10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

Bacterial: febrile neutropenia – duration of therapy - new drugs

Dina Averbuch (Israel), Manuela Aguilar Guisado (Spain), Murat Akova (Turkey), Francesco Baccelli (Italy), Nicole Blijlevens (The Netherlands), Catherine Cordonnier (France), Carol Garcia Vidal (Spain), Malgorzata Mikulska (Italy), Patricia Muñoz (Spain), Dionysos Neofytos (Switzerland), Yuri Vanbiervliet (Belgium), Thierry Calandra (Switzerland)

Final slide set
Post meeting

From September 19th to 21st, 2024

- **Golden Tulip Sophia Antipolis**
  Nice, France

Methods

- Task: revision of the ECIL-4 guidelines (2011) on empirical and targeted therapy in FN patients

Averbuch et al Haem 2013 doi: 10.3324/haematol.2013.091330
Averbuch et al Haem 2013 doi: 10.3324/haematol.2013.091025

- Each subgroup decided on the key questions and analyzed the data accordingly
- Included: original studies (RCT and non-RCT), metaanalyses and guidelines published in English, from 2011 (previous guidelines), in high and middle outcome countries
- Search process performed by 1-2 members of each subgroup; literature list approved by the subgroup (backup slides)
- Detailed data supporting recommendations – in backup slides

Grading

Category, grade		Definition
Strength of recommendation	A	Strongly supports a recommendation for use
	B	Moderate evidence to support a recommendation for use
	C	Poor evidence to support a recommendation
	D	Supports a recommendation against use
Quality of evidence—Level	I	Evidence from ≥1 properly randomized controlled trial
	II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results from uncontrolled experiments
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees
Quality of evidence—Index (for Level II)	r	Meta-analysis or systematic review of RCT
	t	Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation
	h	Comparator group is a historical control
	u	Uncontrolled trial
	a	Published abstract (presented at an international symposium or meeting)

ECIL-10

Part I
Empirical therapy in febrile neutropenia

Francesco Baccelli, Carolina Garcia Vidal, Murat Akova, Thierry Calandra, Dina Averbuch

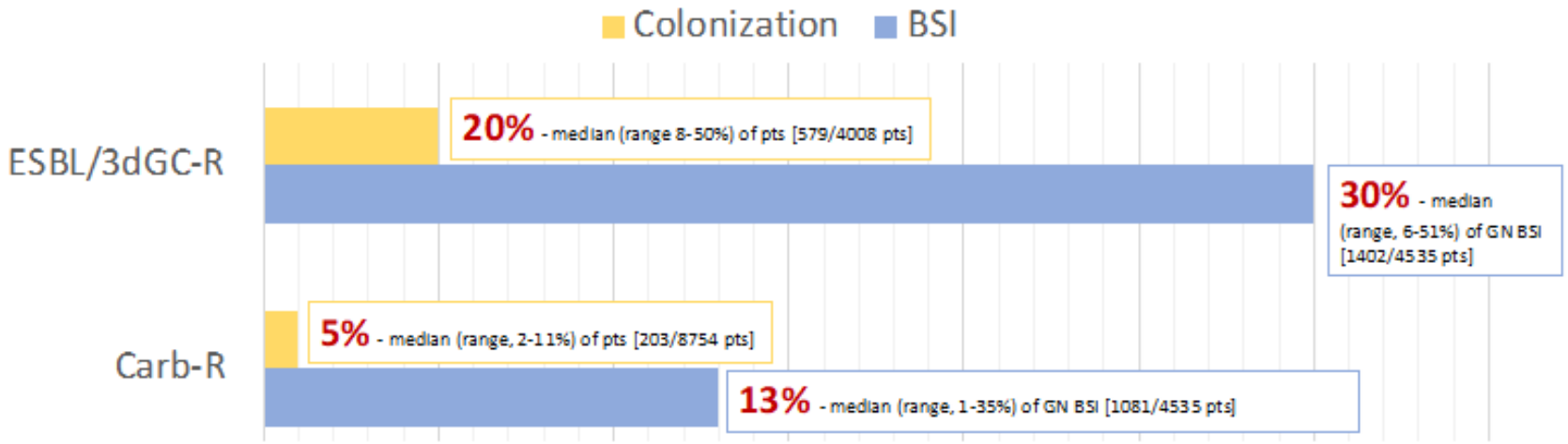
10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

CONFERENCE
From September
19th to 21st, 2024
Golden Tulip Sophia Antipolis
Nice, France

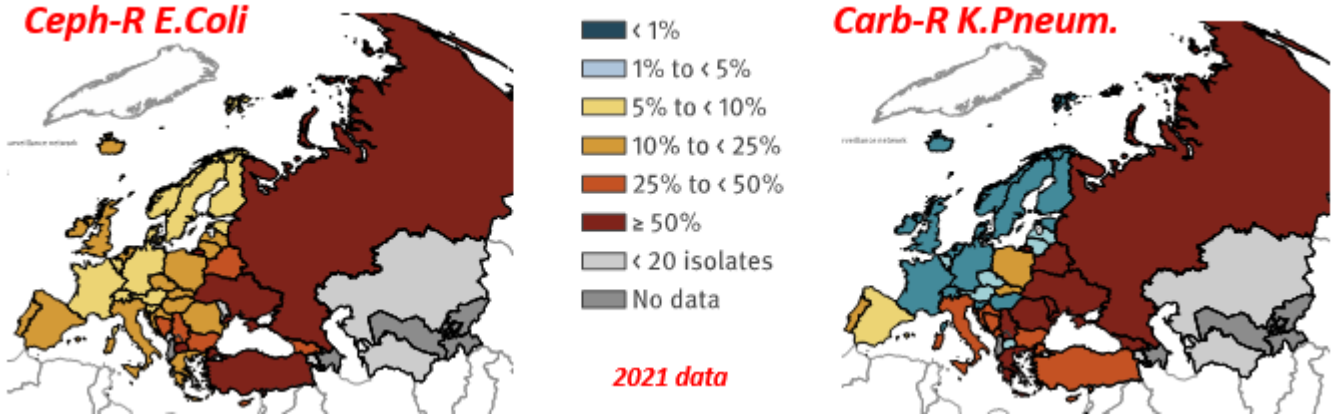
Epidemiology of resistance

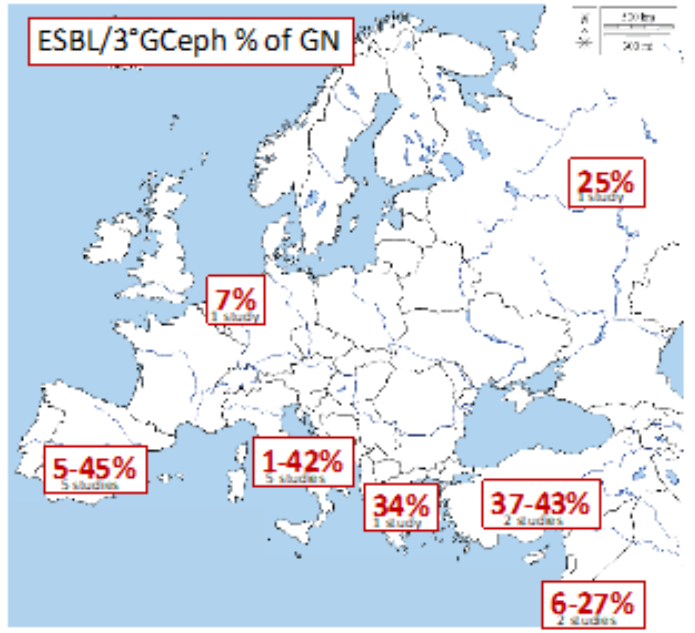
HM/HSCT pts, Europe, publications 2011-2024 (42 studies)

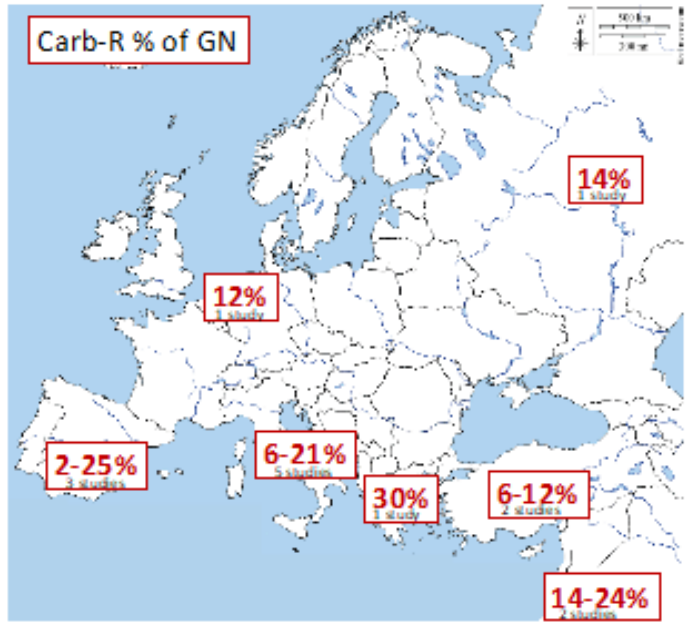
Mainly from South-Eastern countries/high resistance settings



General population: Increase of **Ceph-R** *E. coli* and **Carb-R** *K. pneumoniae* (ECDC-WHO)







ECIL-4: Recommendations for empirical antibiotic therapy: escalation and de-escalation approach

	Escalation approach	De-escalation approach
Indication **B-II for all**	1) Uncomplicated presentation; 2) No known colonization with resistant bacteria; 3) No previous infection with resistant bacteria; 4) In centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia.	1) Complicated presentations 2) Known colonization with resistant bacteria; 3) Previous infection with resistant bacteria; 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia.
Options for initial antibiotic therapy	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) **AI** 2) Piperacillin-tazobactam **AI** 3) Other possible options include: • Ticarcillin-clavulanate • Cefoperazone-sulbactam • Piperacillin + gentamicin	1) Carbapenem monotherapy **BII** 2) Combination of anti-pseudomonal beta-lactam + aminoglycoside or quinolone (with carbapenem as the beta- lactam in seriously ill-patients) **BIII** 3) Colistin + beta-lactam +/- rifampicin (for PsA, AB, SM) **BIII** 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (if risk factors for Gram- positives present) **CIII**

*** Avoid if ESBLs are prevalent**

**** AI for efficacy, but should be avoided in uncomplicated patients lacking risk factors for resistant bacteria, to preserve activity for seriously-ill patients**

Background for the changes of recommendations on empirical antibiotic therapy choice based on colonizing bacteria

Key questions	Answers
1) Is there an increased risk of subsequent BSI due to resistant bacteria in patients colonized with resistant bacteria?	**Yes** for GN (289/1607; 18.0% vs 116/9772; 1.2%; 33 studies) **Yes** for GP (VRE, MRSA) (208/1584; 13.1% vs 50/5549; 0.9%; 16 non-RCT, 1 metaanalysis)
2) Is there a correlation between inappropriate empirical antibiotic therapy and mortality due to resistant bacteria?	**Yes** for GN (92/417; 22.1% vs 104/1070; 9.7%; 27 studies, in 16 studies correlation was statistically significant; others did not reach significance, low numbers) **No** for VRE (24/183; 13.1%; 6 studies vs. 6/41; 14.6%; 3 studies) **No** for VGS (limited data, 2 studies) **No data** for MRSA in HM/HCT patients (data from other patients` population demonstrate correlation between delay in appropriate therapy and mortality in 5/9 non-RCT, 1 metaanalysis)
3) Does decolonization (with fecal microbiota transplantation or pharmacological agents) **prevent** subsequent BSI due to resistant GN in patients colonized with resistant bacteria?	**No** evidence that pharmacological decolonization prevents subsequent BSI with resistant bacteria in colonized patients (11 studies; 2 vs control – 1 no reduction, 1 early reduction, late no difference) **Limited evidence** suggests that FMT prevents BSI with resistant bacteria in colonized patients (6 studies; 1 non-RCT– significant reduction vs control)
4) Shall novel beta-lactams be used empirically in FN patients colonized with resistant Gram-negative bacteria?	Limited data showed good efficacy of empirical ceftazidime/avibactam *(2 non-RCT, 1 higher efficacy in KPC-colonized pts vs colistin-based combinations),* ceftolozane/tazobactam *(1 RCT FN higher clinical cure rates vs other BLs, 1 case-control MDR PsA lower mortality with CT vs controls, CT used as empirical/targeted, 1 non-RCT in colonized pts, 0 mortality);* and imipenem/cilastatin/relebactam *(1 RCT FN, higher clinical response vs comparator)* (total 6 studies, 2 RCT), **only 1 in colonized patients**

Background for the changes of recommendations on empirical monotherapy vs. combination therapy

Key questions	Answers
1) Does **empirical** combination therapy with a beta-lactam plus an aminoglycoside (BL+A) decrease mortality in febrile neutropenic patients?	**No evidence** that BL+A combination therapy improves outcomes, but recent literature is limited: - *6 meta-analyses, some – not the same beta-lactam in mono and in combination* - *3 RCT (1 pip-tazo +/- tigecycline-no diff in mortality, 1 small pediatric study-no diff in IRM, 1 different BL-no diff in mortality)* - *9 observational studies* - *different endpoints and timepoints used*
2) In which patients does empirical combination therapy (primarily BL+A) decreases mortality?	1) In patients who eventually develop **GN bacteremia** or **pneumonia** *(4 non-RCT, 2 of them – PsA BSI or pneumonia)* 2) In patients with BSI and **septic shock** *(1 non-RCT significant decrease with combi, 1 non-RCT – no significant decrease (trend, p=0.07, PsA BSI+shock; 1 non-RCT – no difference in patients with acute hypoxemic respiratory failure and sepsis/septic shock, mixed population (HM majority); 1 non-RCT appropriate empirical combination decreases mortality PsA BSI+shock, mixed population)* **Caveats:** 1) In studies performed mainly in countries from **high resistance setting** *(2 studies: 34 centers: 21 HR, 4 LR, 9 others; 1 study: 5/6 hospitals HR, GN BSI; 1 study: Spain)* 2) In studies including **"old" BLs** (carbapenems and non-carbapenem BLs) 3) Appropriate combination therapy vs. monotherapy addressed in 2 studies
3) Does **empirical** combination therapy targeting resistant Gram-positive bacteria decrease mortality in febrile neutropenic patients?	**No** *(2 metaanalysis, 1 retro, 1 RCT, similar mortality)*

Revision of recommendations for empirical antibiotic therapy: escalation approach

	Escalation approach ECIL 4	Escalation approach ECIL 10
Indication **B-II for all**	1) Uncomplicated presentation; 2) No known colonization with resistant bacteria; 3) No previous infection with resistant bacteria; 4) In centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia	**No change**
Options for initial antibiotic therapy	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) **AI** 2) Piperacillin-tazobactam **AI** 3) Other possible options include: • Ticarcillin-clavulanate • Cefoperazone-sulbactam • Piperacillin + gentamicin	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) **AI** 2) Piperacillin-tazobactam **AI** 3) Other possible options include: • Cefoperazone-sulbactam • Piperacillin + gentamicin

*** Avoid if ESBLs are prevalent**

**** AI for efficacy, but should be avoided in uncomplicated patients lacking risk factors for resistant bacteria, to preserve activity for seriously-ill patients**

Revision of recommendations for empirical antibiotic therapy: de-escalation approach (in red changes vs ECIL4)

	De-escalation approach ECIL 4	De-escalation approach ECIL 10
Indication	1) Complicated presentations **BII** 2) Known colonization with resistant bacteria **BII** 3) Previous infection with resistant bacteria **BII** 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia **BII**	1) Sepsis/Septic shock 2) Known colonization with resistant bacteria; 3) Previous infection with resistant bacteria; 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia.
Options for initial antibiotic therapy	1) Carbapenem monotherapy **BII** 2) Combination of anti-pseudomonal beta-lactam + aminoglycoside or quinolone (with carbapenem as the beta- lactam in seriously ill-patients) **BIII** 3) Colistin + beta-lactam +/- rifampicin (for PsA, AB, SM) **BIII** 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) **CIII**	1) Carbapenem monotherapy 2) Combination of anti-pseudomonal beta-lactam + aminoglycoside 3) Beta lactam targeting the suspected colonizing pathogen based on susceptibility testing 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent if risk factors for Gram-positives present

Revision of recommendations for empirical antibiotic therapy: Specific situations for de-escalation approach

Situations for which carbapenems are indicated as empirical regimen

(in red changes vs ECIL4)

ECIL-4	ECIL-10
1. Seriously-ill patients e.g. presentation with septic shock BII	1. Critically-ill patients e.g. presentation with sepsis/septic shock **and no known colonization or previous infection with carbapenem-resistant bacteria AIIu** *(based on increase in resistant bacteria including 3dGCephalosporin resistant Enterobacterales in community and in hospitals and increased mortality with IEAT)*
2. Known colonization or previous infection with: BII **a. ESBL-producing enterobacteriaceae** **b. Gram-negatives resistant to narrower-spectrum beta-lactams**	2. Known colonization or previous infection with: **AIIu** *(based on increased risk of BSI in colonised patients and increased mortality with IEAT)* a. ESBL-producing Enterobacterales b. Gram-negatives resistant to narrower-spectrum beta-lactams
3. Centres with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia BIII	3. Centres with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia **AIIu** *(based on increased mortality with IEAT)*

Revision of recommendations for empirical antibiotic therapy: Specific situations for de-escalation approach

Situations for which combination with an aminoglycoside is indicated as the empirical regimen (in red changes vs ECIL4)

ECIL-4	ECIL-10
1. In seriously-ill patients e.g. septic shock, pneumonia BIII	1. In critically-ill patients e.g. sepsis/septic shock, pneumonia **AIIu** *(3 non-RCT; in all: appropriate combination vs appropriate mono)*
2. If resistant non-fermenters (*P. aeruginosa* or *Acinetobacter* spp.) are likely, based upon BIII: **a. Local epidemiology** **b. Previous colonization or infection with these pathogens,** **c. Previous use – during the last month – of carbapenems**	2. If Gram-negative bacteria **resistant to the available beta-lactams** are likely **AIIu** *(lower mortality with combination therapy shown in retro studies)*, based upon: a. Local epidemiology b. Known colonization or previous infection with these pathogens c. Previous use of carbapenems within 30 d

Situations for which novel anti-Gram-negative beta-lactams are indicated as the empirical regimen (not covered by ECIL-4)

In patients colonized or previously infected with <u>carbapenem-resistant Gram-negative bacteria</u>:

KPC-producers	ceftazidime-avibactam **(AIIu),** meropenem-vaborbactam **(BIItu),** imipenem-cilastatin-relebactam **(CIIt),** cefiderocol **(CIII)**
OXA-48 -producers	ceftazidime avibactam **(AIItu),** cefiderocol **(CIII)**
MBL- producers	ceftazidime-avibactam plus aztreonam **AIItu ,** cefiderocol **(CIII);**

In patients colonized or previously infected with DTR *<u>Pseudomonas aeruginosa</u>*:

High dose ceftolozane tazobactam (**AIItu),** ceftazidime-avibactam **(AIItu),**

imipenem/cilastatin/relebactam **(BIIt),** cefiderocol (**CIII**);

*Coverage against invasive streptococcal infections should be considered if antibiotics with limited activity against Gram-positive organisms are used (e.g., ceftazidime with or without avibactam or cefiderocol), especially in patients with severe mucositis (**CIII**).

** screening for resistant bacteria should be performed in high-risk setting

The strength of recommendations is based on: 1) on the experience with specific compounds (such as ceftazidime, carbapenems, cefiderocol) in FN in general; 2) Experience in the targeted treatment of patients known to have bacteremia with these resistant bacteria; 3) Experience as empirical therapy in patients colonized with resistant bacteria

Revision of recommendations for empirical antibiotic therapy: Addition of anti-Gram-positive agents

Routine addition of glycopeptides or other antibiotics active against resistant GP bacteria is not recommended (**DIIru**)
(metaanalysis 2014 + update 2017, 1 uncontrolled study, 1 RCT)

Situations for which antibiotics active against resistant Gram-positive bacteria should be used as a part of empirical antibiotic regimen (in red changes vs ECIL4)

ECIL-4	ECIL-10
1. Haemodynamic instability, or other evidence of severe sepsis, septic shock or pneumonia CIII	1. Haemodynamic instability, or other evidence of sepsis, septic shock or pneumonia in patients: a. with known colonization with MRSA (AIIt) *[delay in appropriate therapy in patients with SA BSI and septic shock increases mortality in general population: 1 non-RCT]* b. known colonization with VRE and severe mucositis (CIII) c. without known colonization with MRSA (CIII)
2. Colonisation with MRSA, VRE or penicillin-resistant S. pneumoniae CIII	2. Colonisation with MRSA **BII r t** *[delay in appropriate therapy was associated with increased mortality in meta-analysis of 20 studies, 17 of them included patients with malignancy; 5/9 uncontrolled studies in general population]*
3. Suspicion of serious catheter-related infection: e.g. chills or rigours with infusion through catheter and cellulitis around the catheter exit site CIII	3. Suspicion of serious catheter-related infection: e.g. chills or rigors with infusion through catheter and cellulitis around the catheter exit site **BIII**
4. Skin or soft-tissue infection at any site CIII	4. Skin or soft-tissue infection at any site **BIII**

Recommended strategies in various circumstances for using de-escalation approach: Patient stable at presentation and stable at 72-96 h, FUO

	ECIL-4	ECIL-10	Reasoning
Afebrile	- Stop any aminoglycoside, quinolone or colistin or anti- Gram-positive agent, if given in combination **BIII** - Switch to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin/tazobactam, cefoperazone/sulbactam or ticarcillin/clavulanate **BIII** - Consider stopping antibacterial **BII**	- Stop any aminoglycoside, or anti- Gram-positive agent, if given in combination **BIIuh** - Switch to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin/tazobactam, cefoperazone/sulbactam, if carbapenem or novel beta lactam were used initially **BIIuh** - (Discontinuation addressed later)	Safety of de-escalation approach in pts with **FUO** (irrespective of fever status at re-evaluation): decrease in mortality (*1 non-RCT*) or no increase (*4 non-RCT*). Caveats: - no RCT - no study specific for FUO - evaluation of outcome of de-escalation and discontinuation together - comparative studies mainly pre- vs. post ECIL-4 implementation
Febrile*	- Stop any aminoglycoside, quinolone or colistin or anti- Gram-positive agent, if given in combination **BIII** - Keep on the same beta lactam or Switch to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin/tazobactam, cefoperazone/sulbactam or ticarcillin/clavulanate **BIII**	- Stop any aminoglycoside or anti- Gram-positive agent, if given in combination **BIII** - Keep on the same beta lactam or Switch to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin/tazobactam, cefoperazone/sulbactam **BIII**	

*For febrile patients: diagnostic work up; also consider fungal and other etiologies

Recommended strategies in various circumstances for using de-escalation approach:
Patient stable at presentation and stable at 72-96 h,
clinically documented infection

	ECIL-4	ECIL-10	
Afebrile	- Check appropriateness of antibiotic regimen - Consider stopping any aminoglycoside, quinolone or colistin or anti-Gram-positive agent if given in combination **BIII**	- Check appropriateness of antibiotic regimen - Consider stopping any aminoglycoside or anti-Gram-positive agent if given in combination **BIIuh**	Safety of de-escalation approach (de-escalation or narrowing or spectrum) in pts with **CDI** (irrespective of fever status at re-evaluation): decrease in mortality (*1 non-RCT*) or no increase (*3 non-RCT*)
Febrile*	- Check appropriateness of antibiotic regimen **BIII**	**BIIuh**	

*For febrile patients: diagnostic work up; also consider fungal and other etiologies

ECIL proposal for resistance reporting

Instead of using MDR, XDR or PDR terms, we recommend using the specific description of the most relevant resistance pattern:

- Gram-positive resistance
  - Simply report main resistance pattern, such as methicillin resistance for *Staphylococci*; or vancomycin resistance for *Enterococci*
- For Gram-negative resistance: report the main relevant resistance pattern (per ESCMID/IDSA guidelines)
  - 3rd generation cephalosporin-resistant *Enterobacteriaceae* (3GCephRE)
  - Carbapenem-resistant *Enterobacteriaceae* (CRE), report the enzymatic resistance mechanism, if known
  - *Pseudomonas aeruginosa* with difficult-to-treat-resistance (DTR *P. aeruginosa*: Resistance to all "old" beta-lactams (piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin) and quinolones (ciprofloxacin and levofloxacin)). Report MBL production if available
  - Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
  - *Stenotrophomonas maltophilia*

ECIL-10

Part II
Discontinuation of antibiotic treatment in neutropenic patients with hematological malignancies or following HCT

Dina Averbuch, Manuela Aguilar, Nicole Blijlevens, Thierry Calandra

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

CONFERENCE
From September 19th to 21st, 2024
Golden Tulip Sophia Antipolis
Nice, France

Supportive data

Key question 1: Can we safely discontinue antibiotics in neutropenic patients with FUO?

Search results (2011 – 2024): 5 RCT, 29 non-RCT (21 with comparison, 8 without comparison), 2 metaanalyses

Outcome	Result: short vs long duration (number of studies)
Overall mortality	Increased in short only in febrile at d/c (1), not increased (4 RCT, 19 non-RCT, 2 metanalyses)
Infection related mortality	Increased in short only in febrile at d/c (1), not increased (4 RCT, 13 non-RCT)
ICU admission	Not increased in short (3 RCT, 16 non-RCT)
Development of sepsis/septic shock	Not increased in short (4 RCT, 6 non-RCT)
Recurrence of infections	Increased in short (1 non-RCT, 1 metanalysis); not increased in short (5 RCT, 13 non-RCT),
Recurrence of fever	Increased in short (2 non-RCT); not increased in short (5 RCT, 13 non-RCT, 1 metaanalysis),
Re-initiation of antibiotics	Increased in short (1 RCT, 1 non-RCT); not increased in short (7 non-RCT),
Antibiotic duration	No difference (1 RCT, 2 nonRCT); shorter in the short arm (4 RCT, 15 non-RCT),
Length of stay	Increased in short (3 non-RCT), not increased (3 RCT, 10 non-RCT)
***Clostridium difficile* infection**	Decreased in short (1 non-RCT), not decreased (2 RCT, 17 non-RCT)
Invasive fungal infections	No difference (2 RCT, 7 non-RCT, 1 metaanalysis)
Emergence of resistance	No difference (1 RCT, 7 non-RCT, 1 metaanalysis)

Supportive data: Caveats

1. **RCT (n=5):**
   - EAT stopped before ANC recovery: ~53% in 2 RCT, not reported (3 RCT)
   - Short arm (in all RCT): high risk patients: alloHCT 39 patients; HM 192 pts (66 pts during induction)
   - 2 pediatric RCT – children with respiratory viruses

2. **High and intermediate risk patients reported together** (e.g in 3 RCT in adults)

3. **Overall: high degree of heterogeneity:**

   3.1 Primary endpoints: mortality (1 RCT, 10 non-RCT), fever relapse (11 studies), number of antibiotic-free days/AB duration (11 studies), etc

   3.2 Outcomes assessed at different time points (EON, hospitalization, 7-30 after EON/EAT start, etc)

   3.3 Minimal time until antibiotic discontinuation in FUO per protocol
   - 2-3 d (4 RCT; 14 non-RCT)
   - Non-RCT: 4-7 d (10 studies), 13-14 d (2 studies), NR (4 studies)
   - Duration of apyrexia before d/c: 24 h (9 studies, incl. 1 RCT); 48 h (13 studies); 72 h (3 studies, incl. 1 RCT); 6-9 d (3 studies), regardless of fever (4 studies, incl. 2 RCT), NR (4 studies, incl. 1 RCT)

   3.4 Excluded: HCT, severe mucositis, recent steroids, repeated HCT, relapse, alternative donor, etc

   3.5 Fluoroquinolone prophylaxis policy differs (e.g. RCT: 1 yes, 1 no, 1 ~40%, 1 ~10%, 1 NR)

Revision of recommendation for discontinuation of antibiotic treatment in neutropenic patients with FUO (in red changes vs ECIL4)

ECIL-4	ECIL-10
EAT can be discontinued at ≥ 72 hours of intravenous treatment in patients who are hemodynamically stable since presentation and are afebrile ≥48 hours, irrespective of neutrophil count or expected duration of neutropenia BII.	EAT can be discontinued at ≥ 72 hours of treatment in patients who are hemodynamically stable since presentation and are afebrile ≥48 hours, irrespective of neutrophil count or expected duration of neutropenia High-risk* patients **BI** *(RCT present=I; B as few allo and HM induction/re-induction there)* Intermediate risk** patients **AI** *(RCT present)*
It is important to emphasize that continuous fever in a stable patient is not a criterion to escalate antibiotics, but diagnostic efforts should be continued	We recommend continuation of EAT in stable high or intermediate risk neutropenic patients with FUO and persistent fever **BI** *[2 RCT, 1 of them – increased failure including mortality in those who stopped febrile; few febrile patients in Ram and outcomes not reported separately]* In these patients, diagnostic efforts should be continued searching for infectious focus or alternative explanation of fever. Discontinuation of EAT can be considered later, when bacterial infectious source was reasonably excluded by microbiological tests and imaging (**CIII**). We do not recommend adding coverage against resistant Gram-positive **(D I)** *(RCT),* or Gram-negative bacteria **(D II u)** in a stable patient with persistent fever

EAT - Empirical antibacterial treatment

*High-risk with expected duration of profound neutropenia >10 d: Allo-HSCT, AL induction, AL relapse/refractory

** Intermediate risk with expected duration of profound neutropenia of 7-10 d, e.g. auto-HSCT, lymphoma, CLL

Revision of recommendation for discontinuation of targeted antibiotic therapy for microbiologically or clinically documented infections (MDI/CDI)

Key question 2: Can we safely discontinue antibiotics in neutropenic patients with CDI/MDI

- Patients with CDI/MDI - very heterogenous group of patients
- CDI/MDI were included in 1 RCT and 9 non-RCT on d/c of antibiotics in neutropenic patients
- Conclusion in the previous slide are based on data that included patients with CDI/MDI
- CDI/MDI outcomes reported in 3 studies: **no** increased mortality, **no** increase in infection relapse

ECIL-4	ECIL-10 (modifications vs ECIL-4 in red)
CDI/MDI: Antibiotic treatment should be continued for at least 7 days, until the infection is microbiologically eradicated and all clinical signs of infection are resolved, with the patient afebrile for at least 4 days **BIII** (Treatment of MDI, "Targeted therapy" "Empirical therapy" guidelines)	Antibiotic therapy can be discontinued before recovery from neutropenia in patients with CDI/MDI after completion of intended course of treatment, who are hemodynamically stable, afebrile for ≥72 h, with resolution of all clinical signs and symptoms and microbiological eradication of infection (when re-sampling possible) **BIIu** *(few patients from 1 RCT, 9 uncontrolled studies describing centers` practices including CDI/MDI, specifically CDI/MDI outcomes addressed in 3; in others – in total patients).*

Revision of recommendation for discontinuation of antibacterial treatment in FUO/CDI/MDI

ECIL-4	ECIL-10 (in red changes vs ECIL4)
Centers who give prophylactic antibacterial agents should consider renewing this regimen upon discontinuation of the empiric therapy, if patient is still neutropenic **CIII**.	No change (**CIII**)
The patient should be kept hospitalized under close observation for at least 24-48 hours if he is still neutropenic when antibiotic therapy is stopped. If fever recurs, antibiotics should be re-started urgently after obtaining blood cultures and clinical evaluation.	Close inpatient or outpatient observation is recommended after antibiotics have been discontinued, particularly in patients with persistent neutropenia **A II u** If fever recurs in neutropenic patient, antibiotics should be re-started promptly after obtaining blood cultures and clinical evaluation. **A II u**

ECIL-10

Part III
Targeted Therapy of Gram-negative Infections

Yuri Vanbiervliet, Manuela Aguilar, Dionysios Neofytos, Murat Akova, Dina Averbuch, Malgorzata Mikulska

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

CONFERENCE
From September
19th to 21st, 2024

Golden Tulip Sophia Antipolis
Nice, France

Targeted therapy for (neutropenic) HM/HSCT patients with Gram-negative bacteremia

Key questions:

1. What is currently the **best treatment against resistant gram-negative pathogens** in patients with HM or following HSCT:
    - **Carbapenemase-producing *Enterobacteriaceae* (CPE)** divided into carbapenemase type: KPC, OXA-48, MBL
    - **DTR *Pseudomonas aeruginosa***
    - **Carbapenem-resistant *Acinetobacter* (CRAB)**
    - ***Stenotrophomonas maltophilia***
2. Can antibiotic treatment be **de-escalated** in haematological neutropenic patients with positive blood cultures
3. Duration of treatment for Gram-negative bacteremia

Targeted therapy for (neutropenic) HM/HSCT patients with Gram-negative bacteremia

<u>Scope:</u> Novel *in vitro* active antibiotics *(only FDA/EMA approved)* **+ old AB** with new data

- Main characteristics + spectrum of activity of novel AB (see back up slides)
- Clinical data and recommendations

<u>Literature search:</u>

1. ESCMID-IDSA **guidelines** for **resistant GN pathogens** (general population)
2. **RCTs on the new antibiotics** (+ specifically data on % and outcomes in **immunocompromised** patients and in **resistant gram-negative pathogens)**
3. **Meta-analyses/systematic reviews**
4. **Observational studies** in the HM/HSCT population; if no data – observational studies in general population

Novel beta lactams
Ceftolozane-tazobactam
Ceftazidime-avibactam
Cefiderocol
Imipenem-cilastatin-relebactam
Meropenem-vaborbactam
Aztreonam avibactam
Sulbactam-durlobactam

Targeted therapy: RCT on new beta lactam antibiotics

- Indication-based studies (n=23): pneumonia, complicated intra-abdominal infections, complicated urinary tract infections (+15 pooled/sub-analyses)
  - ✓Non-inferior to comparator
  - ✓Few patients with resistant pathogens included (CRE, DTR PsA, CRAB)
  - ✓Immunocompromised included in 1 RCT
- Pathogen-based studies (n=11)
  - ✓Carb-R GN (2), MDR GN (1), CRE (1), CRAB/XDR/MDR *Acinetobacter* (1 Sulbactam-durolbactam; + 6 RCT other sulbactam combinations)
  - ✓Immunocompromised included in 3 RCT

	Indication-based	Pathogen based
Ceftolozane-tazobactam	8	0
Ceftazidime-avibactam	9	0
Cefiderocol	2	1
Imipenem-cilastatin-relebactam	3	1
Meropenem-vaborbactam	1	1
Aztreonam avibactam	0	1
Sulbactam-durolbactam	0	1

Treatment of carbapenemase-producing *Enterobacteriaceae* (KPC, OXA-48, MBL producers)
General comments on observational studies

- Observational data in **IC/HM/HSCT** (N=33): exist only for some antibiotics and bacteria
  - Most data is available on **ceftazidime-avibactam**
  - Most data available on **KPC CPE***;* to lesser extent on OXA-48 and few data on MBL
- The specific underlying immunocompromised status and the corresponding numbers of patients is not always reported
- In the observational studies that do report HM/HSCT/IC patients, very few report the number of **neutropenic patients**: e.g. in total reported for ceftazidime-avibactam 50 pts (3 studies), meropenem-vaborbactam 9 pts (2 studies), other ABs - no data. Neutropenia is associated with mortality (analyzed in 3 studies).

pts = patients

KPC-producing *Enterobacteriaceae* (class A beta-lactamase) ECIL-10 treatment recommendations

AB	RCTs (N=18)	Observational data in HM/HSCT/IC (N=18)	ECIL-10 grading
Ceftazidime-avibactam	3 pooled analyses of RCTs reporting some class A CPE	**Better outcome** vs controls in 1 comparative study in HM (14 total studies)	**A II t u**
Meropenem-vaborbactam	Not inferior to comparator for CRE (mainly KPC, 1 RCT) *subanalysis 19 IC/HM/HSCT pts showing good survival and clinical cure (1 RCT)	Comparable outcomes to ceftazidime avibactam in 1 comparative study (3 total studies)	**B II t u**
Imipenem-cilastatin-relebactam	Almost no data on KPC, some CRE included (31 pts)	No data (limited data on CRE in general population)	**C II t**
Cefiderocol	2 RCT including IC, few CRE patients	Limited data on KPC (limited data in general population)	**C II t**

N= number of studies, pts = patients

OXA-48 producing *Enterobacteriaceae* (class D beta-lactamase) ECIL-10 treatment recommendations

AB	RCTs (N=9)	Observational data in HM/HSCT/IC (N=5)	ECIL-10 grading
Ceftazidime-avibactam	3 pooled analyses of RCTs reporting some class D CPE	**Better outcome** vs controls in 1 comparative study (4 total studies)	**A II t u**
Cefiderocol	No data on OXA-48	Almost no data on OXA-48 (some data in general population)	**C II t**

N= number of studies, pts = patients

MBL producing *Enterobacteriaceae* (class B beta-lactamase) ECIL-10 treatment recommendations

AB	RCT (N=3)	Observational data in HM/HSCT/IC (N=6)	ECIL-10 grading
Ceftazidime-avibactam + aztreonam	No data	**Better outcome** vs controls in 2 comparative studies (5 total studies)	**A II t u**
Cefiderocol	Pooled analysis for 34 pts MBL from 2 RCT, IC included in 1 RCT	Limited data in mixed general + HM/HCT population	**B II t**
Aztreonam-avibactam	Not published, provisional – not inferior (number of MBL producers not specified)	No data	**Insufficient data**

N= number of studies, pts = patients

Treatment of carbapenemase-producing *Enterobacteriaceae*: Combination therapy

- **Recommendations:** In carbapenem-resistant infection combination therapy with another non-BL active agent is generally discouraged but might be considered until clinical improvement in:
  - **Critically-ill** (sepsis) patients **(C III)**
  - In **difficult to treat infections** (such as source control not performed, pneumonia), **OR** due to CRE with **MIC-value close to resistance breakpoint** **(C III)**

Background

- International guidelines do not recommend combination therapy based on the analysis of data in general population
- RCT: almost all used as monotherapy
- Systematic reviews/meta-analyses are only available for **ceftazidime-avibactam**: no benefit of combination therapy, **BUT:** no stratification for antibiotic drugs used in combination, no subanalysis for IC/HM/HSCT, pooled data only from observational trials with poor quality
- All observational studies (mainly for **ceftazidime-avibactam)** show no difference in (overall) survival between mono and combination therapy (poor quality data). However we cannot exclude the benefit of combination therapy as it is usually administered in more critically-ill patients (bias)

DTR *Pseudomonas aeruginosa:*
ECIL-10 treatment recommendations

AB	RCTs (n=24)	Observational data in HM/HSCT/IC (n=22)	Metaanalyses* (n=11)	ECIL-10 grading
Ceftolozane-tazobactam	MDR/CRPA included	**Better outcome** vs controls in 2 comparative studies (3 total studies)	**Better outcome** vs comparator (n=1) (not specifically R)	**A II t u r** **High 9 g/d dose**
Ceftazidime-avibactam	MDR PsA (+pooled analysis)	**Better outcome** vs controls in 1 comparative study (5 total studies)		**A II t u**
Imipenem-cilastatin-relebactam	MDR PsA included; CRPA (24 pts): not inferior to comparator (1 RCT)	No data (3 studies in general population)		**B II t**
Cefiderocol	IC included in 2 RCT; CRPA (22 pts): not inferior to comparator (1 RCT)	1 comparative study: **no difference** in mortality (14 total studies) Mainly used as salvage	**No difference** in clinical response vs comparator (n=1) (not specifically R)	**B II t u r**

*Meta-analysis MDR PsA: Strong association between treatment with new (C/A, C/T, I/R) antibiotics and clinical success (Wilson, RCT+nonRCT)

DTR *Pseudomonas aeruginosa:* combination therapy

➢ Recommendation:

Combination of active non-beta lactam antibiotic (amikacin, tobramycin, fosfomycin, FQ – particularly for pneumonia) might be considered in patients who are **critically-ill** (sepsis, septic shock, pneumonia), infections due to PsA with **MIC-value close to resistance breakpoint** OR **uncontrolled infection**, in combination with **ceftolozane-tazobactam BII r, ceftazidime-avibactam (BIII), imipenem-cilastatin–relebactam (BIII), cefiderocol (BIII)**

<u>Background</u>

- ➢ Metaanalyses: immunocompromised included, no separate analysis
  - ❑ Ceftolozane-tazobactam: significant reduction of mortality in patients receiving ceftolozane-tazobactam **combination** therapy, OR: 0.31, 95% CI: 0.10–0.97, p = 0.045; In 238 of the 391 patients included (60.8%), ceftolozane-tazobactam was used for the treatment of infections caused by *Pseudomonas aeruginosa (Fiore)*
  - ❑ Ceftazidime-avibactam: No difference in monotherapy vs combination
  - Onorato (CRE+CRPA): in total population and excluding PsA (19 CRPA patients);
  - Aslan: CRE (19 studies) and MDR PsA (3 studies)
- ➢ Observational data in HM/HCT: new antibiotics frequently used in combination
- ➢ Resistance can develop on treatment

Carbapenem-resistant *Acinetobacter baumanii* (CRAB)
ECIL-10 treatment recommendations

We recommend combination therapy for CRAB **A II t**

AB	RCTs	Observational data in HM/HSCT/IC	Proposed grading
Sulbactam-durlobactam* + high-dose imipenem	Not inferior to comparator	Not available	**A II t**
High-dose sulbactam (≥ 9gr/day) + other drug[1, 2]	Good efficacy in general populations	No data in HM/HSCT Data in general population	**B II t**
Other combinations[3]	Data on cefiderocol[4], tigecycline [5]	Some data on cefiderocol[4] in HM; Some data on fosfomycin, tigecycline[5] minocycline[6] in general population	**B II t**

***durlobactam not EMA approved**

(1) In case sulbactam-durlobactam is not available

(2) In combination: colistin is preferred. If colistin cannot be used, considered addition of one of cefiderocol [4] , tigecycline [5], minocycline [6].

(3) If sulbactam MIC>16 (resistance): consider combination of any of the following: colistin, cefiderocol, tigecycline/minocycline, fosfomycin.

(4) Although cefiderocol **monotherapy** has been associated with increased mortality in RCT, cefiderocol-based **combinations** have been associated with improved clinical outcomes in meta-analyses and retrospective studies. It can be favored if sulbactam-R isolates and/or when colistin cannot be used.

(5) Tigecycline studied as mono- and combination therapy with variable outcomes. High-dose tigecycline can be used if tolerated. Should be avoided in cases of bacteremia, pneumonia or urinary tract infections; or if MIC>2.

(6) Minocycline: limited clinical data on CRAB. Based on MIC and PK/PD data, high-dose minocycline IV/PO may be an alternative to tigecycline

Stenotrophomonas maltophilia: ECIL-10 treatment recommendations

AB	Recommendation	Grading
If TMP/SMX feasible	TMP/SMX in combination with other agent: levofloxacin, or tetracycline derivate (HD minocycline or HD tigecycline) or cefiderocol	**B II tu**
If TMP/SMX resistant or intolerant	Two-drug combination of levofloxacin (if susceptible), tetracycline derivate (HD minocycline or HD tigecycline) or cefiderocol	**B II u**
	Combination of ceftazidime/avibactam+aztreonam and levofloxacin (if susceptible) or tetracycline (HD minocycline or HD tigecycline)	**C III**
Step down to monotherapy can be considered after clinical (and microbiological, if applicable) response is obtained and susceptibility to the single agent confirmed		

High 30-d mortality rates in HSCT (>50%); limited number of agents with breakpoints available; new drugs with anti-Sm activity have very limited data

Cefiderocol: in 1 RCT, 5 patients with Sm included (2 with CRAB co-infection); outcome: 3 failures, 2 indeterminate, 4/5 died; other single cases and small cohorts

Ceftazidime/avibactam+aztreonam: only case reports, mainly in ICU patients

For TMP/SMX, only observational studies, 3 meta-analyses of retrospective studies, mainly in ICU pneumonia setting: no difference between TMP/SMX vs. FQ or tetracycline derivates, and between monotherapy vs. combination; **one retrospective study reported the benefit of combination therapy in case of high APACHE score or immunocompromised patients**

New PK/PD animal models for efficacy of FQ based on MIC (levofloxacin 750mg QD or ciprofloxacin oral 750mg BID/IV 400mg TID), need for high dose of minocycline (200 BID) or tigecycline (100mg BID after loading dose of 200mg)

Recommendations on de-escalation of antibiotics in HM/HCT neutropenic patients with blood stream infection (BSI)

10 non-RCT: no increased mortality when de-escalation implemented

ECIL-4	ECIL-10 (modifications vs ECIL-4 in red)
Whatever the initial approach was (escalation or de-escalation) the patient should be treated according to the organism identified (assuming it is a plausible pathogen) using narrower-spectrum agents, guided by in vitro susceptibility tests, including minimum inhibitory concentration (MIC) when available, and based on knowledge on drugs with specific activities **AI**.	**Statement unchanged** **Grading updated A II u h**
	If patient` presentation suggests, in addition to BSI, a clinically documented infection with polymicrobial aetiology, we recommend to de-escalate to an agent active against the main potential pathogens including covering *Pseudomonas aeruginosa* in case of intraabdominal infection

Recommendations on duration of antibiotics in HM/HCT neutropenic patients with Gram-negative BSI

✓ **Recommendation:** In patients with Gram-negative bloodstream infections, we recommend a duration of antibiotic treatment of at least 7 days with recovery of neutropenia **(AIIu)** or without **(BIIu)** recovery of neutropenia.

Background

- ✓ 4 non-RCT, 3 included *Pseudomonas aeruginosa*; Short antibiotic duration: 7-11 d (n=432 pts)
- ✓ AB stopped before ANC recovery: 11-46 pts (10.5-52.2%) short (3 studies)
- ✓ Presence of source (mainly abdominal or CVC): 45-70%
- ✓ Source control (including CVC removal): 69.2-100% cases in short
- ✓ Results: no increased mortality, ICU admission, septic shock or infection relapse (including in neutropenic patients in 1 study)

ECIL-10

Part IV
Non-culture-based diagnostic test in hematology / febrile neutropenic patients

Dionysios Neofytos, Catherine Cordonnier, Patricia Munoz

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

CONFERENCE
From September 19th to 21st, 2024
Golden Tulip Sophia Antipolis
Nice, France

Goal and methods

- ✓Goal of the literature search: to assess the role of non-culture-based Dg tests (identification and susceptibility testing) in the management of bacterial infections in febrile neutropenic (FN) patients.
- ✓Focus on BLOOD samples and mainly on bacterial infections
- ✓Studies published ≥ 2011
- ✓Only the tests available for routine practice in Europe

Selected questions to be addressed:

- Does the test improve the microbiological documentation of the infection(s)?
- Does the test shorten the time to diagnosis?
- Does the test impact on the optimal/appropriate therapy?
- Does the test affect treatment duration?
- Does the test improve the outcome (survival) of FN?

New diagnostics techniques use in FN or in HM patients: Literature review

	Multiplex PCR	NGS	T2MR	MALDITOF directly on positive BC	Specific PCR
Specific tests assessed	Verigene, BCID2 FilmArray, ePlex	Illumina NextSeq, MGISEQ-2000, DISQVER, iDTECT® Dx Blood v1®	T2MR	Malditof on positive BC	Staphylococcus, VRE, Carbapenemases
No. papers identified through PubMed	293	35	18	16	32
No. studies selected for the analysis	8	6	1	4	0
FN patients/total pts (% of FN) (no. studies reported)	209/509 (11.5-100%, mean: 30%) (4 studies)	335/459 (52-100%, mean: 68%) (6 studies)	309/648 (47.7%) (1 study)	98/475 (20.6%) 3 studies	-
Sensitivity result (no. studies)	80.5%, 100% (2)	40%, 90%, 100%	84.2%	63% (GP), 89%, 93%, 92.6% (GN) 3 studies	-
Specificity result (no. studies)	NA	40%, 63%, 84%	85.9%	NA	
PPV result (no. studies)	88.5% (1)	28%, 79%, 84%	NR		-
NPV result (no. studies)	NA	40%, 81%, 100%	NR		-

New diagnostics techniques use in FN or in HM patients

	Multiplex PCR	NGS	T2MR	MALDITOF directly on positive BC	Specific PCR
Specific tests assessed	**Verigene, BCID2 FilmArray, ePlex**	**Illumina NextSeq, MGISEQ-2000, DISQVER, iDTECT® Dx Blood v1®**	**T2MR**	**Malditof on positive BC**	**Staphylococcus, VRE, Carbapenemases**
Does the test improve NF microbiological documentation?	**Yes 1/8** **Not specifically reported in FN: 7/8**	**Yes 5/6** **No 1/6**	**Yes, 11 samples**	**No**	**No**
Does the test shorten time to diagnosis?	**Yes 4/8** **Not reported: 4/8**	**Not reported 6/6**	**Yes: 4.4 vs 65.7 h**	**Yes** BC collection to species id (27.4 h vs 46.6 h) Egli	**Yes** (> 20 h)
Does the test affect treatment selection and timing?	**Yes 3/8** **« Likely » 1/8** **No 2/8** **Not reported 2**	**Yes 2/6** **Not reported 4/6** **Timing not reported**	**Not addressed** Sensibility 84.2% (60% for *E. faecium*); Specificity:85.9%	**Yes:** (3.7 versus 6.7 h from Gram stain, p 0.003- Oshtoff).	**Likely** if used with AMS programs. No data on NF
Does the test affect antibiotic treatment duration?	**Not reported 8/8**	**Not reported 6/6**	**Not reported**	**No** (Oshtoff)	**Not reported**
Does the test improve NF outcomes (survival, LOS, ICU transfer)?	**No 3/8** **Not reported 5/8**	**Not reported 6/6** **(1/6: «relief» in 42% of patients)**	**Not addressed**	Better optimal Tx (Torres) and less ICU admission (23.1 versus 37.2%, p 0.02).	

ECIL survey: Real life use of the new diagnostics techniques

- Responses: 28 centers
  - Specialists: 22 microbiologists (14 only micro, 8 micro + specialist), 6 ID (4/6 with micro), 5 Heme specialists (3/5 with micro), 3 other (pediatrician with micro, clinical scientist, not specified)
  - Countries: 4 Spain, 4 Italy, 2 UK, 2 Portugal, 2 Poland, 2 France, 2 Switzerland, 1: NS, Turkey, Sweden, Norway, Germany, Netherlands, Austria, Israel, Saudi Arabia, Brazil
- mNGS
  - Access at your center: 19/28 Yes
  - Platform: 17/19 specified (10 Illumina, 2 Nanopore, 1 Karius, PacBio, Minion, Salmona, Sanger)
  - Do you use it routinely for bacterial infections in FN patients: 1 Yes
- Multiplex PCR
  - Access at your center: 25/28 Yes
  - Platform: 19 Biofire/Filmarray, 3 respiratory/GI/encephalitis, 3 BD max, 1 Biopharm, 1 Seegene
  - Do you use it routinely for bacterial infections in FN patients: 14 Yes
- T2MR
  - Access at your center: 4/28 Yes
  - Platform: T2MR 3/4 specified
  - Do you use it routinely for bacterial infections in FN patients: 1 Yes
- MALDI
  - Access at your center: 24/28 Yes
  - Platform : 19 Bruker, 2 Vitek, 2 Biomerieux, 1 BD Bactec
  - Do you use it routinely for bacterial infections in FN patients: 23 Yes

Summary on the New diagnostics techniques use in FN or in HM patients

1. Although most of these new tests improve microbiological documentation and time to identification or susceptibility data, there is no evidence that these new tests change survival in FN/HM patients.
2. Blood cultures must be routinely used. If available, new tests should be used in conjunction with the routine microbiological techniques.
3. Large prospective interventional studies are needed to assess their benefit and cost effectiveness in FN/HM patients.