Critically ill **H**ematolog**I**cal **P**atients Antimicrobial **S**tewardship

A Global Cross-sectional Survey

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C.H.I.P.S.

WHY ?

- Hematological patients represent a high risk population for severe infections, particularly during prolonged and severe neutropenia.

- Challenges on treatment of the infections due to MDR bacteria

- Infection control practices and educational priorities differ among centres

- Limited number of studies published about antimicrobial stewardship programs (AMS) on haematological patients admitted in ICUs

The complexity of hematological patients admitted in ICUs needs a personalized treatment.

OBJECTIVES

Objective: Overview of severe haematological patient in the perspective of AMS

Case Reports covering:

- Empiric therapy in infection in non FN
- Directed therapy in non FN: old or new antibiotics?
- How to de-escalate?
- Patients colonized by MDR bacteria
- When to use combination therapy?
- Duration of empirical treatment
- Patients with FN and lung opacities

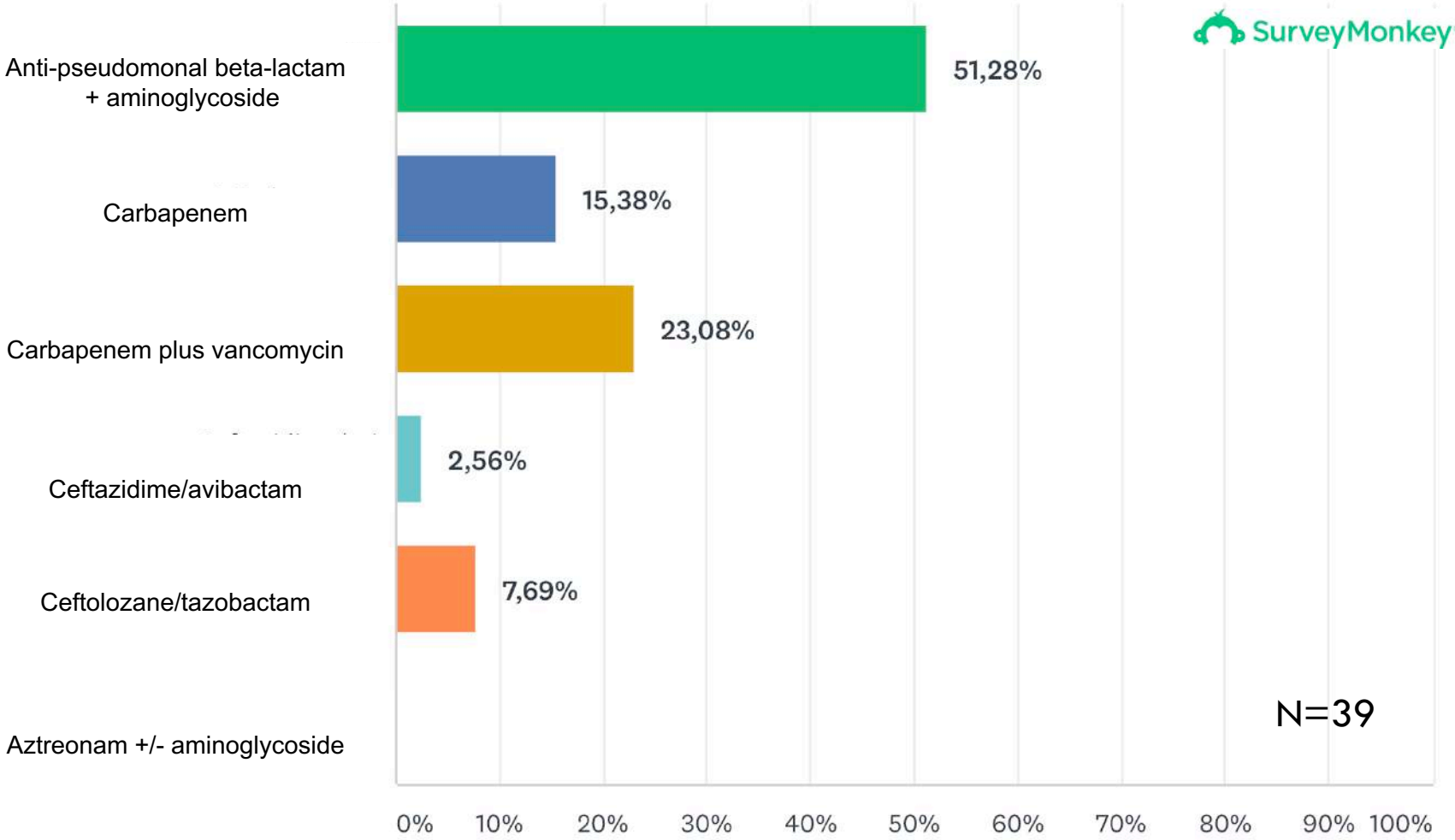
Case Report: Empiric therapy in CLL

A 60-year old male with CLL, admitted to hospital 8 days before for chemotherapy cycle with Rituximab.
Two days before his admission he reported productive cough and currently presented with fever and chills, hypotension and desaturation < 90% (5lx' nasal O2). Blood chemistry shows neutrophil leukocytosis and elevated inflammatory biomarkers.

After collecting blood, urine and sputum for microbiological investigations, in your opinion, which is the most appropriate empirical therapy?

A. An anti-pseudomonal beta-lactam plus an aminoglycoside
B. A Carbapenem
C. A Carbapenem plus vancomycin
D. Ceftazidime/avibactam
E. Ceftolozane/tazobactam
D. Aztreonam +/- aminoglycoside

Case Report: empiric therapy in non FN



What is your choice?

Guideline for Implementing an Antibiotic Stewardship Program. IDSA. CID 2016.
Antimicrobial Stewardship. Infect Dis Clin N Am 25 (2011) 245–260
Antimicrobial Stewardship. ESCMID.

Take Home Message

PCT and IL6 are more useful biomarkers than CRP for confirmation of bacterial infection in FN

Single-agent anti-pseudomonal betalactam is the standard of care for High risk febrile neutropenia.

In standard risk FN (MASCC score above 20), absence of FQ prophylaxis and some conditions, it might be treated as outpatient with oral A/C plus ciprofloxacin.

P/T might be inferior to meropenem for therapy of BSI by *E. coli* or *K pneumoniae* resistant to ceftriaxone

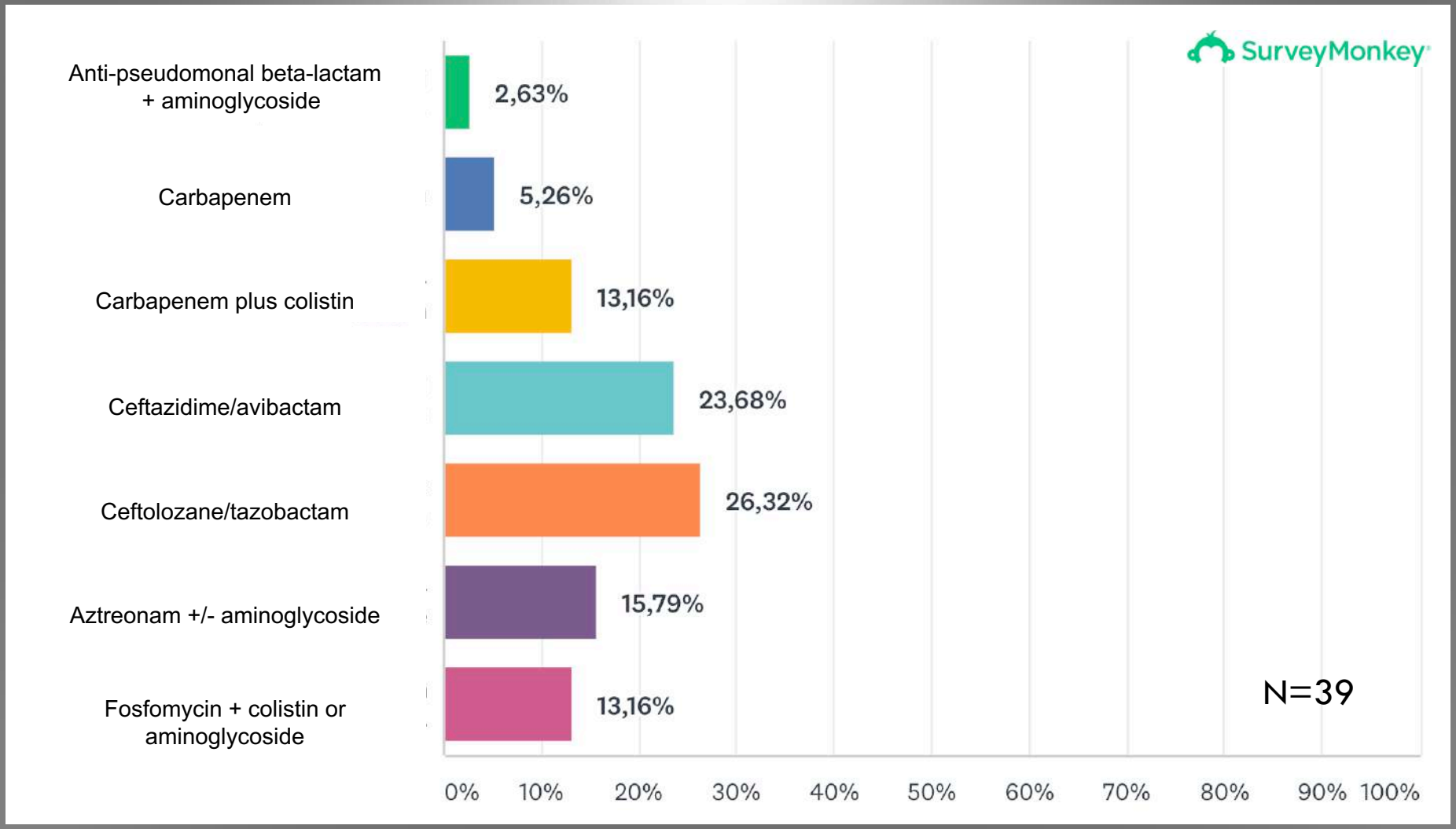
Harris et al. JAMA 2018;320:984-994

…. 24 hours later…

the laboratory confirms the isolation of *Pseudomonas aeruginosa* from blood cultures, being a carbapenem-resistant strain with a metallo beta-lactamase (MBL)-production.
What would be the most suitable choice of antimicrobial therapy?

A. An anti pseudomonal beta-lactam plus an aminoglycoside
B. A carbapenem (continuous or prolonged infusion)
C. A carbapenem (continuous or prolonged infusion) plus colistin
D. Ceftazidime/avibactam
E. Ceftolozane/tazobactam
F. Aztreonam +/- aminoglycoside
G. Fosfomycin plus colistin or plus an aminoglycoside

Case Report MBL: Old or new atb?



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Take Home Message

Ceftolozane/Tazo is not active against class B betalactamases (NDM)

Ceftolozane/Tazo is not active against Class D Betalactamases, plasmidic ampC or KPC-2-3

Not active against Gram positive or anaerobes

Excellent activity against ESBL

Not affected by PA AmpC, OprD or expulsion pumps.

Good choice for MDR Pseudomonas

Take Home Message

Ceft/Avi is not active against class B betalactamases (NDM)

Ceft/Avi is not active against many Class D Betalactamases produced by *Acinetobacter baumannii (Oxa-23, OXA-24 …) although still active against OXA-48*

Not active against Gram positive or anaerobes

Excellent activity against ampC and ESBL

Good activity against KPC

WHEN AND HOW SHOULD COLISTIN BE USED

- **COLISTIN SHOULD BE PRESERVED TO TREAT ENTEROBACTERIACEAE SHOWING RESISTANCE TO ALL BETALACTAM OPTIONS.**
- 9-12 MU LOADING DOSE (+ 4.5MU/12H)
- RENAL FUNCTION SHOULD BE CLOSELY MONITORED !
- IN HD: 2MU/12H IS SUGGESTED
- IN CRRT 9MU/DAY IS SUGGESTED

Alp E, et al. Aust Crit Care 2018;31(6):339.
Modified from Rodriguez-Baño J, et al. Enf Inf Microbiol Clin 2015;33:337e1

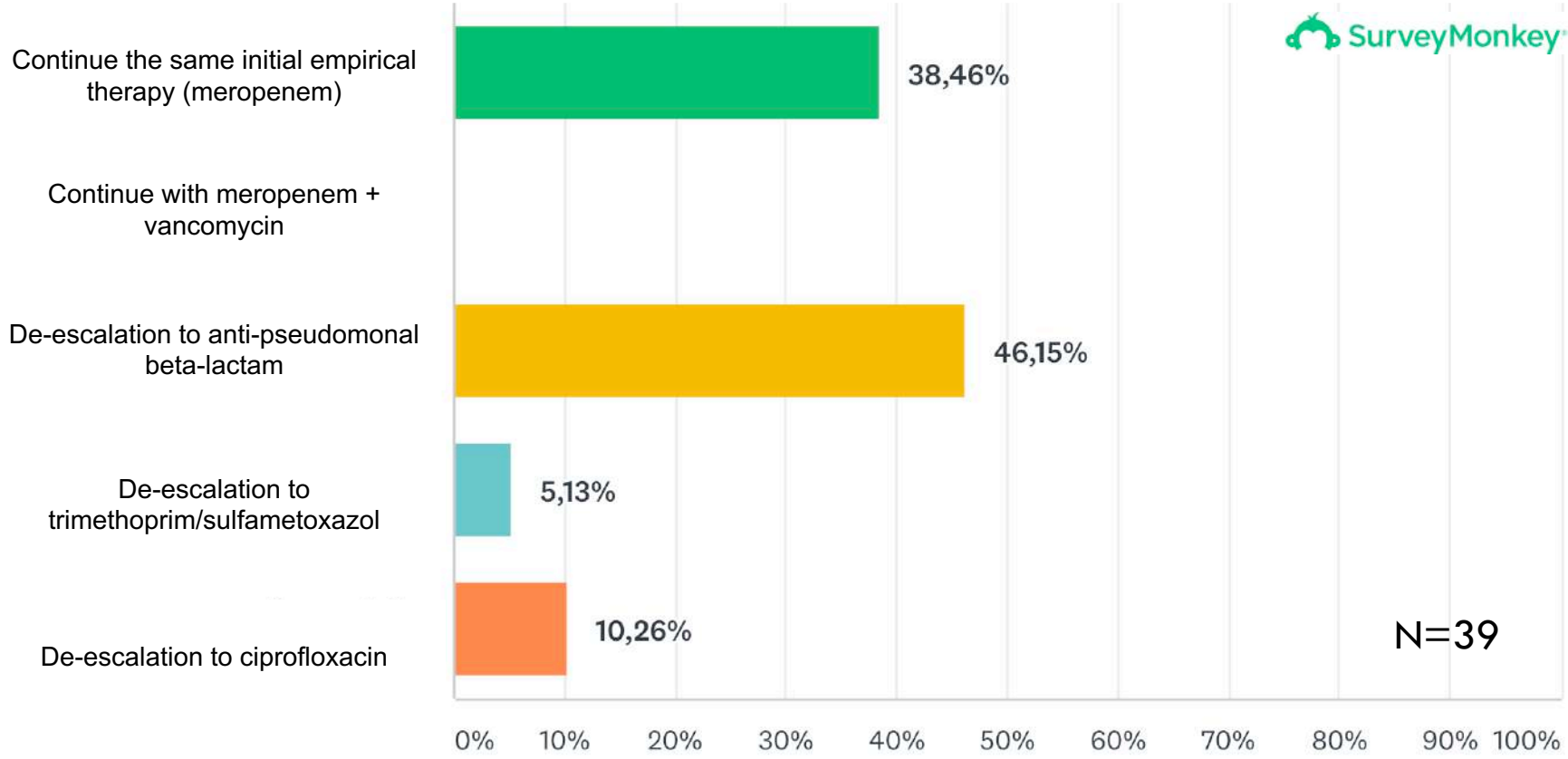
Case Report: How to de-escalate

18-yr old woman with Hodgkin's lymphoma. After febrile episode with chills and simultaneous rise of inflammatory index, empirical therapy with meropenem was started. An urgent chest X-ray showed new lung consolidations and *Pseudomonas aeruginosa* strain was isolated from BAL. The strain was susceptible to cotrimoxazol, ciprofloxacin but resistant to levofloxacin.
Normal renal function and hemoglobin 12 g/dl.
Blood culture results are pending.

What changes would you consider in antibiotic therapy?

A. Continue with the same initial empirical therapy.
B. Continue with meropenem plus vancomycin
C. De-escalation to anti-pseudomonas beta-lactam
D. De-escalation to trimethoprim/sulfametoxazol
E. De-escalation to ciprofloxacin

Case Report: How to de-escalate



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Take Home Message

Antimicrobial de-escalation and discontinuation should be considered whenever possible.

Rational use is urgently required to minimize emergence of MDR bacteria and to reduce costs and side effects.

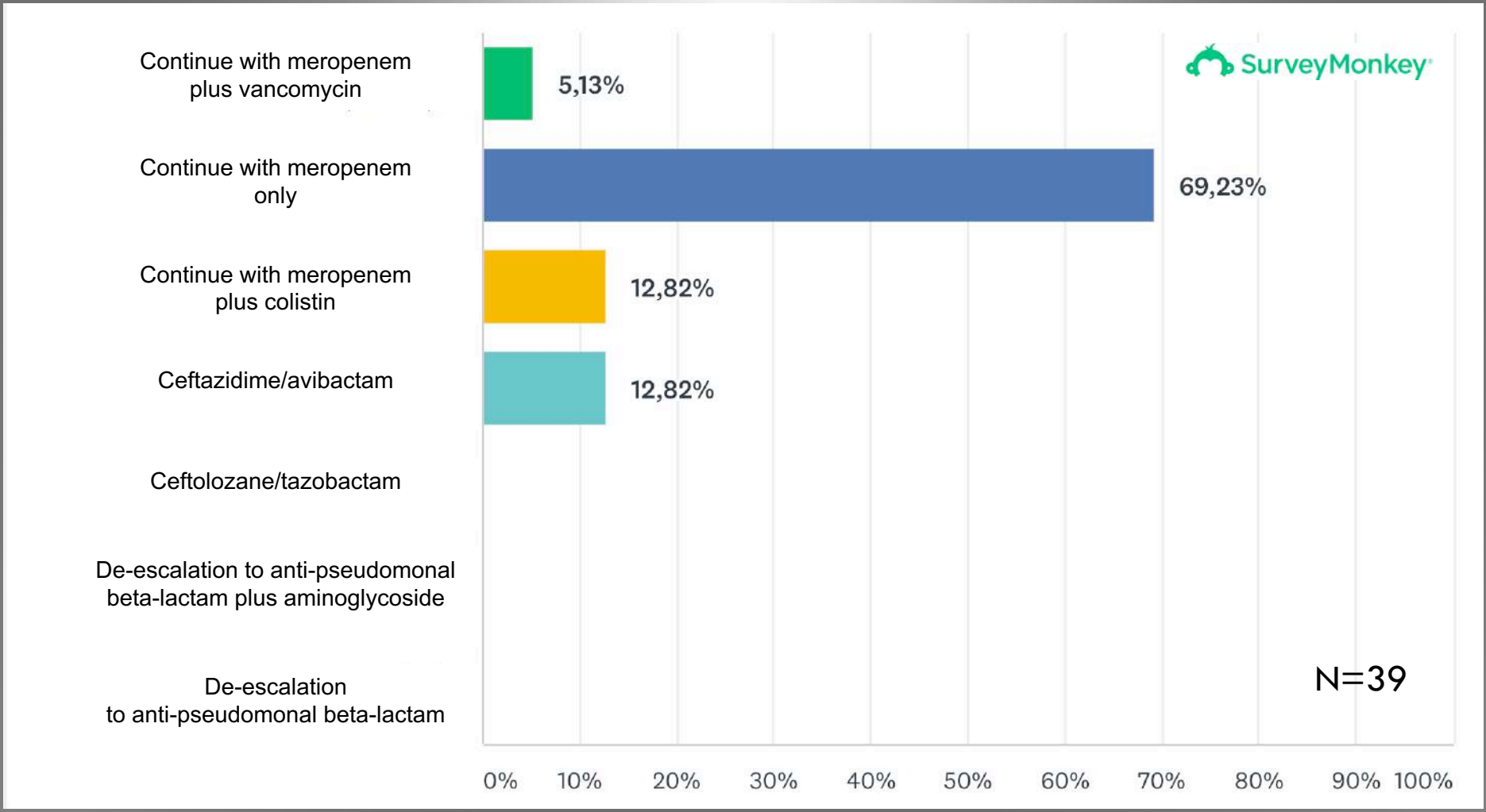
Papst L, et al Clin Microbiol Infect 2018; 24:1070-1076
Tabah A, et al. Intensive Care Med 2019; epub Ahead of print

Case report: Patients colonized by MDR bacteria

A female SCAT patient develops fever and general impairment with mental confusion. Blood gas analysis analysis shows metabolic acidosis with hyperlactacidemia. Simultaneous neutrophil leukocytosis and elevated inflammatory biomarkers were detected in blood chemistry.
Empiric therapy with meropenem and vancomycin was started, with prompt clinical response.
There were no infectious foci but *Pseudomonas aeruginosa* with ESBL production was detected in blood cultures.
What changes would you consider in antibiotic therapy?

A. Continue with meropenem plus vancomycin
B. Continue with meropenem, only
C. Continue with meropenem and add colistin
D. Ceftazidime/avibactam
E. Ceftolozane/tazobactam
F. De-escalation to an anti pseudomonal beta-lactam plus an aminoglycoside
G. De-escalation to an anti pseudomonal beta-lactam

Case report. Allogenic SCHT with ESBL Pa



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Take Home Message

Single-agent anti-pseudomonal betalactam is the standard of care for High Risk febrile neutropenia.

AGIHO/DGHO recommend to use a carbapenem for primary empirical therapy of patients with FN & known colonization by ESBL-producing pathogen.

CVC removal is advised for CVC infections caused by *S. aureus* or *Candida spp.*

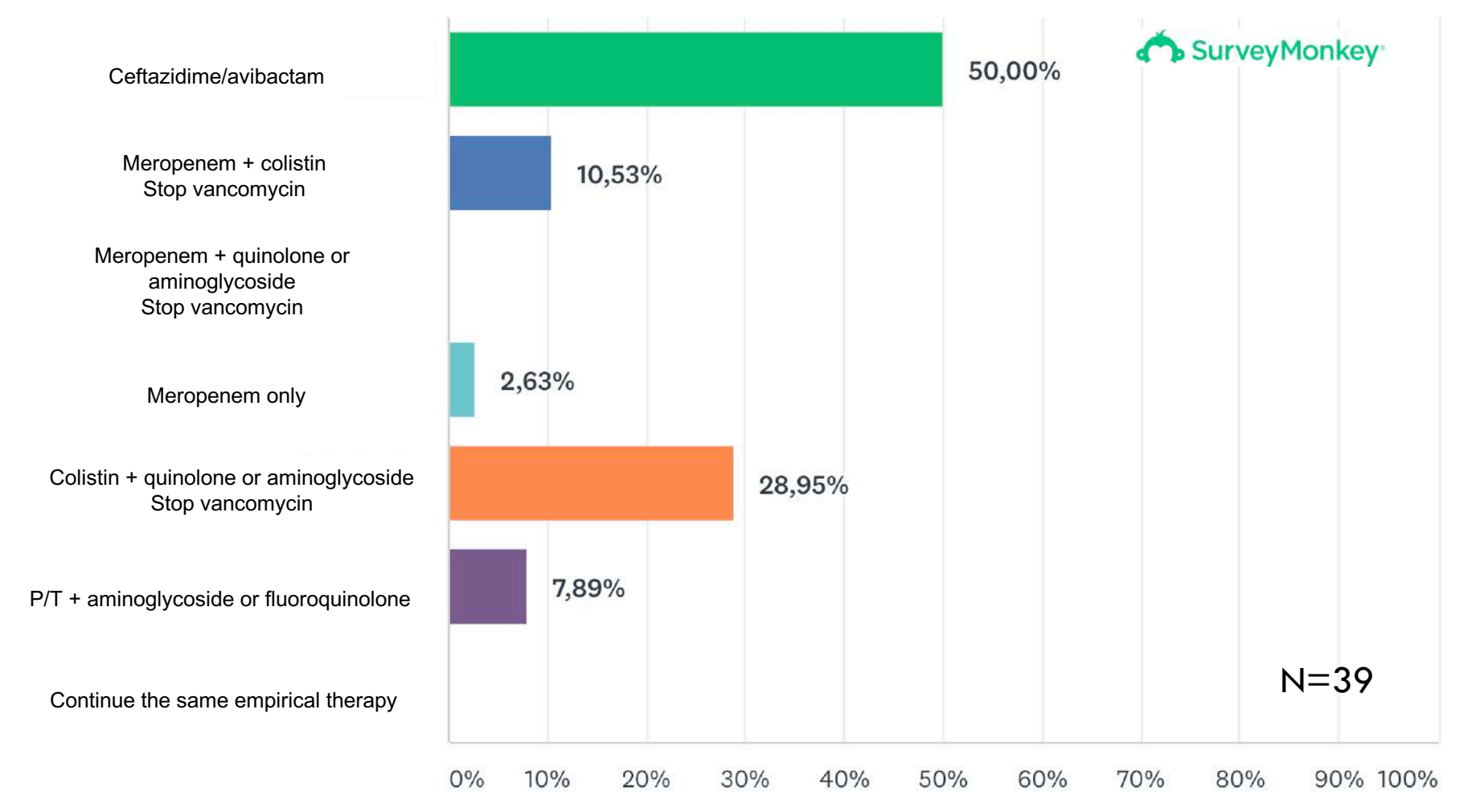
Averbuch et al. Haematologica 2013;98:1826-35

Case report: Combination in FN

Severe neutropenic patient (< 100/mm^3) with fever and signs of shock requiring admission to ICU and empirical therapy whit meropenem plus vancomycin.
After isolation of MDR *Pseudomonas aeruginosa* (producing KPC, a serine carbapenemase) from blood cultures, which is the best reassessment of therapy?

Ceftazidime/avibactam
Meropenem (continued or prolonged infusion) plus colistin and stop vancomycin
Meropenem (continued or prolonged infusion) plus aminoglycoside or fluoroquinolone and stop vancomycin
Meropenem (continued or prolonged infusion) only and stop vancomycin
Colistin plus aminoglycoside or fluoroquinolone and stop meropenem and vancomycin
Piperacillin tazobactam/Ticarcillin clavulanate plus aminoglycoside or fluoroquinolones and stop meropenem and vancomycin
Continue of the same empirical therapy

Case report: Colonization by MDR bacteria



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Take Home Message

Glycopeptide-based combination might be considered in MRSA colonized patients, especially if unstable.

VRE might be rather a marker for overall disease burden than a frequent cause of infection-related mortality

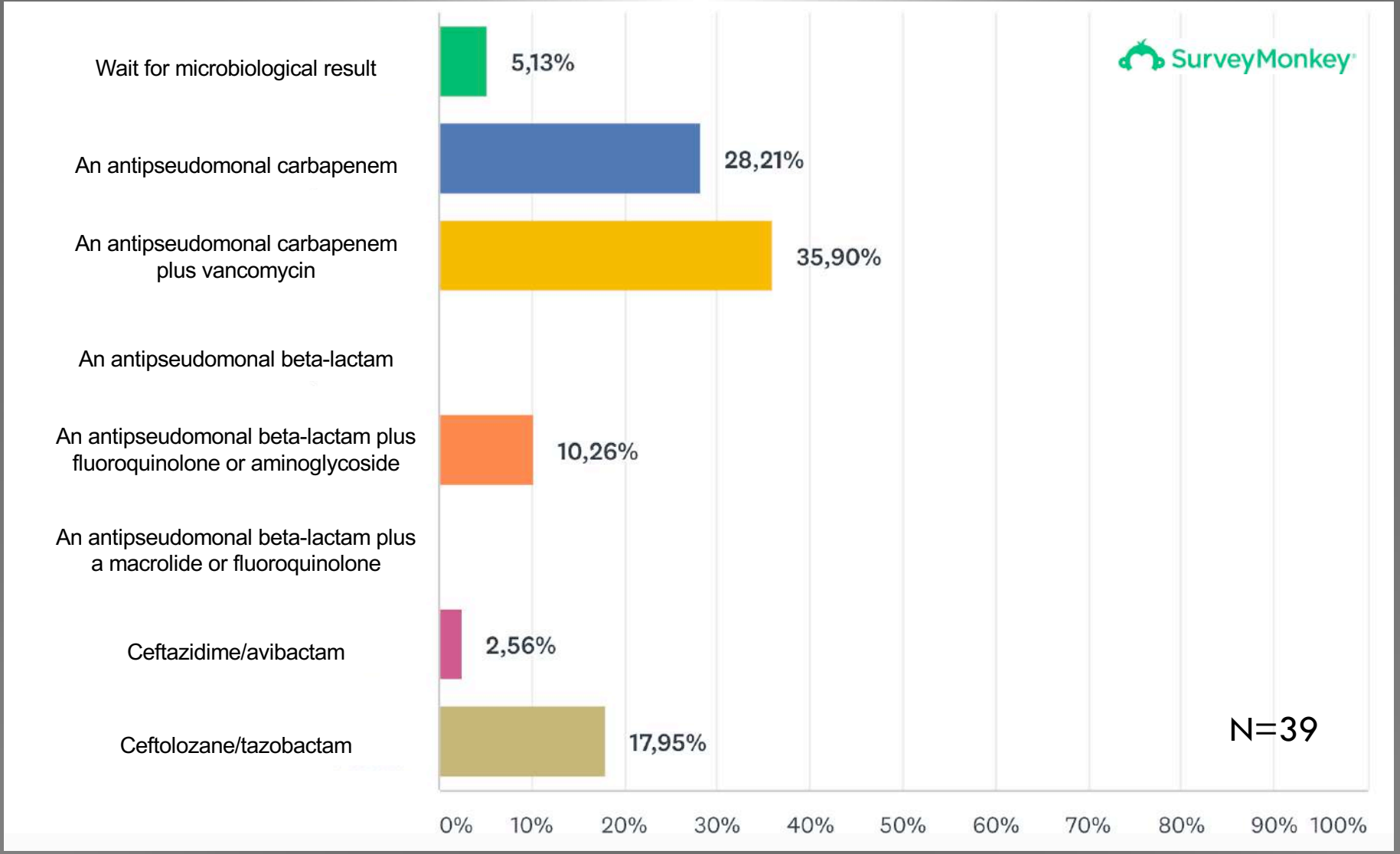
Schmidt-Hieber et al. Exp Rev Antiinfective Ther 2019. Epub Ahead of print

Case Report: Time of therapy

Patient with chronic myeloid leukemia, treated with BCR-ABL target therapy 1 month ago, was admitted to your hematological ward for persistent fever. At admission chest X-ray didn't show abnormalities; blood chemistry revealed severe neutropenia, elevated C reactive protein levels. Blast cells on peripheral blood were < 10%.
After developing hypotension, vasopressors were required.
Medical history indicated previous sepsis due to AmpC producing *Pseudomonas aeruginosa*
Microbiological results (blood and urine cultures) are pending, what do you do?

A. Wait for microbiological results
B. Give an anti-pseudomonal carbapenem
C. Give an anti-pseudomonal carbapenem plus vancomycin
D. Give an anti-pseudomonal beta-lactam.
E. Give an anti-pseudomonal beta-lactam plus an aminoglycoside or a fluoroquinolone
F. Give an anti-pseudomonal beta-lactam plus a macrolide or a fluoroquinolone
G. Ceftazidime/avibactam
H. Ceftolozane/tazobactam

Case Report. Time of therapy



How long do you maintain therapy in FN?

1- Five days

2- At least until neutrophil recovery (>500)

3- Clinical recovery and 72 h of apyrexia.

4- 14 days

5- Guided by PCT

What is your choice?

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Take Home Message

Discontinuation of the primary atb regimen prior to neutrophil reconstitution is considered to be safe: if the patient is afebrile for several days and all clinical symptoms of infection have been resolved.

Therapy delay may increase mortality

"How Long RCT" in haematological FN reported 13 days of therapy guided by 72h apyrexia vs 16 days until neutrophil recovery

ANTIBIOSTOP: not late than 5 days, irrespective of the temperature and WBC count: comparable outcomes

In AML, fever recurrence shortly after discontinuation if WBC did not recover

Mico J-B et al. Clin Microbiol Infect 2014;20:453-5
Aguilar-Guisado M, et al. Lancet Haematol 2017;4:e573-e583
Le Clech L, et al. Infect Dis (Lond) 2018;50:539-549

Case Report: FN and lung opacities

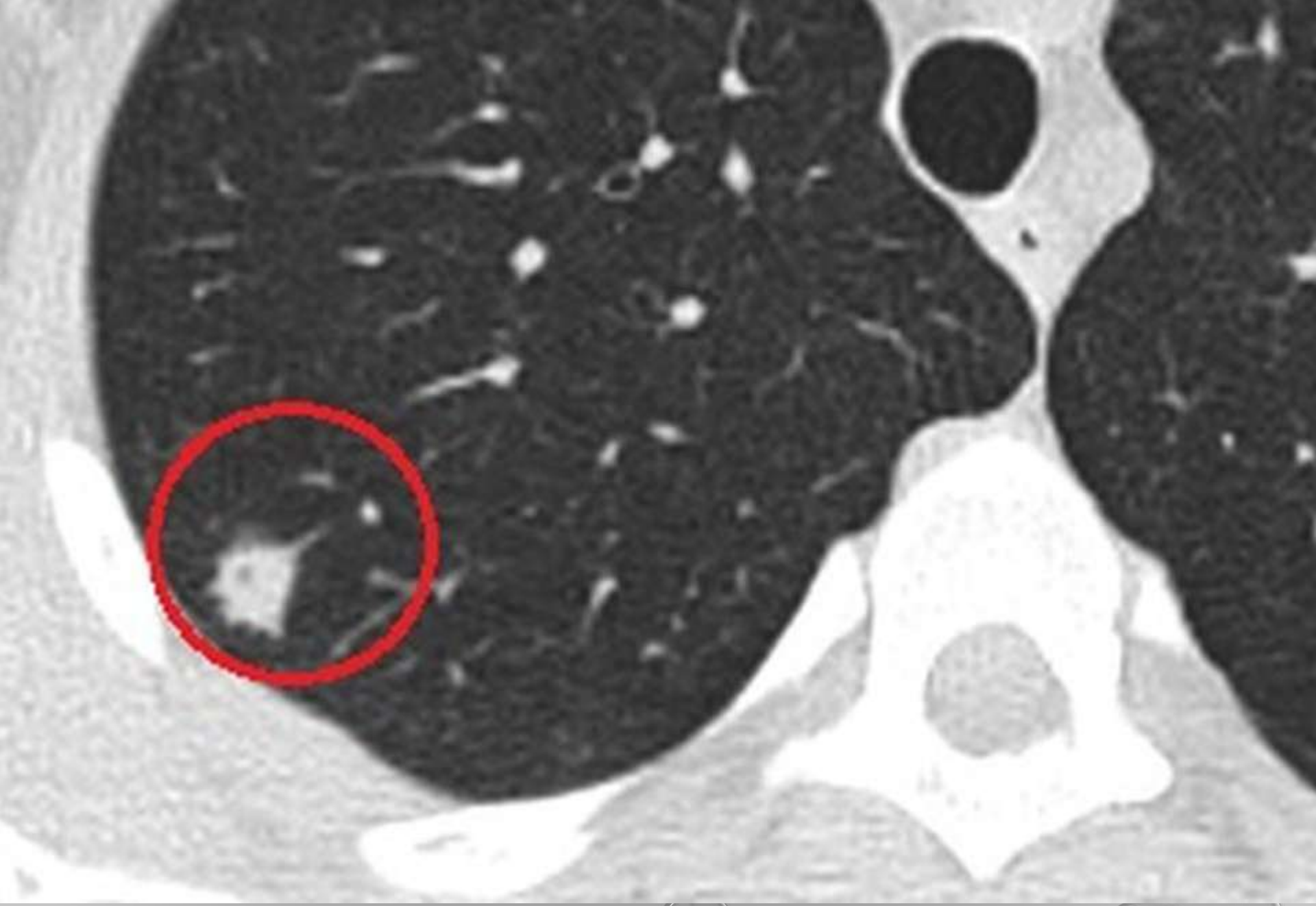
A 26-yr-old man with ALL developed neutropenic fever 12 days after induction chemotherapy. Prophylaxis for PJP was received.

No infection site could be identified. No respiratory symptoms

Empiric therapy with a beta-lactam was started, without improvement.

Do you suggest?:

1- Prolong therapy adding aminoglycoside and linezolid
2- Add Mold active pre-emptive therapy and order lung CT scan
3- Add Oseltamivir and test for respiratory viruses.
4- Add Ganciclovir and test for CMV
5- Replace cotrimoxazol for systemic pentamidine
6- Start steroid boluses because it is a condition that mimics pneumonia
7- Probably it is a lung lymphocytes infiltration.



Source: Durhan G et al. ICDM 2019.

Take Home Message

Atypical bacteria, including legionellosis, does not play a significant role

Therapy has to be pre-emptive, avoiding macrolides & FQ

BAL for bacteria, mycobacteria, molds, CMV, RV & PJP to be performed

Plasma and BAL galactomannan to be tested.

Start Cotrimoxazole if PJP prophylaxis was not compliant

Early start of voriconazole, isavuconazole or liposomal ampho B

HRCT cans to be performed if it does not respond within 72h

Schmidt-Hieber et al. Exp Rev Antiinfective Ther 2019. Epub Ahead of print

How to Implement?

TO IDENTIFY EFFECTIVE INTERVENTIONS

- **EDUCATION**

II. Is Didactic Education a Useful Antibiotic Stewardship Intervention for Reducing Inappropriate Antibiotic Use?

Recommendation

2. We suggest against relying solely on didactic educational materials for stewardship *(weak recommendation, low-quality evidence).*

Table 7. The Golden Rules of Antimicrobial Prescribing "MINDME".

M	Microbiology guides therapy wherever possible
I	Indications should be evidence based
N	Narrowest spectrum required
D	Dosage appropriate to the site and type of infection
M	Minimise duration of therapy
E	Ensure monotherapy in most cases

Adapted from Antibiotic Expert Group. Therapeutic guidelines: antibiotic. Version 14. Melbourne: Therapeutic Guidelines Limited; 2010.

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Antimicrobial Stewardship. ESCMID.

Protocol online at JECCM

Survey Open in April 2019

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