

Optimizing the Use of Antifungal Agents with Fungal Biomarkers

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Relacionamento profissional com a indústria farmacêutica envolvendo antibacterianos

Pesquisa clínica, apoio eventos científicos

Bayer, Pfizer, Astra-Zeneca & United Medical

Resolução CFM no 1595/2000, 18/05/2000

RDC ANVISA no 102, 30/11/2000

Biomarker

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- Commonly used biomarkers in clinical practice
 - Blood glucose levels in diabetes
 - C-reactive protein or procalcitonin in infection

Fungal Biomarkers

- Galactomannan
- 1,3-Beta-D Glucan

Fungal Biomarkers: Galactomannan (GMI)

- Cell wall polysaccharide released from growing hyphae of *Aspergillus*; not released by the colonizing fungal structure (conidia)
- Cross-reaction with some fungi, including *Fusarium* and *Histoplasma capsulatum*
- Test: immunoenzymatic sandwich assay, relatively easy to perform (results within 3 h), good reproducibility
- Results expressed in index values. Cutoff:
 - Blood: 0.5
 - BAL: 0.7? 1.0?

Fungal Biomarkers: Galactomannan (GMI)

- Serum GMI increased with increased fungal burden in tissue
 - Good correlation with outcome

Nouer et al. CID 2011;54:e173-e83

- False-positive:
 - Antibiotics: piperacillin-tazobactam (no longer a problem), amoxicillin-clavulanate
 - Enteral nutrition, intravenous fluids containing gluconate

Schuetz. Clin Lab Med 2013;33:505-25

Clinical Use of Galactomannan

■ Serum

- Monitoring of high-risk patients: early diagnosis of invasive aspergillosis
- Diagnosis of aspergillosis
- Monitor treatment response

■ BAL

- Diagnosis of aspergillosis (fusariosis, histoplasmosis)

Fungal Biomarkers: 1,3 Beta-D-Glucan

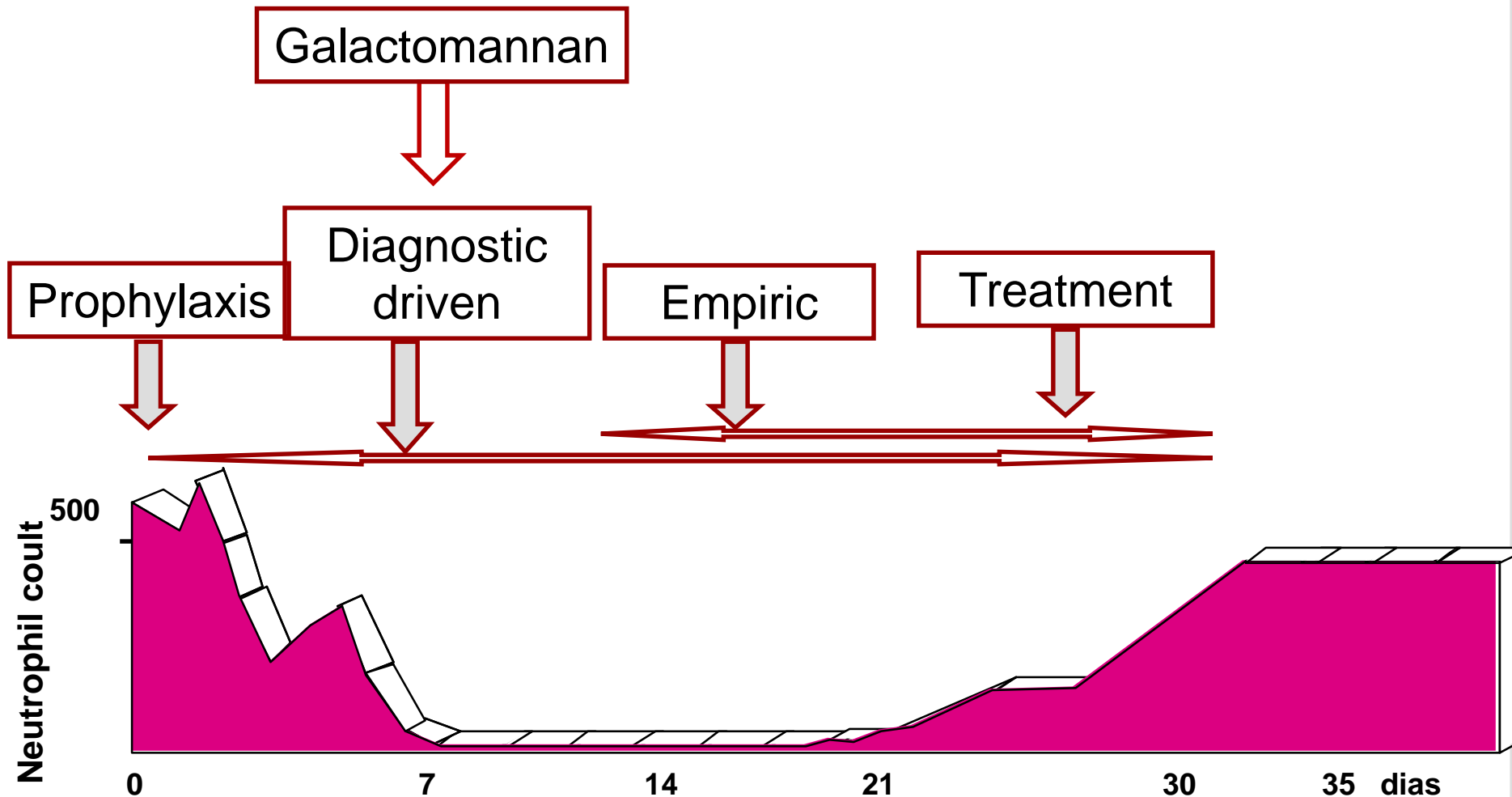
- Cell wall component of many fungi
 - *Candida*, *Aspergillus*, *Fusarium*, *Pneumocystis*, *Trichosporon*, *Acremonium*
- Negative in: mucormycosis, cryptococcosis
- Many false-positives
 - Dialysis filters with cellulose, bacteremias, infusion of albumin or immunoglobulin, use of gauze during surgery, reconstitution of antibiotics (ertapenem, colistin, kefazolin, cefotaxime, bactrim, ampicillin-sulbactam)

Clinical Use of Beta Glucan

- High sensitivity, high rates of false-positive
 - Low positive predictive value → not good to confirm diagnosis
 - High negative predictive value → good to rule out disease
- Cutoff: 80 pg/ml – not sure if appropriate
- Applications
 - Candidiasis, aspergillosis, fusariosis, pneumocystosis

Galactomannan in Hematologic Patients

When Antifungal Agents Should be Used in Neutropenic Patients?



Empiric or Diagnostic-Driven Antifungal Therapy in Neutropenic Patients?

■ Empiric

- Antifungal started after 3-6 days of antibiotics if fever persists
- Problem: Fever may be caused by other reasons (too sensitive)
- Consequence: overuse of antifungal agents

■ Diagnostic-driven

- Antifungal started in high risk patients if a biomarker is positive
- Advantage: optimizes the use of antifungals
- Requirement: biomarkers available 2-3x/week, results within 48 h

Preemptive vs. Empiric Antifungal Therapy in Neutropenic Patients

- Randomized, open-label, hematopoietic cell transplantation or acute leukemia (ALL or AML)
- Empiric: persistent fever
 - Cultures of blood, urine, sputum, feces, serum 2x/wk (frozen)
 - Chest CT scan
 - Start antifungal therapy ALWAYS
- Preemptive: serum (GMI and PCR 2x/wk). If positive PCR or galactomannan or persistent fever but negative biomarkers
 - Chest CT scan
 - Start antifungal therapy ONLY if possible or probable IFD

Preemptive vs. Empiric Antifungal Therapy in Neutropenic Patients

	Empiric	Preemptive	P value
Antifungal use	32%	15%	0.002
Fluco prophylaxis	38%	10%	0.005
Vori or posa prophylaxis	23%	16%	0.7
Mortality	5%	3%	0.5
Proven/probable IA	1%	15%	<0.001

Preemptive vs. Empiric Antifungal Therapy in Neutropenic Patients

- GMI and PCR in the empiric group (retrospective evaluation):
 - 9% probable IA (vs. 15% in preemptive group)*
 - *8% would not receive 2ary px !!
 - 64% who received antifungal therapy had negative PCR and GMI
- 55% of cases of invasive aspergillosis diagnosed by the biomarker-based approach had no persistent fever

Strategies of Diagnostic-Driven Antifungal Therapy

- Active monitoring of ALL patients
 - Start at the beginning of the period at risk
 - Fungal biomarker: 2-3/week galactomannan +/- PCR
 - CT scan if
 - Positive biomarker
 - Persistent or recurrent fever
 - New sign or symptom
 - BAL if image and negative biomarker
- Intensive workup triggered by clinical findings
 - Start if persistent (>3d) or recurrent fever, or a new sign or symptom appeared
 - Galactomannan for 3 consecutive days AND
 - CT scan
 - Additional tests as indicated

Serial Galactomannan Monitoring: Early Diagnosis of Invasive Aspergillosis

- Probable Aspergillosis without pre-specified radiology: A New Clinical Entity
- 125 patients with hematologic malignancies and invasive aspergillosis screened with daily galactomannan
 - 83 with typical radiologic findings (well-circumscribed lesions, air crescent or cavitary lesions)
 - 42 patients with atypical radiologic findings (micronodules, ground-glass infiltrates, ill-defined consolidations)

Non-specific Radiologic Findings Represent Early Invasive Aspergillosis

53 cases of probable without
pre-specified radiology



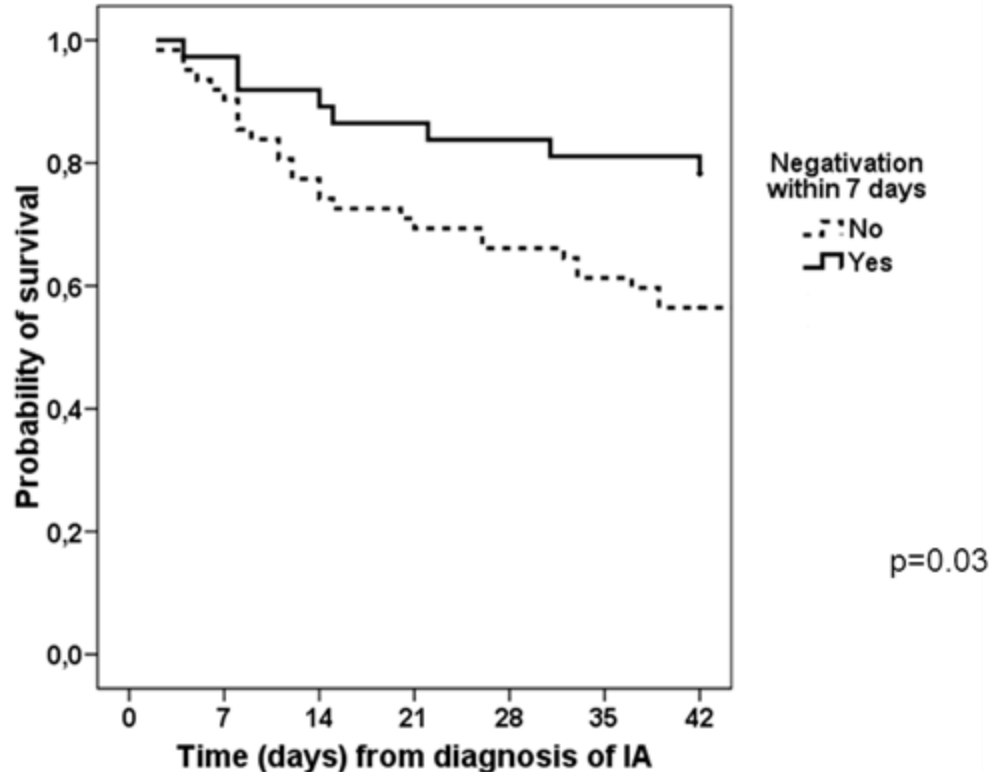
25 with subsequent CT or
PET/CT scan within 7-14 days



11 (44%) were reclassified as Probable
because CT or PET/CT scan showed
well-circumscribed lesions (including
nodules with or without halo sign)

Optimizing the Duration of Treatment of Aspergillosis: Look at the Galactomannan Curve

Probability of 6-week Survival According to GMI Normalization within 7 days from First Positive Test



Aspergillosis

Duration of Treatment

IDSA Guide 2008

6 weeks treatment

- Outcome and duration of treatment correlate with fungal burden
 - High fungal burden: prolonged treatment
 - Low fungal burden: shorter treatment
- 125 patients with IA
 - Median duration of treatment: 23 days (1 – 83)
 - 18% received treatment ≤ 7 d
 - 34% received treatment ≤ 14 d

Nouer et al. Clin Infect Dis 2011;53:671-6

Benefits and Limitations of the Diagnostic Driven Approach

BENEFITS

- Reduce the unnecessary use of antifungals
- Diagnose invasive fungal diseases (IFD) more frequently
- Early diagnose IFD, with potential reduction in morbidity and mortality, and reduction in treatment duration

LIMITATIONS

- Needs serial serum monitoring with biomarkers and CT scans, results in a timely fashion
- Needs a multidisciplinary approach
- Test performance is not good if anti-mold agent is used as prophylaxis or in non-neutropenic patients

Galactomannan and Consumption of Antifungal Agents in the Hospital

Preemptive (diagnostic-driven) antifungal therapy

- Do not use persistent fever as a trigger for starting antifungal therapy
- Define a smaller group of patients to receive antifungal therapy
- Potential reduction in the use of antifungal agents in febrile neutropenic patients

Monitor treatment response in invasive aspergillosis

- Reduce treatment duration in patients with fast (<7 days) normalization of galactomannan

Optimizing Antifungal Use in the ICU

A case:

- 63-years old male, heavy smoker, COPD
- Last 6 months: weight loss, constipation → colon carcinoma
- Colectomy, transferred to the ICU because of ↓ PO₂
 - Mechanical ventilation, broad-spectrum antibiotics
- D9 PO: still on mechanical ventilation, ↑ creatinine, abdominal distention, hypotension
 - Image, new blood cultures, antibiotic change

Optimizing Antifungal Use in the ICU

A case: Post-operative colectomy

- D11 PO: refractory shock, respiratory failure, renal failure
 - Death
- On the following day
 - Blood culture obtained on D9 PO was positive; Gram stain: yeast
- 2 days later
 - *Candida glabrata*
- What was wrong in this case?

What different would you have done in this case?

1. Antifungal prophylaxis on the 1st day PO
2. Empiric antifungal therapy when the patients worsened (D9 PO)
3. Serial serum 1,3-beta-D glucana (BDG) since surgery, and start of antifungals if ≥ 2 +ve BDG
4. Evaluation of colonization 3x/week, calculation of Candida Score (CS) and start antifungals if $CS \geq 3$

Script 1: Antifungal Prophylaxis

- Prospective study, 4 hospitals, 1 year (BR)
- 2148 patients screened
- 40% surgical (~860 patients)
- Give antifungal prophylaxis to 860 patients?
- Which agent?
 - Fluconazole?
 - Echinocandin?

Script 2: Empiric Antifungal Therapy when Clinical Conditions Worsened

■ Problems:

1. What is the patient profile for empiric antifungal therapy?
2. Empiric therapy has not been validated
3. What is the antifungal agent?
 - Fluconazole?
 - Echinocandin?
4. When empiric therapy should be discontinued?

Echinocandin-resistant *Candida* species: An Emerging Problem in ICU

- Breakthrough candidemia in patients receiving echinocandins as prophylaxis or empiric therapy
- *C. albicans* (<1%), *C. tropicalis* (<5%), *C. krusei* (<7%), *C. glabrata* (4.9% in 2001 → 12.3% in 2010): haploid
- 7 days of exposure to echinocandin is sufficient to induce mutation (FKS genes 1 and 2)
- Problems:
 - Detection of echinocandin resistance needs molecular methods (do not rely on “regular” susceptibility tests)
 - FKS mutation is associated with ~80% clinical failure

Candidemia due to Echinocandin-resistant *Candida* species

- 72 patients with candidemia due to *Candida glabrata*
- 13 (18%) with FKS mutation
- Predictors of candidemia due to FKS mutation: echinocandin exposure (odds ratio 19.9)
- Treatment failure in 60% of patients receiving echinocandin and candidemia with FKS mutation
- Predictors of echinocandin treatment failure: gastrointestinal disease (OR 4.7) and prior echinocandin exposure (OR 8.3)

Identifying Patients for Early Antifungal Treatment in the ICU

- Prediction rule
 - Risk factors
 - with or without colonization
 - Clinical characteristics
- Prediction rule + surrogate markers
 - Beta 1-3 glucan?
 - Others?

Risk Scores for Candidemia in ICU Patients

Pittet, 1994	Leon, 2006	Ostrosky-Zeichner, 2007
Colonization index (no. colonized sites/ no. sampled sites) Corrected colonization index: CI x no. sites with intense colonization / no. sampled sites	1 point: TPN, surgery, multifocal colonization, 2 points: sepsis Candida score	ATB, CVC + at least 2: surgery, TPN, immunosuppressive, steroids, pancreatitis, dialysis

Beta-glucan, Candida Score (CS) and Colonization Index

- 95 patients with sepsis and >5 days in the ICU
 - Cultures of rectum, oropharynx, skin, urine days 0, 3 and 1x/week
 - BDG and culture at baseline (sepsis)
 - 14 episodes of candidemia (15%)

	Sen	Spe	PPV	NPV
BDG	93%	94%	72%	99%
CS ≥ 3	86%	89%	57%	97%
CI >0.5	64%	70%	27%	92%
BDG + CS	100%	84%	52%	100%

Beta-glucan-Driven Preemptive Antifungal Therapy in the ICU

Randomized Pilot Study

- 354 adults in surgical for ≥ 3 d, ICU eligible
- 64 randomized 3:1 to receive anidulafungin (100 mg/d x 14 d) as
 - empiric (based on clinician judgment, N=17) or
 - preemptive (based on ≥ 1 BDG test ≥ 60 pg/ml, N=47, 45 evaluable)
- BDG at baseline and 2x/week in both groups, but data available in the preemptive group

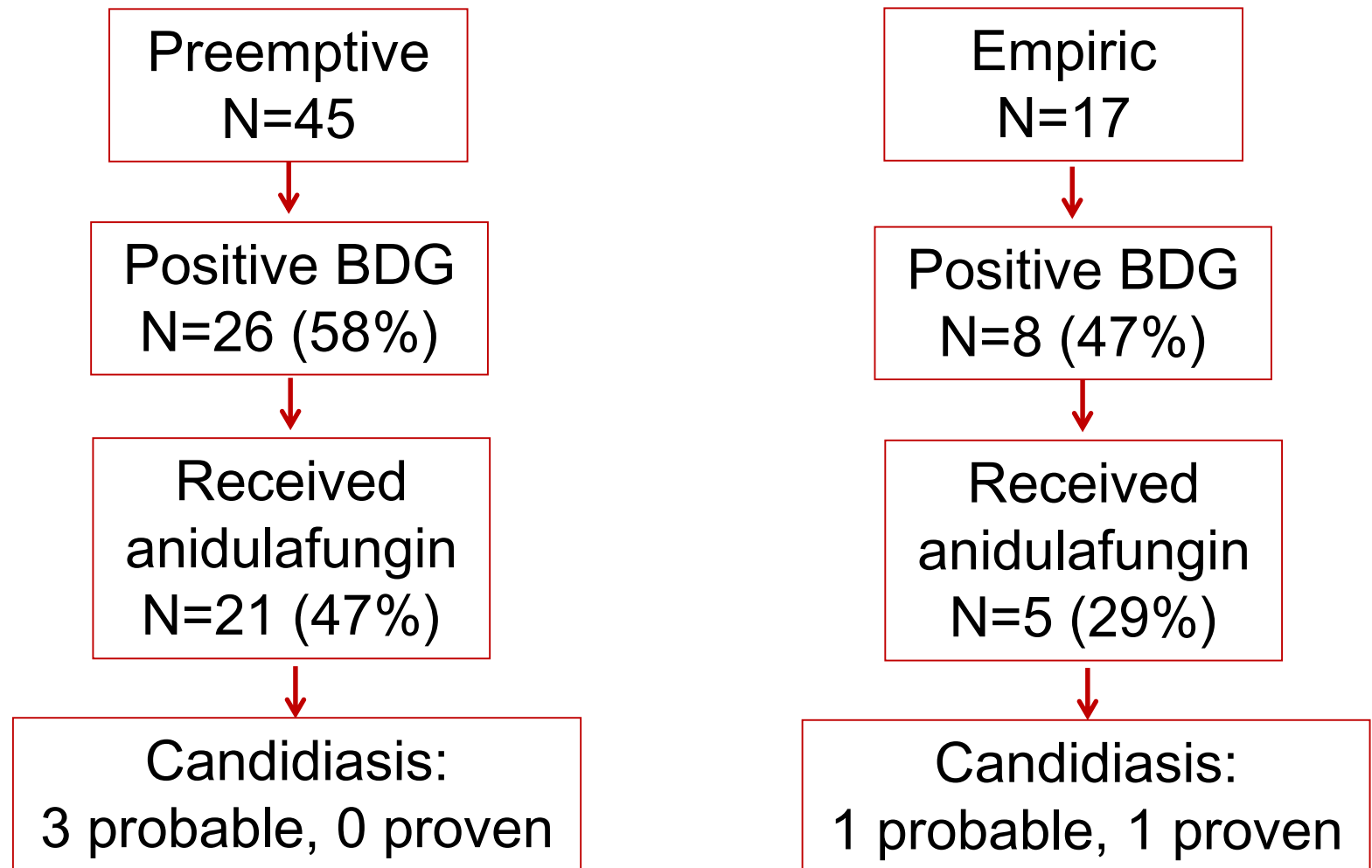
Beta-glucan-Driven Preemptive Antifungal Therapy in the ICU

Randomized Pilot Study

- Probable candidiasis
 - Fever + leukocytosis and/or hypotension + colonization (>1 site)
 - Symptomatic Candida urinary tract infection
 - Esophagitis

Beta-glucan-Driven Preemptive Antifungal Therapy in the ICU

Randomized Pilot Study



Randomized Study of Prophylaxis Followed by Empiric Therapy for Candidiasis in ICU

- Double-blind, randomized, caspofungin vs. placebo
- Ostrosky's rule
 - Prophylaxis
 - Beta glucan 2x/week
- Primary endpoint: no proven or probable invasive candidiasis
 - Probable: 2 BDG positive AND at least one:
 - ◆ Fever, hypothermia, hypotension, leukocytosis
- If invasive candidiasis: preemptive caspofungin

Randomized Study of Prophylaxis Followed by Empiric Therapy for Candidiasis in ICU

Prophylaxis group

	Caspo N=102	Placebo N=84	P
Proven + probable candidiasis	9.8%	16.7%	0.14
Use of antifungals	13.7%	17.9%	0.36
Mortality within 7 days after end of treatment	16.7%	14.3%	0.78

Randomized Study of Prophylaxis Followed by Empiric Therapy for Candidiasis in ICU

Empiric group

	Caspo	Placebo	P
Baseline probable candidiasis	13.7%	10.2%	0.43
Probable candidiasis	17.9%	25.3%	0.17
Proven candidiasis	0.9%	6.9%	0.02
Proven + probable candidiasis	18.8%	30.4%	0.04

Beta-glucan to Discontinue Antifungal Therapy in ICU Patients

Pilot Study

- 4 hospitals, 1 year, prospective cohort, October 2012 to November 2013
- All patients in the ICU (2,148) screened
- 85 (4%) fulfilled entry criteria and signed an informed consent

Beta-glucan to Discontinue Antifungal Therapy in ICU Patients

Inclusion Criteria

- **In the ICU for >2d AND**
 - Systemic antibiotics >2 d AND
 - Central venous catheter >2d
- **And at least 2 of the following:**
 - Parenteral nutrition
 - Dialysis
 - Surgery
 - Pancreatitis
 - Steroids or other immunosuppressive agent
- **AND at least 1 of the following:**
 - Fever
 - Hypothermia
 - Hypotension
 - Acidosis
 - Leukocytosis
 - Increase in C-reactive protein

Nucci, Nouér, Esteves et al. ICAAC 2014

Beta-glucan to Discontinue Antifungal Therapy in ICU Patients Procedures

- D1
 - Blood culture
 - BDG
 - APACHE, swabs
 - Anidulafungin (200 mg)
- D2
 - Blood culture
 - BDG
 - Anidulafungin (100 mg)
- D3
 - BDG
 - Anidulafungin (100 mg)
- D4: Check results
 - Cohort 1: Positive blood culture: candidemia
 - Treat for >2 weeks
 - Cohort 2: Negative blood cultures, positive BDG
 - Treat for >2 weeks
 - Cohort 3: Negative blood cultures and BDG
 - Discontinue anidulafungin
- D28
 - Survival
 - Positive blood cultures for *Candida*

Beta-glucan to Discontinue Antifungal Therapy in ICU Patients

Performance of the Score

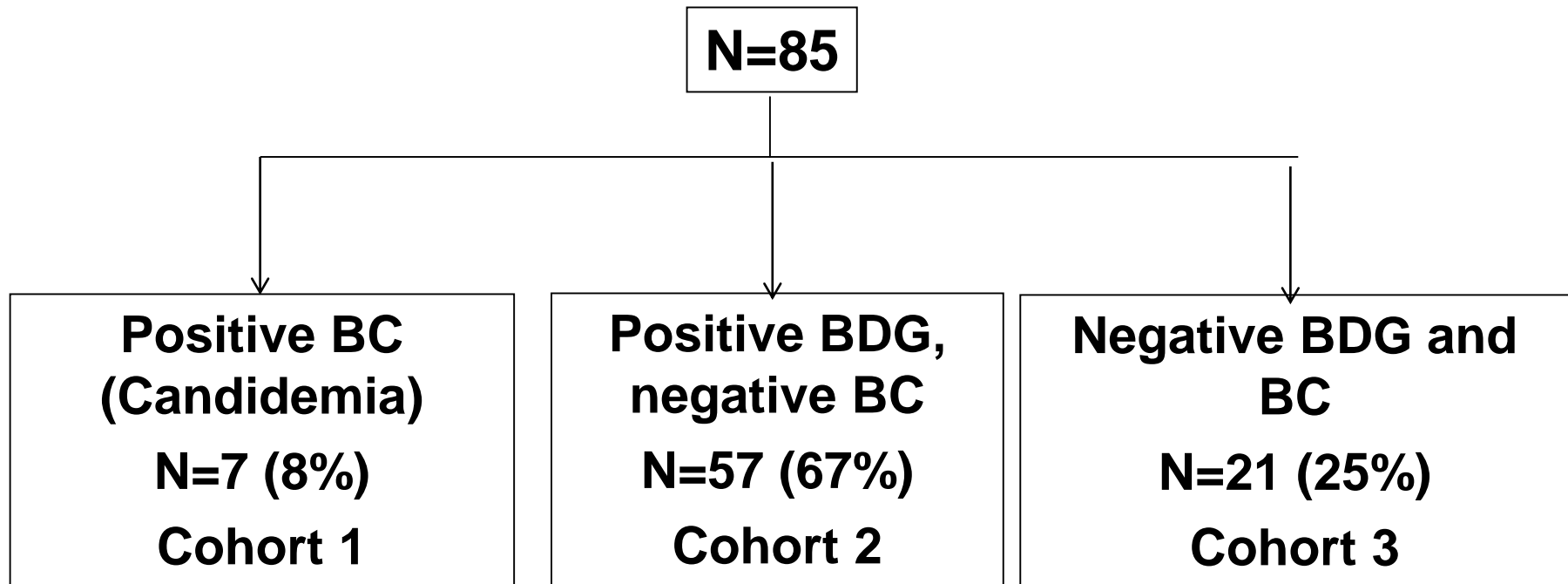
- Patients screened: 2,148
- Patients in the study: 85 (4%)
- Candidemia in patients not in the study: 10 / 2,063 (0.5%)
- Candidemia in selected patients: 7 / 85 (8.2%)
- Relative risk: 16.9 (95% CI: 6.63 – 43.55)

Beta-glucan to Discontinue Antifungal Therapy in ICU Patients

Patients' Characteristics

Characteristic	N
Age (y), median (range)	63 (22 – 89)
Male : Female	41 : 44
Time (d) from hospital admission to ICU admission	2 (0 – 57)
Time (d) in the ICU before study entry	7 (1 – 114)
Median APACHE II score on D1 of study	20 (2 – 70)
Cancer	24 (28%)
Cardiac disease	31 (36%)
Lung disease	16 (19%)
Renal failure	38 (45%)
Surgery	40 (47%)

Classification of the Patients on D4 Based on the Results of Blood Cultures (BC) and BDG



Positive BDG: ≥ 80 pg/ml

BDG Value in the 3 Cohorts

	Negative BDG N=21	Positive BDG n=57	Candidemia N=7	P
Baseline value, median (range)	33 (8 – 79)	255 (83 – 6860)	515 (203 – 3660)	<0.001
No. positive tests, median (range)	-	3 (1 – 3)	3 (1 – 3)	0.77
Highest value, median (range)	-	420 (131 – 3240)	4575 (532 – 8660)	0.007

Beta-glucan to Discontinue Antifungal Therapy in ICU Patients

Patients' Outcomes

	Negative BDG N=21	Positive BDG n=57	Candidemia N=7	P
Duration (d) of antifungal, median (range)	3 (2 – 26)	9 (1 – 20)	14 (1 – 37)	0.001
Candidemia during study period	0	0	-	1.0
Discharge from ICU D14	6 (29%)	12 (21%)	3 (43%)	0.40
Alive D14	16 (76%)	31 (54%)	6 (86%)	0.09
Discharge from ICU D30	7 (33%)	18 (32%)	4 (57%)	0.40
Alive D30	12 (57%)	25 (44%)	5 (71%)	0.28

Beta-glucan to Discontinue Antifungal Therapy in ICU Patients

Conclusions

- This dynamic prediction rule was able to select patients at very high risk to develop candidemia
- BDG is frequently positive in high-risk ICU patients
- Discontinuation of empiric antifungal therapy may be attempted in patients with persistently negative BDG

Optimizing the Use of Antifungal Agents with Fungal Biomarkers

- Galactomannan
 - Optimize antifungal use in high-risk hematologic patients
- Beta-glucan
 - Optimize antifungal use in high-risk ICU patients