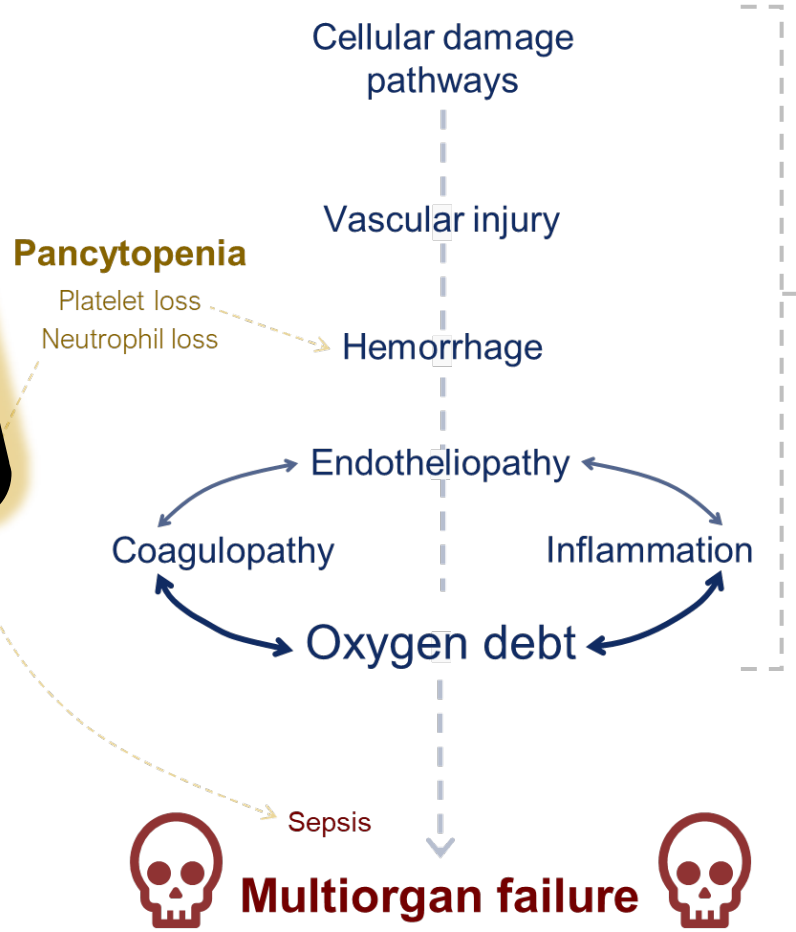
EFFECTIVE ANTIMICROBIALS
- Therapeutics needed to effectively treat patients
- Diagnostic tools needed to appropriate prescribing
- Allows patients to fully recover from the emergency

Radiological and Nuclear Threats and Injuries

Exposure – Penetrating radiation



Acute Radiation Syndrome



Products and supportive care therapeutics

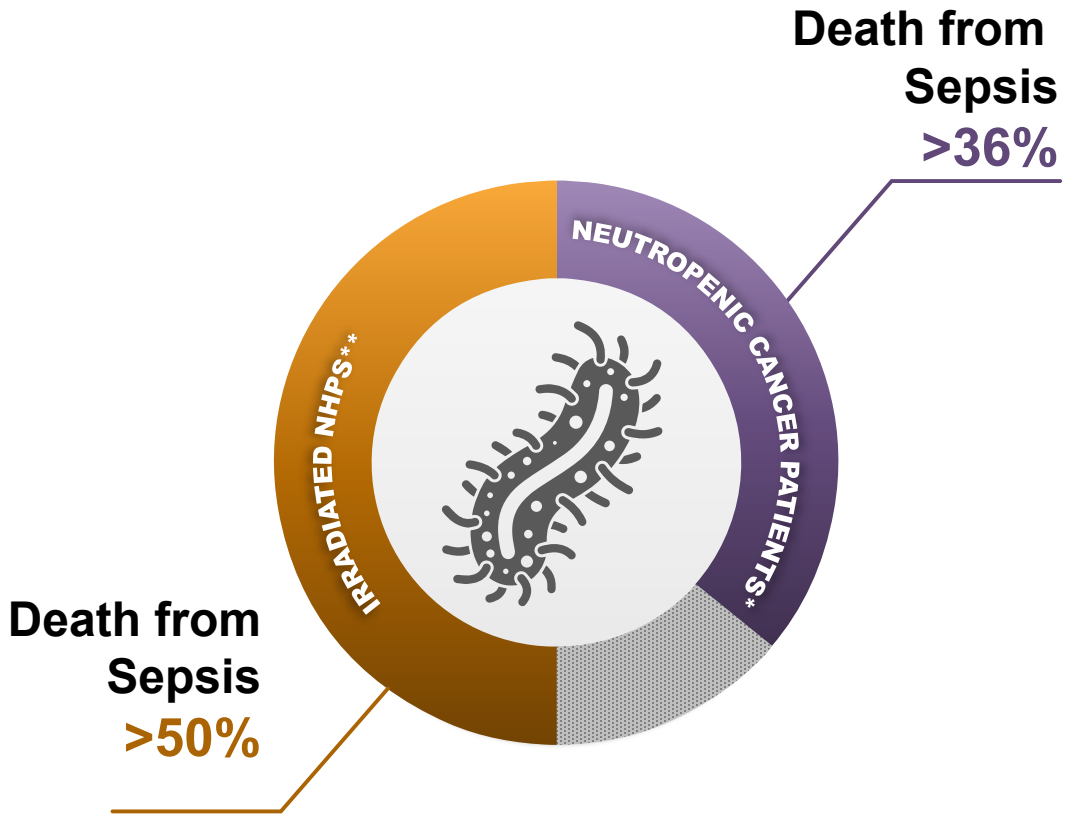
- **Broad spectrum antibiotics**
- **Antifungals**

- **Antivirals**
- **Blood products**
  - **Whole blood**
  - **Plasma**
  - **Platelets**
  - **Cryoprecipitate**

- **Fluids**
- **Anti-emetics (ondansetron)**
- **Pain management**
- **Corticosteroids**
- **Anti-inflammatories**
- **Topical creams (radiation and thermal burns)**

Threat Posed by Antimicrobial Resistant (AMR) Bacteria

- **Infections caused by ESKAPE pathogens are associated with significant morbidity and mortality globally**
- **AMR in ESKAPE pathogens is expected to increase the rate of treatment failure in patients** *(Hematopoietic acute radiation syndrome (H-ARS) and Severe neutropenia in oncology patients)*
- **Lack of robust clinical data in patients with H-ARS in the setting of increasing AMR**



*Bacteria identified in neutropenic cancer patients include: *Staphylococcus aureus*, *Enterococcus* spp., viridans group streptococci, *Klebsiella pneumoniae*, *Escherichia coli, and Pseudomonas aeruginosa*

**Bacteria identified in NHPs post-TBI include: *S. aureus*, viridans group streptococci, *Enterococcus spp.*, and *E. coli.*

Clin Med (Lond). 2013 Apr; 13(2): 185–187

The Need for Next Generation Antimicrobials

Next generation antimicrobials are critical for the treatment of increasingly common multidrug-resistant secondary infections

https://www.bmj.com/content/379/bmj.o2731.long https://wwwnc.cdc.gov/eid/article/29/8/23-0567_article https://www.ijidonline.com/article/S1201-9712(23)00523-4/fulltext

Gaps in Antibiotic Management in Prolonged Neutropenic Patients during Public Health Emergencies

Availability of antibacterial treatment options for patients with febrile neutropenia in the mass causality incident (MCI)

+

Understand the role of prophylaxis in patients at high risk of neutropenia in case of an MCI

Need for clinical consensus about both types of treatment paradigms

---

Understand clinical need for such indications in daily practice

---

Understand feasibility in design of clinical development plan for these types of programs

---

Ideal TPP based on clinicians' experiences

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Clinical Development of Antibiotics for Empiric Therapy of Febrile Neutropenia: Industry Perspective

Douglas Girgenti, MD
VP, Head of Development
Melinta Therapeutics, LLC

melinta therapeutics

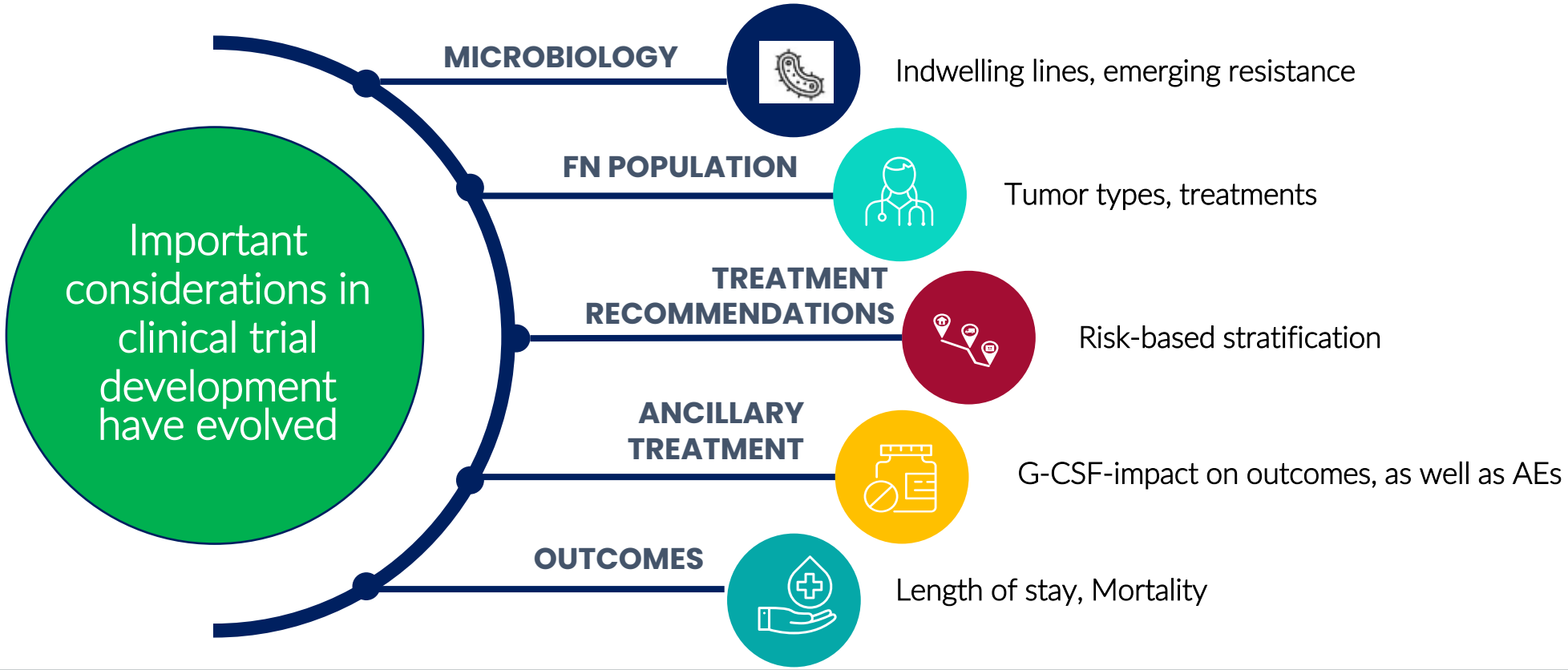
Disclosures

I am a full-time employee of Melinta Therapeutics, LLC.

I have no other conflicts to disclose.

The views and opinions expressed in this presentation are solely my own and do not necessarily represent the views or opinions of my employer. I am not speaking on behalf of my employer or any other entity, but in my personal capacity as an expert in the field.

Currently Recommended Antibiotics for Empiric Therapy of FN Largely Based on Decades-Old Research



Advancements in the treatment of FN have important implications for clinical trial design

Antibiotics Recommended for Empiric Therapy of FN

Indicated and/or Recommended (IDSA, ESMO, ASCO) for Empiric Inpatient Treatment

Drug	RCT	Clinical Response	Licensed
Cefepime	Cefepime vs ceftazidime 2 RTCs, 317 episodes (Cefepime USPI)	51 vs 55%	Yes-IV monotherapy
Ciprofloxacin	Ciprofloxacin/piperacillin vs tobramycin/piperacillin 470 episodes (Cipro USPI)	63 vs 52%	Yes-in combination with piperacillin sodium
Ceftazidime	Meropenem vs ceftazidime 192 episodes (Lindblad, 1998)	50 vs 56%	No
Piperacillin-tazobactam	Pip-tazo vs pip-tazo + amikacin 760 episodes (delFavero 2001)	49 vs 53%	No
Imipenem-cilastin	Imipenem-cilastin vs cefepime 270 episodes (Cherif 2004)	51 vs 40%	No
Meropenem	Meropenem vs ceftazidime 471 episodes (Feld 2000)	54 vs 44%	No

Current Research of Antibiotic Candidates for Empiric FN Treatment

Few registered randomized comparative antibiotic trials for empiric treatment of FN (Clinicaltrials.gov, 09 Apr 2024)	
Not yet recruiting	• Ceftolozane/Tazobactam Versus Meropenem for Febrile Neutropenia on Patients Colonized With or at Risk for Infection With Extended Spectrum Beta Lactamase-Producing Pathogens
Recruiting	• A Trial of Fosfomycin vs Ciprofloxacin for Febrile Neutropenia
Terminated	• Daptomycin Versus Placebo in Patients With Neutropenia and Fever • Comparative Study of Ceftazidime-Avibactam Versus Standard of Care as Therapy in Febrile Neutropenic Adults With Cancer
Completed	• Comparing Ciprofloxacin (CPFX) With Cefepime (CFPM) in Febrile Neutropenic Patients With Hematologic Diseases • Comparison of Teicoplanin and Vancomycin in Initial Empirical Antibiotic Regimen for Febrile Neutropenic Patients • Piperacillin/Tazobactam for Empirical Therapy of Febrile Neutropenia • Meropenem Versus Meropenem Plus Glycopeptide in Patients With Febrile Neutropenia After Allogenic Blood Stem Cell Transplantation • Cefepime vs Ceftazidime as Empirical Therapy for Neutropenic Fever • Study Comparing the Safety and Efficacy of Piperacillin/Tazobactam to Cefepime in Patients With Hematologic Malignancy or Lymphoma

Numerous potential antibiotic candidates for empiric treatment of FN	
Class	**Drug/combination**
B-lactam, B-lactam/BLI combination	• Ticarcillin/clavulonate • Cefoperazone • Ceftolozone/tazobactam • Ceftazidime/avibactam • Cefiderocol
Carbapenem, carbapenem/BLI combinations	• Doripenem • Meropenem/vaborbactam • Imipenem/relebactam
Monobactam	• Aztreonam
Fluoroquinolone	• Delafloxacin

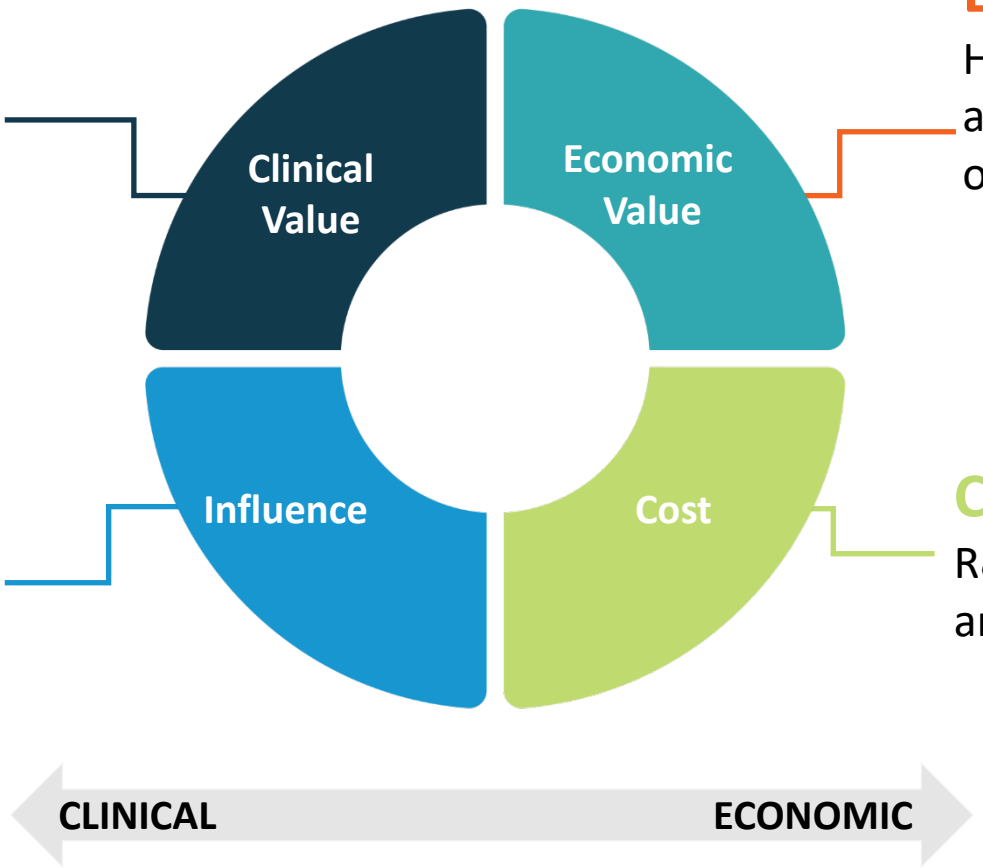
What is to Be Invested /Gained For an FN Indication?

CLINICAL VALUE

Clinical differentiation based on efficacy, safety, outcomes

ECONOMIC VALUE

Health economics, outcomes, quality, and other factors that could support or detract from perceived value



INFLUENCE

Weights/pressures on formulary decision makers (e.g., guidelines, advocacy)

COST

R&D/PDUFA + manufacturing costs vs anticipated revenue

What does the Current FN population look like?

…Relevant to Clinical Trial Considerations

- Approximately 60,000 US patients/year experience FN, with an estimated impact of $15,000/event
- Estimates of incidence range 13-21% for metastatic solid tumors, 30% or higher for hematologic malignancies

Important changes in chemotherapy use over the past 2 decades include

- Increased breadth of solid tumor/late-stage malignancies treated
- Newer myeloablative as well as targeted/ immunological therapies
- Increased utilization of allogeneic HSCT
- Increased use of central lines
- Shift towards a predominance of gram-positive pathogens
- Increased antimicrobial resistance/rise of invasive fungal infections
- Use of G-CSF and other supportive modalities
- Prophylaxis-antibiotic as well as antiviral, antifungal
- Reduced duration of therapy with introduction of step-down/short-course therapy
- Reduction in mortality to ~5-10%

Estimates of the Adult FN Population

- Median age ranging from 40s (e.g., breast) to 60s (lung, colon, hematologic)
- No overall gender differential (disease-specific)
- Overall population MASCC score median 19
- CVC-use ranging from majority to nearly all patients
- Fluoroquinolone prophylaxis in the majority of patients
- G-CSF use if FN risk >20% (or 10-20% with risk factors)
- ANC nadir will occur approx. 7-8 days post chemotherapy
- FN will typically occur 7-12 days post-chemotherapy
- 1/3 to as many as 2/3 of FN episodes will occur after 1st cycle
- Fever duration may be as brief as 2 days
- ANC recovery approx 7 days (solid), 15 days (hematologic)
- Duration of hospitalization likely to be 5-10 days
- Mortality <5% if MASCC $\geq$21, 40% if MASCC <15

What Does the Microbiology of FN Look Like?

…Relevant to Clinical Trial Considerations

- It is likely that 50% or more of patients will be diagnosed as fever of unknown origin only
  - Infectious as well as non-infectious (e.g., tumor-related, transfusion reaction, drug-induced) contributors
- Microbiologically-defined infection will be documented in 15-30% of patients
  - Slight gram-positive predominance over gram-negative organisms, with few anaerobes, viruses
- The remainder will be clinically-defined infection (e.g., pneumonia) without defined microbiologic etiology
  - Respiratory and abdominal sites likely to predominate over UTI, SSTI, BSI, CVC-related

Is there opportunity to use advanced testing to refine the clinical trial population and increase microbiological-ITT population?

- Inclusion based on biomarkers such as procalcitonin as predictor of sepsis?
- Exclusion based on galactomannan, 1,3-beta-D-glucan (likelihood of fungal/candidal infection), or rapid viral testing?
- Utilize rapid diagnostics to improve and reduce time to microbial identification?

Enigma of Existing Drugs as Candidates for Empiric FN Treatment?

Microbiology Label Indication vs Microbiological Spectrum of FN

With consideration of newer β-lactam/β-lactamase inhibitor combinations which target ESBL and CRE (e.g., cefepime/enmetazobactam, meropenem/vaborbactam)

- Original β-lactam antibiotic is recommended for empiric FN treatment
- Respective β-lactam/β-lactamase inhibitor ***should*** have superior if not noninferior efficacy vs original β-lactam alone
    - Yet, β-lactam/β-lactamase inhibitor is indicated specifically for treatment of gram-negative pathogens, as evaluated in previous Phase 3 studies (e.g., cUTI)

Would a RCT Phase 3 study using the original β-lactam as comparator support a label indication for FN?

Would an indicated β-lactam/β-lactamase inhibitor be utilized empirically, considering antibiotic stewardship, cost?

How Should FN Be Evaluated in RCTs?

Clinical Trial Design Considerations

"The results of many clinical trials on empirical therapy in febrile, neutropenic cancer patients cannot be readily transferred to the clinical practice, because the methodology is often flawed and definitions, study endpoints and eligibility criteria differ from trial to trial."*

Primary endpoint considerations:

- Clinical response (i.e., success without any modification) favored over outcomes (e.g., mortality: low occurrence, not infection-related)
- Is it sufficient to design the study to demonstrate noninferiority vs. SoC drug, or is superiority required?
- What will be the anticipated label indication, considering the population and endpoint evaluated?

Additional endpoints for consideration:

Clinical:

- Modification of the initial antibiotic regimen
- Eradication of the pathogen (if documented)
- Relapse of primary infection
- No modification of the initial antibiotic regimen

Outcomes:

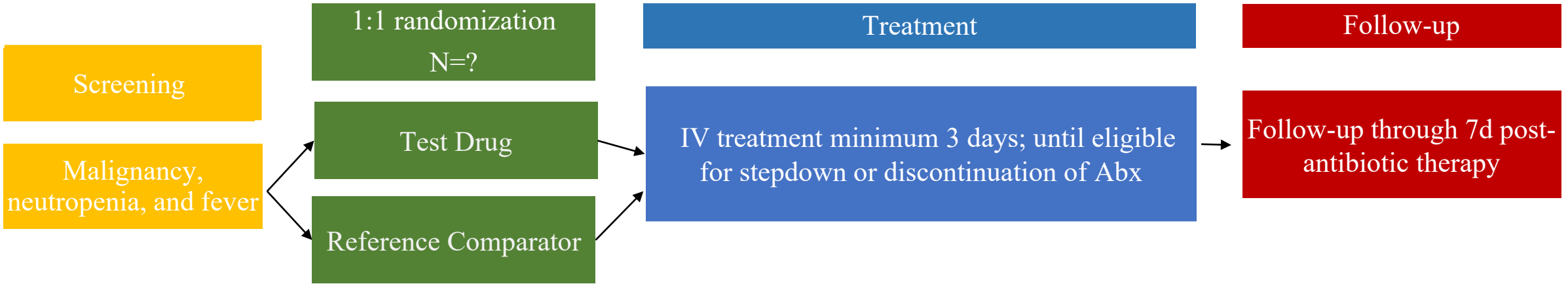
- Time to defervescence, clearing of symptoms and signs
- Length of hospital stay
- Mortality/mortality due to infection

Other design considerations:

- Stratification (e.g., disease type, G-CSF usage, prophylaxis)?
- Re-enrollment of previously enrolled subject (e.g., resolved without treatment for >7d, previous organism susceptible)?
- Permit early de-escalation (e.g., >72 hours) to narrow-spectrum IV or oral step-down?

* Viscoli et al., Eur J Cancer, 1995

Hypothetical Efficacy Study in Febrile Neutropenia



Inclusion/exclusion:
- Malignancy type
- Duration of FN
- Prior FN occurrence

Stratification:
- Malignancy type
- Prophylaxis
- G-CSF

Randomization:
- Eligible comparator
- Monotherapy

Concomitant:
- Antivirals
- Antifungal
- PCP

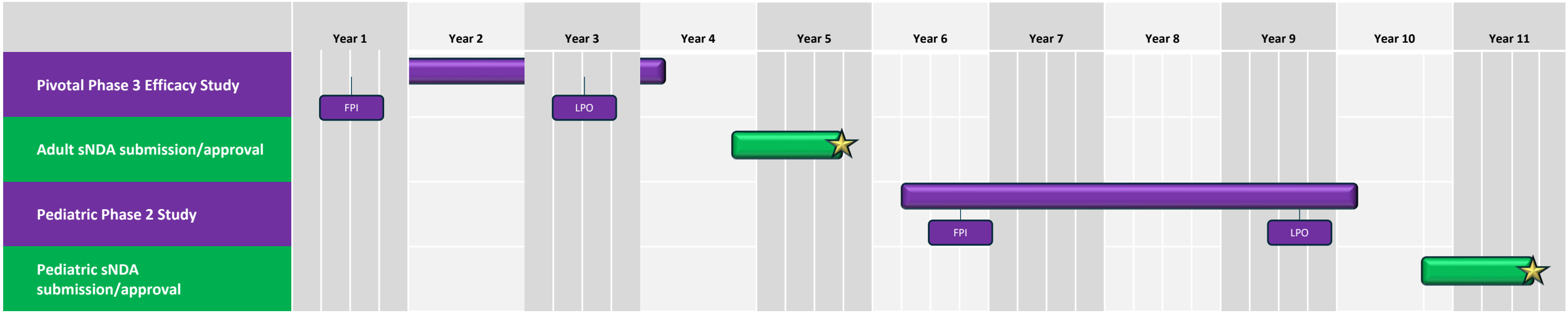
Endpoints:
- Clinical/micro
- Outcomes
- Time to defervescence

Expectations:
- FUO >50%
- Micro-defined 15-30%
- Clinically-defined ~20-35%

Subgroup analysis:
- Malignancy type
- Severe neutropenia
- BMT
- Prophylaxis?
- Antifungal/viral
- G-CSF
- Early discontinuation/ stepdown

Hypothetical FN Clinical Development Program

Likely Timeline, Costs



Crude assumptions:

- N~400, rand 1:1
- 3 countries, 15 sites
- 24m enrollment
- Cost ~$30-40M

Crude assumptions:

- N~100, open-label
- Similarly-3 countries, 15 sites
- 36m enrollment
- Cost ~$10-12M

Are There Opportunities for More Streamlined Clinical Development?

Could approval for empiric treatment of FN be obtained based on existing indication (e.g., UTI, HABP/VABP), with PK-PD modeling and simulation of PTA against relevant FN pathogens?

- Would inclusion of patients with neutropenia in pivotal trials for other indications support an FN indication?
- Would Pragmatic Studies / Real-World Evidence support approval?

Could evaluation of multiple candidate antibiotics be considered in a platform trial design?

- Sample size and cost reduction per drug evaluated
- Multiple ‘shots on goal’ for success reduces overall risk
- Reduction of start-up and overall timelines for new drug added to study
- Potential to evaluate efficacy across multiple antibiotic classes

Acknowledgements

Thanks to my esteemed colleagues for contributing to this presentation

- Aaron Dane
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- Peter Piliero
- Mark Redell

U.S. FOOD & DRUG ADMINISTRATION

Virtual Public Workshop:
Drug Development Considerations for Empiric Antibacterial Therapy in Febrile Neutropenic Patients

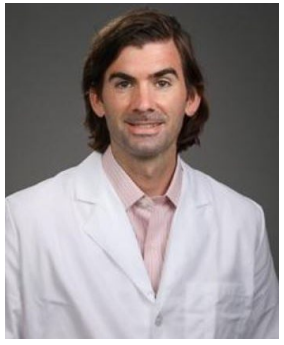
Hosted by: Center for Drug Evaluation and Research, Office of Infectious Diseases (OID) U.S. Food and Drug Administration

BREAK

Session 2: Regulatory Perspective and Trial Design Challenges and Considerations

Radu Botgros, MD

Daniel Rubin, PhD



Robert Pease, MD

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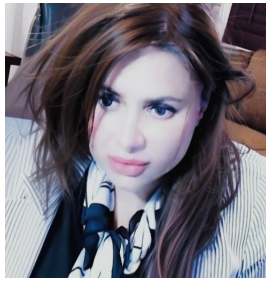

Rama Kapoor, MD

Katsukiko Ichimaru

Daniel Rubin, PhD

Empiric Antibacterial Therapy in Patients with Febrile Neutropenia: Regulatory Pathways and Programs to Expedite Drug Development

Robert C. Pease, MD, MPH
Medical Officer, Division of Anti-Infectives, FDA

Antibacterial Therapy Febrile Neutropenia Workshop
April 23, 2024

Outline

- Approved Antibacterials for Febrile Neutropenia
- Statutory Standards
- Confirmatory Evidence
- Regulatory Pathways/Expedited Programs
- QIDP
- Orphan Drug Designation

Background

- Two FDA approved antibacterials for empiric therapy for febrile neutropenic patients
  - Cefepime (1997)
  - Ciprofloxacin intravenous in combination with piperacillin sodium (1997)
- **No new antibacterials approved for this indication in > 25 years**
  - No oral drugs have been approved for this indication
- Scientific and practical challenges that need to be addressed

Statutory Standards

- A drug's effectiveness must be established by substantial evidence defined as:
  - "evidence consisting of **adequate and well-controlled** investigations, including clinical investigations,…" [The United States Federal Food, Drug, and Cosmetic 505(d) 21 USC 355(d)]
  - Interpreted generally as requiring two adequate and well-controlled (A&WC) trials, each convincing on its own
- Section 115(a) of the Modernization Act amended the provision to make clear that FDA may consider "data from one A&WC clinical investigation and confirmatory evidence"

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft, December 2019): https://www.fda.gov/media/133660/download

Types of Confirmatory Evidence

A. **Clinical Evidence from a Related Indication**
B. Mechanistic or Pharmacodynamic Evidence
C. Evidence from a Relevant Animal Model
D. Evidence from Other Members of the Same Pharmacological Class
E. Natural History Evidence
F. Real-World Data/Evidence
G. Evidence from Expanded Access Use of an Investigational Drug

Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (Draft, September 2023)
https://www.fda.gov/media/172166/download

Clinical Evidence from a Related Indication

Submission for a new indication for an already approved therapy, where one adequate and well-controlled clinical investigation of the drug for the new indication is **supported by the results from the clinical investigation or investigations that formed the basis of the previous approval** (for a different but closely related indication).

- Example: Single Phase 3 trial for febrile neutropenia plus confirmatory evidence in a relevant indication (e.g., HABP/VABP)

Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (Draft, September 2023)
https://www.fda.gov/media/172166/download

Regulatory Pathways

- **Approval Pathways**
  - **Traditional:** based on a clinical endpoint measuring how a patient **feels**, **functions**, or **survives**
  - **Accelerated:** Expedited pathway based on **a surrogate endpoint** that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality; [21 CFR 314.500, (Subpart H)
  - **Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD):** For drugs that are intended to treat a serious or life-threatening infection in a **limited population** of patients with unmet needs

Limited Population Pathway for Antibacterial and Antifungal Drugs – The LPAD Pathway (Draft, August 2020)
https://www.fda.gov/media/113729/download

Overview of Expedited Programs

	Fast Track	Breakthrough Therapy	Priority Review
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Actions to expedite review	Shorter clock for review of marketing application (6 months compared with the 10-month standard review)
Additional Considerations	Designation may be rescinded if it no longer meets the qualifying criteria for fast track	Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy	Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Expedited Programs for Serious Conditions—Drugs and Biologics (Draft, May 2014)
https://www.fda.gov/media/86377/download

Qualified Infectious Disease Product (QIDP) Designation

- Incentives for antibacterial or antifungal drugs intended to treat *serious or life-threatening conditions* and demonstrate the potential to address unmet medical needs
  - 5-year extension of marketing exclusivity for certain drugs
  - Priority review for the first application for a QIDP
  - Eligible for fast-track designation
- > 35 designated products have been approved

Qualified Infectious Disease Product Designation (Draft, May 2021)
https://www.fda.gov/media/148480/download
https://www.fda.gov/drugs/drug-approvals-and-databases/compilation-cder-new-molecular-entity-nme-drug-and-new-biologic-approvals

Orphan Drug Designation

- Rare diseases or conditions (affecting fewer than 200,000 people in the US)
- Incentives:
  - Tax credits for qualified clinical trials
  - Exemption from user fees
  - Potential for 7 years of market exclusivity after approval
- May use expedited programs during their development, should they qualify

Summary

- No new approved antibacterials for febrile neutropenia in > 25 years
- No oral antibacterials have been approved for febrile neutropenia
- Sources of Confirmatory Evidence
- Regulatory pathways are available to expedite development

Regulatory Perspective on Clinical Trial Design Considerations for Empiric Antibacterial Therapy in Febrile Neutropenia

Rama Kapoor, MD

Senior Medical Officer

Division of Anti-Infectives

Office of Infectious Diseases/OND/CDER/FDA

Drug Development Considerations for Empiric Antibacterial Therapy in Febrile Neutropenic Patients Workshop

April 23, 2024

Presentation Outline

- General regulatory considerations for a febrile neutropenia indication
- The challenge of heterogeneity – impact on inclusion/exclusion criteria and choice of the primary analysis population
- Primary efficacy endpoint considerations
- Unmet need in the treatment of FN
- Summary

Regulatory Considerations
Regarding Development for a Febrile Neutropenia Indication

- At least one adequate and well-controlled trial will be needed.
- FDA recognizes that heterogeneity among patients with febrile neutropenia presents unique challenges for designing a trial that will be both interpretable and feasible.
- These challenges impact both inclusion/exclusion criteria and choice of the primary analysis population.
- A main focus of this workshop is discussing ideas that may address these challenges.

Characteristics of Adequate and Well-Controlled Trials

1	There is a clear statement of the objectives and proposed methods of analysis
2	Permits valid comparison with a control to provide quantitative assessment of drug effect
3	Method of selecting subjects provides assurance they have the disease being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.
4	Method of assignment to study arms minimizes bias and is intended to ensure comparability between groups.
5	Measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.
6	Methods of assessing treatment response are well-defined and reliable.
7	Analysis of the results is adequate to assess the drug effects. Analytic methods used, comparability of test and control groups, effects of any interim analyses should be described.

21 CFR 314.126

Heterogeneity:
Febrile Neutropenia Categories

Based on clinical course, FN episodes are categorized as follows:

- **Microbiologically defined infection**
  - bacteremia without a definable site of infection
  - a microbiologically defined site of infection (e.g., pneumonia, cellulitis), with or without bacteremia
- **Clinically defined infection**: A site of infection is diagnosed (e.g., pneumonia, cellulitis), but without confirmatory microbiologic data.
- **Unexplained fever (possible infection):** Fever that is not accompanied by either clinical or microbiologic evidence of infection and is not considered non-infectious.
- **Non-infectious fever**

Adapted from: From the Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. J Infect Dis. 1990 Mar;161(3):397-401.

Heterogeneity:
Distribution of FN Categories in Previously Conducted Trials

	Microbiologically Defined	Clinically Defined	Unexplained Fever
Pizzo et al. NEJM 1986	15% (81/550)[a]	14% (75/550)	72% (394/550)
EORTC NEJM 1987[b]	35% (305/872)	26% (225/872)	39% (342/872)
Sanz et al. JAC 2002	35% (308/867)	27% (231/867)	38% (328/867)
Gil L et al. Infection 2007	39% (113/290)	9% (27/290)	52% (150/290)
Verlinden et al. OFID 2022	31% (419/1367)	24% (329/1367)	45% (619/1367)

a: Only patients with bacteremia included; b: 135 episodes with doubtful infections were excluded from analysis; EORTC: The European Organization for Research and Treatment; JAC: Journal of Antimicrobial Chemotherapy; NEJM: The New England Journal of Medicine; OFID: Open Forum Infectious Diseases

Note: All studies listed here evaluated number of episodes; Study by Gil et al looked evaluated patients (one episode per patient)

Superiority vs. Non-Inferiority Trial Designs

Superiority Trial	Non-Inferiority (NI) Trial
• Demonstrates efficacy by showing test drug is superior to control • Generally, the strongest evidence of effectiveness	• Demonstrates efficacy by showing test drug is not less effective than active control by more than a pre-defined amount (NI margin) • Relies upon an assumption, not confirmed in the trial, that the control had its anticipated effect (which is the basis for the NI margin)

Note that either trial design can utilize an active comparator.

Impact of FN Heterogeneity

Superiority Trial	Non-Inferiority (NI) Trial
• Including subjects in the primary analysis population who ultimately are classified as “unexplained fever” does not impact trial interpretability if superiority is demonstrated. • However, including subjects with “unexplained fever” in the primary analysis population will likely make it more difficult to demonstrate superiority in the trial.	• For the trial to be interpretable, the characteristics of the patients in the primary analysis population of the current trial need to be sufficiently similar to the patients in the historical placebo-controlled trials that support the NI margin (e.g., patients with FN in historic placebo-controlled trials had confirmed bacteremia (microbiologically defined).

Possible Enrichment Strategies to Improve Trial Feasibility

- Use of clinical characteristics such as selection of specific Inclusion/exclusion criteria to increase the likelihood of bacterial infection.
- Use of rapid diagnostic tools such as polymerase chain reaction, microbial cell-free DNA for bacteria, or advanced imaging techniques.
- We hope to discuss further and include other ideas during the panel discussion.

Trial Endpoints

- The methods assessing the response to the drug should be well-defined and reliable.
- Endpoints should be clinically meaningful.
- Clinical endpoint
  - Characteristic/variable that directly measures a therapeutic effect (how a patient feels, functions, or survives)
  - Microbiological outcomes are not clinical endpoints
- For an NI trial, the primary endpoint also needs to be sufficiently similar to the historical trials justifying the NI margin, e.g., most historical trials demonstrated a mortality advantage.

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft, December 2019): https://www.fda.gov/media/133660/download; BEST resource https://www.ncbi.nlm.nih.gov/books/NBK453484/

Primary Endpoint Considerations for FN Trials

All cause mortality

- Objective and highly clinically relevant
- Limitations
  - Death may not be related to a bacterial infection.
  - Patients who survived after modification of study therapy due to poor clinical response or adverse events may be considered success.
  - All-cause mortality in FN has decreased over time. This advance impacts sample size.

Primary Infection-related Mortality

- More reflective of the efficacy of the study drug. However, the cause of death may not be reliably adjudicated, and lowers event rate further.

Clinical Success

- Includes other outcomes of interest. May improve feasibility.
- Some endpoint components may be subjective, e.g., modification of antibacterial therapy or initiation of rescue therapy to define failure.
- Blinding or other strategies to address observer bias are important considerations.

Mortality Rates in FN Trials

	All Deaths	Deaths due to Primary Infection	Timing of Evaluation
EORTC NEJM. 1987	26% (34/129)	13%* (17/129)	During study Period
EORTC AAC, 1991	22.7% (23/101)	10** (10/101)	During study Period***
EORTC CMI, 2006	8% (53/763)	2.4% (18/763)	30 days
Bucaneve et al. 2014	8% (31/390)	6% (22/390)	7-10 days after completion of therapy
Bhardwaj et al. 2021	12% (23/193)	-	Inpatient
Paret et al. 2022	2% (6/297)	1% (3/297)	30 days
Verlinden et al. 2022	1.8% (17/958)	1.1% (11/958)	During hospitalization

AAC: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, CMI: Clinical Microbiology and Infectious disease
*9% died due to Gram-negative bacteremia
**majority of deaths within 3 days. All died due to infection were bacteremic.
***Death occurred within 2 weeks

Primary Efficacy Endpoints in FN Trials

- Most FN trials described in published literature used a composite endpoint to evaluate response to therapy, but the definition and timing of the endpoints varied.
- Success was generally defined as resolution of infection and eradication of infecting microorganism without modification of study therapy.
- Failure was generally defined as death, persistence of symptoms or causative pathogens, or modification of study therapy.
- Patients with fungal or viral infection, non-infectious fever, protocol violations, discontinuation secondary to severe adverse effects were considered non-assessable for response in some trials.
- In general, a trial for regulatory purposes would be expected to use an ITT or modified ITT analysis.

Unmet Needs for the Treatment of FN

Outpatient Treatment?

- In the setting of increasing prevalence of quinolone-resistant and ESBL-producing pathogens, clinicians may be reluctant to use currently recommended oral therapies for outpatient empiric treatment of FN.
- An oral drug with activity against drug-resistant pathogens may be a suitable option for developing for outpatient management of FN.

Other Unmet Needs?

Summary

- A major goal of the workshop is to discuss ideas to address the challenges in the design of FN trials:
  - Heterogeneity of the population of patients with FN is a major challenge impacting trial feasibility for all trials and interpretability for an NI trial.
  - Strategies to enrich the trial population for patients with bacterial infections needed.
  - With the decrease in mortality rate, choosing a primary efficacy endpoint also challenging.
  - Greater flexibility for superiority trial designs, but clinical meaningfulness of measured outcomes, strategies to address observer bias, and an ITT or modified ITT analytic approach are important considerations.
- Another goal of the workshop is to understand unmet need in the treatment of FN and discuss strategies to develop drug products to address these needs.

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Thank you

Statistical considerations in clinical trials in febrile neutropenia

Daniel Rubin, PhD

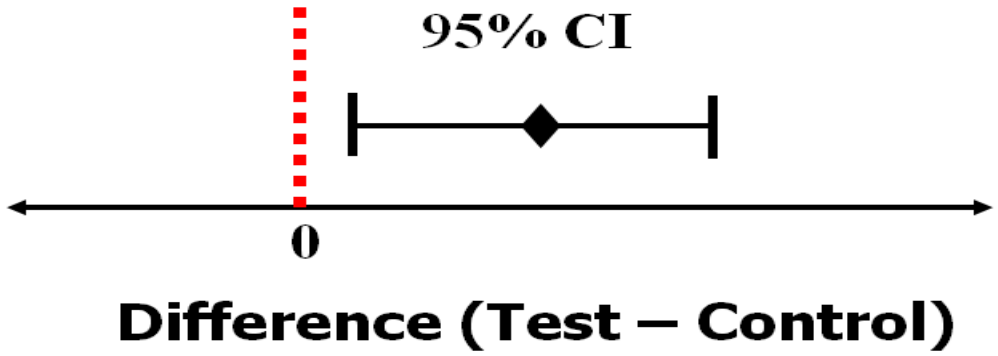
April 23, 2024

Outline

- Superiority trials
- Noninferiority trials and noninferiority margins
- Statistical tradeoffs
- Sample size projections

Superiority trials

- In a superiority trial the objective is to determine whether the experimental arm is better than the control arm

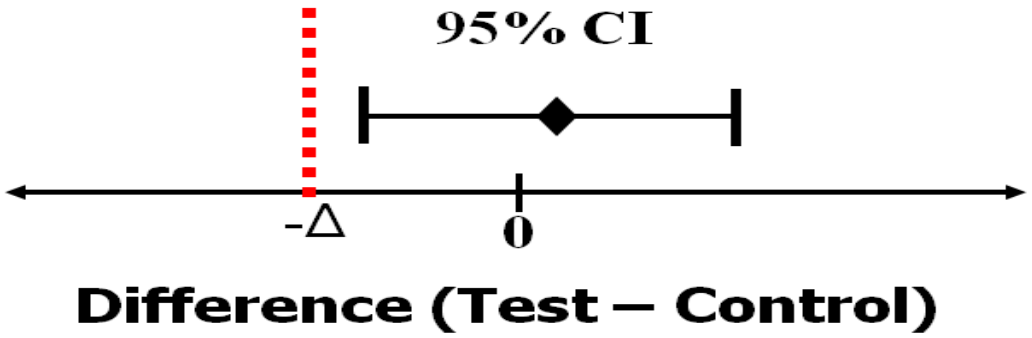


Superiority trials

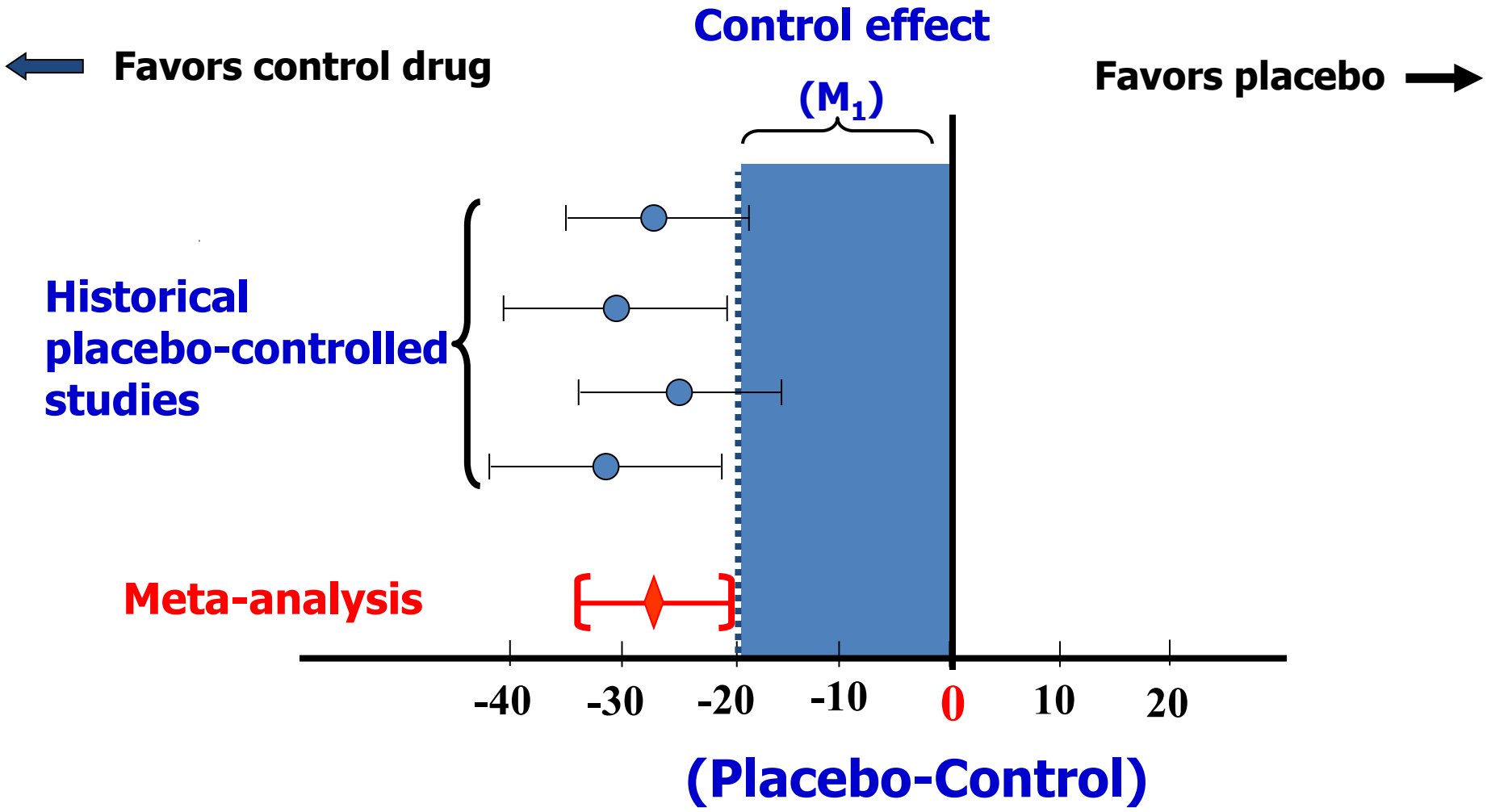
- Head-to-head comparison:
  - Experimental drug versus standard of care control drug
- Add on design:
  - Standard of care + experimental drug versus standard of care + placebo
- Could consider enriching the inclusion/exclusion criteria or the analysis population for patients in whom superiority may be achievable
- The main challenge relates to feasibility

Noninferiority trials

- In a noninferiority trial the objective is to determine whether the experimental drug is unacceptably worse than the control drug



Noninferiority margins



Noninferiority margins

- Discounting:
  - Estimated M_1 should be reduced if one needs to account for uncertainties about assumptions that have been made
- Preservation:
  - To prevent clinically unacceptable loss of efficacy, control effect over placebo (M_1) should be reduced to margin M_2
- For example, if the noninferiority margin M_2 is 10% the clinical trial must show with statistical confidence that the success rate for the experimental arm is no more than 10% worse than the success rate for the control drug

Noninferiority margins

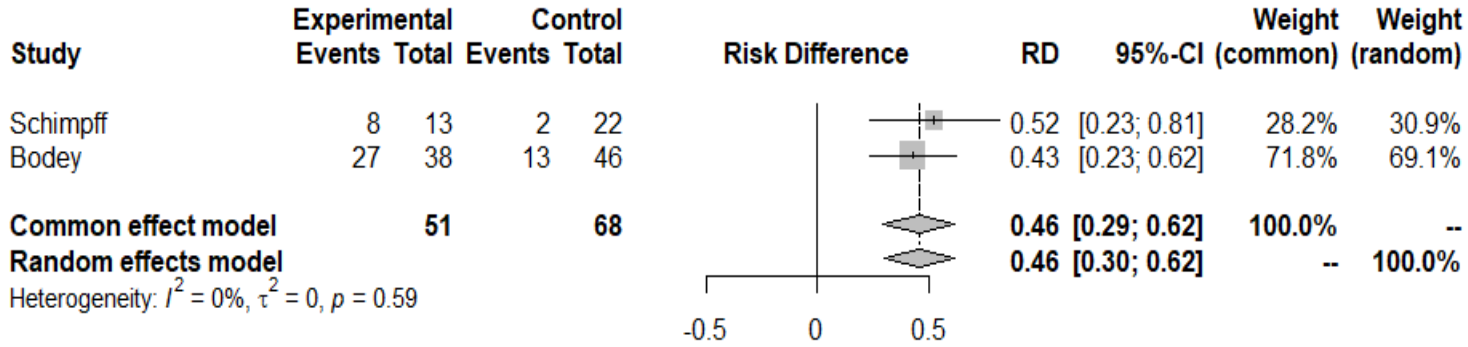
- For febrile neutropenia we are not aware of any randomized controlled trials comparing empiric antibacterial treatment to placebo
- Nevertheless, there is evidence that for certain populations and endpoints, empirical antibacterial therapy would have a very large treatment effect compared to a hypothetical placebo

Noninferiority margin

- Schimpff, S., Satterlee, W. & Young, V. M. (1971). Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *New England Journal of Medicine* **284,** 1061–7.
  - In the year before use of empiric treatment with carbenicillin and gentamicin for leukemia patients, the survival rate for patients with *P. aeruginosa* bloodstream infections was only 2/22 (9%), and half of deaths were ≤72 hours of drawing a first positive blood culture
  - After empiric treatment, the survival rate increased to 9/13 (69%)
  - After empiric treatment, the rate of complete improvement was 8/13 (62%)
- Bodey, G.P., Whitecar, J.P., Middleman, E. & Rodriguez V. (1971). Carbenicillin therapy for Pseudomonas infections. *Journal of the American Medical Association* **218,** 62-66.
  - In cancer patients treated from 1965-1968 with a polymyxin the survival rate within 10 days from the onset of septicemia was 13/46 (28%)
  - After introducing empiric treatment with carbenicillin the survival rate within 10 days from the onset of septicemia increased to 22/27 (81%)
  - After introducing empiric treatment with carbenicillin the rate of complete response for *P. aeruginosa* bacteremia episodes increased to 27/38 (71%)

Noninferiority margin for clinical response

- Meta-analysis of Schimpff et al. 1971 and Bodey et al. 1971 studies



- This analysis estimates the (antibacterial – hypothetical placebo) difference in clinical response rates is at least 30%
- Limitations and reasons for discounting the large estimated treatment effect
  - Non-randomized comparisons
  - Differences in background care compared with contemporary patients
  - Higher certainty of lethal bacterial infections than in pragmatic clinical trials

Statistical tradeoffs

- Consider whether analysis populations should include or should restrict to
  - Fever of unexplained origin
  - Clinically documented infection
  - Microbiologically documented infection
  - Bloodstream infection
- As analysis population becomes more restrictive to ensure bacterial infections
  - Gain: Trial becomes more sensitive for differentiating antibacterial drugs
  - Gain: Noninferiority margin justification on surer footing
  - Drawback: Trial feasibility decreases
  - Drawback: Harder to generalize results to an all-comer target population

Statistical tradeoffs

- Consider different potential composite primary endpoint definitions
  - All-cause mortality: Death within 30 days of randomization
  - Development of serious medical complications: including but not limited to hypotension, admission to an intensive care unit, confused or altered mental state, respiratory failure, renal failure, or progression to sepsis
  - Failure to respond to empiric antibacterial therapy: persistent fever, worsening of clinical signs of infection, or the need to escalate or change the antibacterial regimen due to lack of efficacy
- As the endpoint becomes more restrictive to only include major events
  - Gain: Treatment effects may be more meaningful (e.g., mortality effect)
  - Gain: Endpoint may be more objectively defined
  - Gain: Noninferiority margin on surer footing
  - Drawback: Trial population may need to be more restrictive to ensure patients are at risk for major events
  - Drawback: Trial feasibility likely decreases

Statistical tradeoffs

- Consider decreasing the noninferiority margin
  - Gain: Reduces potential efficacy decrements of new antibacterial drugs
  - Gain: Noninferiority margin justification on surer footing
  - Drawback: Trial feasibility decreases

Superiority trial sample sizes

(two-sided α = 0.05, power = 90%, 1:1 randomization)

Evaluability	Control arm success rate	Treatment arm success rate	Total sample size
100%	65%	80%	N = 369
	65%	75%	N = 879
	65%	70%	N = 3684
66.7%	65%	80%	N = 554
	65%	75%	N = 1318
	65%	70%	N = 5526
33.3%	65%	80%	N = 1107
	65%	75%	N = 2637
	65%	70%	N = 11052

Noninferiority trial sample sizes

(two-sided α = 0.05, power = 90%, 1:1 randomization)

Evaluability	Success rate per arm	Noninferiority margin	Total sample size
100%	70%	15.0%	N = 391
		12.5%	N = 564
		10.0%	N = 881
	65%	15.0%	N = 421
		12.5%	N = 609
		10.0%	N = 953
	60%	15.0%	N = 443
		12.5%	N = 641
		10.0%	N = 1004
66.7%	70%	15.0%	N = 586
		12.5%	N = 846
		10.0%	N = 1322
	65%	15.0%	N = 632
		12.5%	N = 914
		10.0%	N = 1430
	60%	15.0%	N = 664
		12.5%	N = 962
		10.0%	N = 1506
33.3%	70%	15.0%	N = 1173
		12.5%	N = 1692
		10.0%	N = 2643
	65%	15.0%	N = 1263
		12.5%	N = 1827
		10.0%	N = 2859
	60%	15.0%	N = 1329
		12.5%	N = 1923
		10.0%	N = 3012

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Antibiotics for the management of febrile neutropaenia

Regulatory considerations from the EU

FDA Virtual Public Workshop on Drug Development Considerations for Empiric Antibacterial Therapy in Febrile Neutropenic Patients

Presented by Dr. Radu Botgros on 23 April 2024
Senior Scientific Officer, EMA Department of Public Health Threats

Febrile neutropenia-a coined entity…

A. Fever in febrile neutropenia

1. A single oral temp > 38.3° C (101 ° F) or
2. A temperature of >38 ° C(100.4F) on two occasions separated by1 hour

B. Neutropenia in febrile neutropenia

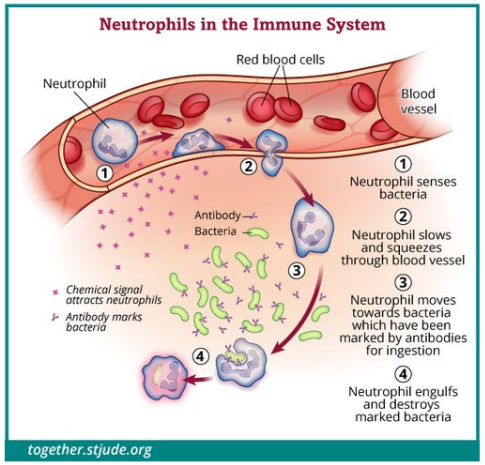
1. ANC < 500/mm3

   or

2. < 1000/mm3 and predicted to decline to< 500/mm

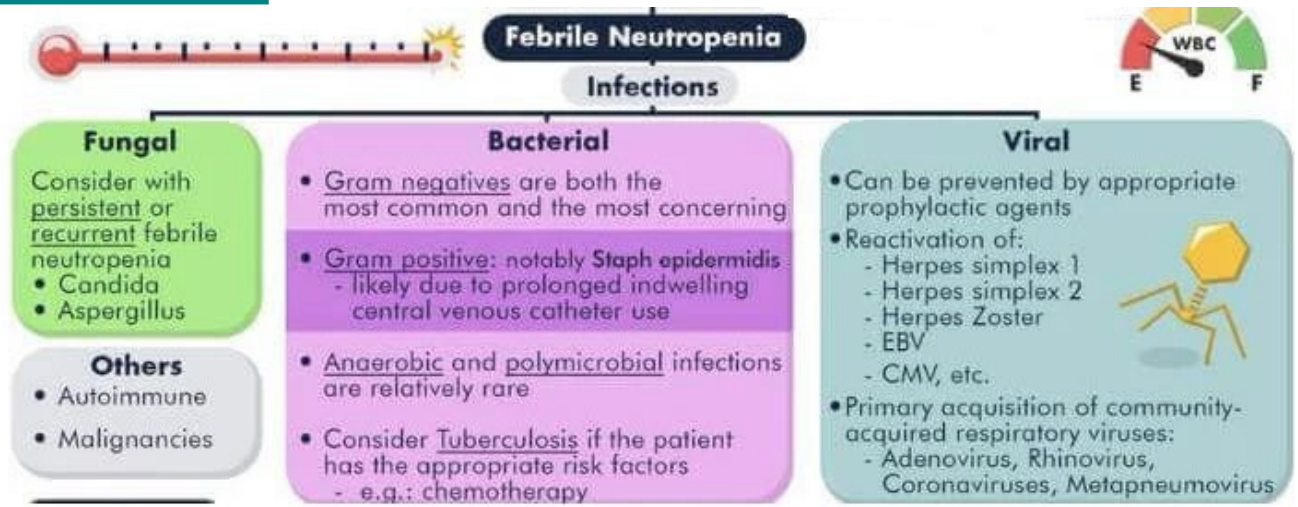
How to calculate absolute neutrophil count?

ANC = (Total WBC count) x (% of total neutrophils)



Severity of neutropenia

1. Normal ANC 1500 to 8000 cells/mm3
2. Neutropenia: ANC < 1500 cells / mm3
   1. Mild Neutropenia: 1000-1500 cells/ mm3
   2. Moderate Neutropenia: 500-999 cells/mm3
   3. Severe Neutropenia: < 500 cells / mm3
   4. Profound Neutropenia: <100 cells/ mm3



…in which antibiotics are frequently used

Table 1. MASCC febrile neutropaenia risk index

Characteristics	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Patients with scores ≥21 are at low risk of complications. Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is therefore 26 [2]. Reprinted with permission. © 2000 American Society of Clinical Oncology. All rights reserved.
BP, blood pressure.

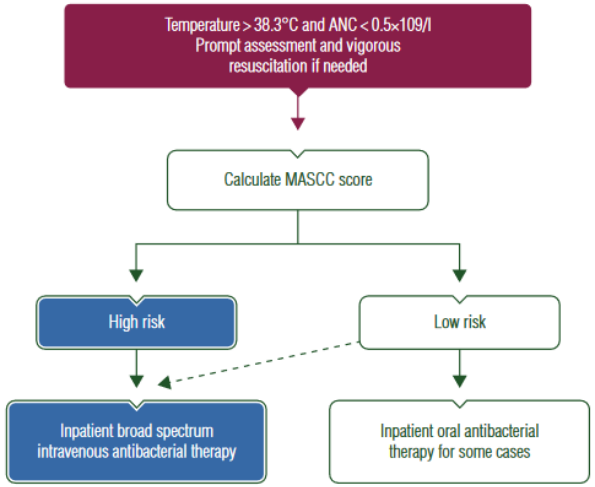


Figure 2. Initial management of febrile neutropaenia. ANC, absolute neutrophil count; MASCC, Multinational Association of Supportive Care in Cancer.

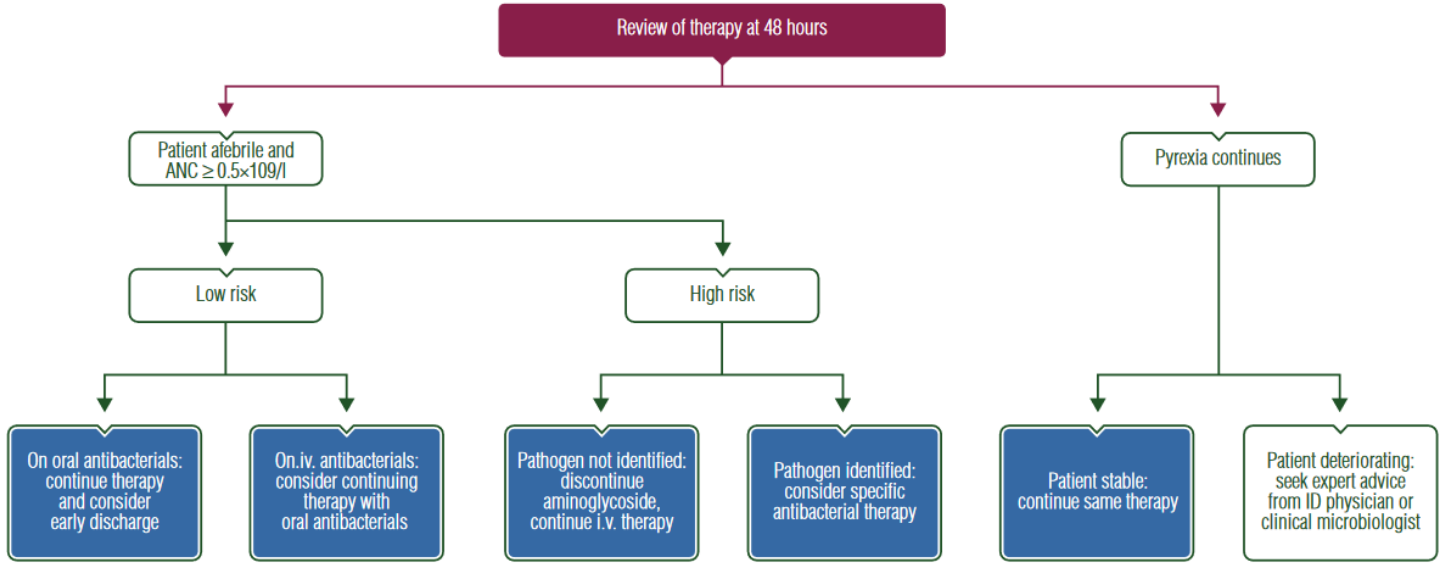


Figure 3. Assessment of response and subsequent management. ANC, absolute neutrophil count; i.v., intravenous; ID, infectious disease.

Some of the PIs of old antibiotics still retain the indication "empiric treatment of FN", both in the US and in the EU

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CEFEPIME Injection safely and effectively. See full prescribing information for CEFEPIME Injection.

CEFEPIME injection, for intravenous use
Initial U.S. Approval: 1996

----------**INDICATIONS AND USAGE**----------
Cefepime Injection is a cephalosporin antibacterial indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms: pneumonia (1.1); empiric therapy for febrile neutropenic patients (1.2); uncomplicated and complicated urinary tract infections (1.3); uncomplicated skin and skin structure infections (1.4); and complicated intra-abdominal infections (used in combination with metronidazole) (1.5).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefepime Injection and other antibacterial drugs, Cefepime Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.6)

AUTORIZAȚIE DE PUNERE PE PIAȚĂ NR. 11929/2019/01-02-03
11930/2019/01-02-03
Anexa 2
Rezumatul caracteristicilor produsului

REZUMATUL CARACTERISTICILOR PRODUSULUI

1. DENUMIREA COMERCIALĂ A MEDICAMENTULUI

Cefepimă MIP 1 g pulbere pentru soluție injectabilă/perfuzabilă
Cefepimă MIP 2 g pulbere pentru soluție injectabilă/perfuzabilă

2. COMPOZIȚIA CALITATIVĂ ȘI CANTITATIVĂ

Cefepimă MIP 1 g pulbere pentru soluție injectabilă/perfuzabilă:
Fiecare flacon conține cefepimă 1 g sub formă de diclorhidrat de cefepimă monohidrat.

Cefepimă MIP 2 g pulbere pentru soluție injectabilă/perfuzabilă
Fiecare flacon conține cefepimă 2 g sub formă de diclorhidrat de cefepimă monohidrat.

Pentru lista tuturor excipienților, vezi pct. 6.1.

3. FORMA FARMACEUTICĂ

Pulbere pentru soluție injectabilă/perfuzabilă.
Pulbere albă până la galben pal.
pH-ul soluției reconstituite este cuprins între 4,0 - 7,0.

4. DATE CLINICE

4.1 Indicații terapeutice

Cefepima este indicată pentru tratamentul infecțiilor severe enumerate mai jos, cauzate de agenți patogeni sensibili la cefepimă (vezi pct. 4.4 și 5.1).

La adulți și copii cu vârsta peste 12 ani și greutate corporală ≥ 40 kg:
- Pneumonie
- Infecții ale tractului urinar complicate (inclusiv pielonefrită)
- Infecții intra-abdominale complicate
- Peritonită asociată dializei la pacienții cu dializă peritoneală ambulatorie continuă (CAPD)

La adulți
- Infecții acute ale tractului biliar

La copii cu vârsta de la 2 luni până la 12 ani și cu greutate corporală ≤ 40 kg:
- Pneumonie
- Infecții ale tractului urinar complicate (inclusiv pielonefrită)
- Meningită bacteriană (vezi pct. 4.4)

Tratamentul pacienților cu bacteriemie care apare cu, sau se presupune că e cauzată de, una din infecțiile de mai sus.

Cefepima poate fi utilizată în tratamentul empiric la adulți, adolescenți și copii de la 2 luni la 12 ani cu neutropenie febrilă despre care se presupune că ar fi din cauza unei infecții bacteriene.

1

EU regulatory considerations on prospectively granting such an indication (I)

- During the process of harmonising PIs of old antibiotics in the EU it was agreed a decade ago that granting an indication for an antibacterial agent for "febrile neutropenia" was not supported any longer
- CHMP agreed to the following wording to replace these outdated indications in the post-harmonisation SmPCs: *X may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection*
- Prospectively, an extremely limited number of applications were received in the EU
- Therefore, any further discussion on the design of CTs that would underpin such an indication has not taken place.
- It was acknowledged that the institution of an antibacterial agent prior to or at the time of onset of expected neutropenia is now a common practise in some patient populations and centres so that rates of breakthrough infections may be comparatively low compared to other patient groups

EU regulatory considerations on prospectively granting such an indication (II)

- The study population enrolled with acute bacterial infections during neutropenia will comprise:
  - some ratio of patients with breakthrough infections despite prophylaxis and
  - patients who have not received routine prophylaxis.
  - the two sub-groups may be substantially different in terms of their underlying conditions and are likely to be enrolled at different centres with variable routine management protocols.
  - On this basis stratification according to prior or no prophylaxis may be appropriate. The protocol should provide clear criteria to be met in terms of neutropenia (cut-off and expected duration). The definition of fever will also require alignment across sites.

EU regulatory considerations on prospectively granting such an indication (III)

- If the test agent must be co-administered due to its spectrum of activity, then:
  - the additional agent(s) should be specified, including:
    - dose regimen and
    - any dose adjustments.
- If possible, the range of agents allowed should be standardised.
- Clear criteria for stopping therapy in the trial protocol (susceptibility data, clinical progress, culture results and recovery of the granulocyte count).
- Criteria for failure need to be very carefully specified.

EU regulatory considerations on prospectively granting such an indication (IV)

- To agree on key elements of any CT underpinning this indication it is highly recommended to have discussions with the EU regulators during development
  - EMA CHMP scientific advice
  - EMA ITF (for innovative products only, in early stages of development)

Any questions?

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Send us a question Go to www.ema.europa.eu/contact

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Review of Febrile Neutropenia in Japan

Katsuhiko Ichimaru
Pharmaceuticals and Medical Devices Agency

Clinical Practice Guideline for FN in Japan

Developed by Japanese Society of Medical Oncology, 2024

Definition of FN

Fever: Axillary temperature 37.5 ℃(99.5F) or
Oral temperature 38.0 ℃(100.4F)

Neutrophil count: ＜500/mm^3 or ＜1,000/mm^3 with predicted decline to ＜500/ mm^3

Empiric Therapy

Approved Ab: Cefepime, Meropenem, Tazobactam/Piperacillin

Off-label Ab: Imipenem/cilastatin, Ceftazidime

Approved anti-infectives for FN in Japan

Anti-infectives	Dosage	
	Adult	Pediatric
Amphotericin B	2.5mg/kg QD	2.5mg/kg QD
Caspofungin	Day 1: 70mg QD Day 2～: 50mg QD	Day 1:　70mg/m2 QD Day 2～: 50～70 mg/m2 QD (Max: 70mg QD)
Cefepime	2g BID	-
Tazobactam/Piperacillin	4.5g QID	90mg/kg QID (Max: 4.5g QID)
Vancomycin (suspected MRSA or MRCNS infection)	0.5g QID or 1g BID	29 days old ≦:10mg/kg QID or 20mg BID 7 days old ≧: 10-15mg/kg BID 8-28 days old:10-15mg/kg TID
Meropenem	1g TID	40mg TID (Max: 1g TID)

Cefepime

- Approved as a new indication in 2004
- The first antimicrobial agent approved for FN in Japan
- Data package
  - 9 clinical studies in FN patients, US
  - 3 published scientific articles in foreign countries
  - 2 published scientific articles in Japan

Based on existing data and clinical evidences
To avoid duplication

Meropenem

- Approved as a new indication in 2009
- Data package
  - A phase 1 high-dose repeated-dose study in healthy adult Japanese men
  - A phase 3 clinical study in Japanese FN patients
  - The results of PK/PD analysis
    - in Japanese FN patients
    - In Japanese pediatric patients with infectious disease patients

Clinical data packages for other products

Amphotericin B (Liposome)	RCTs for FN patients in foreign countries. Comparator: Amphotericin B (Conventional) Equivalence in clinical efficacy was demonstrated.
Caspofungin	RCT for persistent FN patients in US Comparator: Amphotericin B Liposome Non-inferiority at overall efficacy was demonstrated.
Tazobactam/Piperacillin	RCTs for FN patients in US & Canada Comparator: Imipenem/cilastatin or ceftazidime etc. Clinical efficacy was demonstrated
	RCT for FN patients in Japan Similarity between foreign and Japan CT was confirmed
Vancomycin	Based on published scientific articles

Summary

- Definition of FN and recommended therapy is almost same in US.
- Foreign data is utilized to obtain regulatory approval in Japan.
  - Efficacy is extrapolatable from US/EU's to Japanese population.
- Multi-regional clinical trial must be an efficient development tool to develop new products for FN.

U.S. FOOD & DRUG ADMINISTRATION

Virtual Public Workshop:
Drug Development Considerations for Empiric Antibacterial Therapy in Febrile Neutropenic Patients

Hosted by: Center for Drug Evaluation and Research, Office of Infectious Diseases (OID) U.S. Food and Drug Administration

BREAK

Moderated Panel Discussion

Randy Taplitz, MD
Moderator

Dmitri Iarikov, MD
Co-Moderator

FDA: John Farley, Dmitri Iarikov, Rama Kapoor, Peter Kim, Robert Pease, Daniel Rubin, Adam Sherwat

External (see full panelist Affiliations and Disclosures using the workshop webpage link on the agenda):

Radu Botgros, European Medicines Agency (EMA); **Juan Gea-Banacloche**, National Institute of Allergy and Infectious Diseases (NIAID); **Alison Freifeld**, University of Nebraska Medical Center; **Douglas Girgenti**, Melinta Therapeutics; **Kimberly Hanson**, University of Utah; **Katsuhiko Ichimaru**, Pharmaceuticals and Medical Devices Agency (PMDA); **Gary Lyman**, Fred Hutchinson Cancer Center; **Catherine Liu**, Fred Hutchinson Cancer Center; **Kieren Marr**, Elion Therapeutics; **Michael Satlin**, Weill Cornell Medicine; **Anita Sheoran**, Biomedical Advanced Research and Development Authority (BARDA); **Lynne Strasfeld**, Oregon Health and Science University; **Randy Taplitz**, City of Hope National Medical Center; **Andrea Zimmer**, University of Nebraska Medical College

Panel Discussion Questions

1. Please discuss the greatest unmet needs for empiric treatment of febrile neutropenia.
   - Please comment on an ideal drug profile.
2. Discuss strategies for enrichment of the study population in patients most likely to have a bacterial etiology for their fever (e.g., clinical characteristics, diagnostics, etc.).
3. Regarding trial design considerations in febrile neutropenia:
   - Please discuss what would be an appropriate primary endpoint and when it should be assessed.
   - Please discuss the primary efficacy population.
   - Are there strategies to make trials more feasible?
4. We note that there are limited data on the use of new antibacterial drugs in neutropenic patients. If time allows and recognizing that this question is not directly related to empiric treatment of febrile neutropenia, please comment on the need, utility and feasibility of obtaining efficacy and safety data for new drugs in the treatment of neutropenic patients with defined systemic bacterial infections.

Summary and Closing Remarks

Dmitri Iarikov, MD
Deputy Director, Division of Anti-Infectives,
Office of Infectious Diseases (OID)
Office of New Drugs (OND)
CDER, FDA