ECIL-8 - The Pediatric Group

Group members:

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Guideline Methodology

Population and Search Criteria (1)

- **Leukemia-, lymphoma-, and auto / allo HSCT patients**

- Literature search
  - **English language only**

  - **PubMed and references from the retrieved studies**
  - **Bacterial infections (new guideline): 2000 – June 2019**

  - **Conferences: 2017, 2018, 2019; including ECCMID, ID-Week - ! only supportive as data are preliminary**

Population and Search Criteria (2)

- **Randomized and larger observational pediatric (≥90% ≤ 18 y) or mixed pediatric/adult studies with separately retrievable pediatric data from high- and middle income countries**

- **Adult ECIL guidelines plus important adult randomized or observational studies published between the respective conference until 6/2019**

- Deposit of PDFs in Dropbox, organized in folders according to topics (open)

- Each working group *selects and records* their MeSH terms

- Each working group *records the flow of their literature selection* process

- ! Each working group dealing with interventions *selects the critical endpoints* for the recommendations (column: 'intention'; f.e. to impact on overall survival, to prevent infections, to cure)

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Grading

ESCMID/ECMM grading system *

Two Independent Evaluations:

1. Strength of Recommendation   =   SoR
2. Quality of Evidence   =   QoE

→ Allows strong recommendations in the absence of highest quality of evidence.

Grading – Strength of Recommendation

Grade of Recommendation	Definition
Grade A	The guideline group **strongly** supports a recommendation for use
Grade B	The guideline group **moderately** supports a recommendation for use
Grade C	The guideline group **marginally** supports a recommendation for use
Grade D	The guideline group supports a recommendation **against** use

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Grading – Quality of Evidence

Level of Evidence	Definition
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 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 of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

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Grading – *Source of Level II Evidence*

Added Index	Source of Level II Evidence
r	Meta-analysis or systematic review of RCT
t	**Transferred evidence i.e. results from different patients' cohorts, or similar immune-status situation**
h	Comparator group: historical control
u	Uncontrolled trials
a	For published abstract presented at an international symposium or meeting

Antibacterial prophylaxis

ECIL recommendations (adults)

❏ ECIL - 1: Bucaneve, 2007:

Fluoroquinolone prophylaxis is recommended in high risk patients (neutropenia ≥ 7 days) AI/BI (depend on agent)

❏ ECIL – 6: Mikulska, JI 2017:

*The decision of using FQ prophylaxis should be taken responsibly in light of the abundant literature on the harms associated with the extensive use of antibiotics, the indications stemming from our analyses [**no decrease in mortality** in RCT and observational studies published since 2005], and the recent warnings on FQ-related toxicity. The possible benefits of FQ prophylaxis on BSI rate, but not on overall mortality, should be weighed against its impact in terms of toxicity and changes in local ecology in single centers.*

Study questions

Influence of any antibacterial prophylaxis in children on:

- ✓ Mortality

- ✓ Bacterial blood stream infections

- ✓ Febrile neutropenia

- ✓ Resistance emergence

- ✓ Collateral damage: *Clostridium difficile*-associated disease and invasive fungal infections

- ✓ Adverse effects

Relevant studies for the analysis (published 2000 - 2019):

5 RCT, 6 meta-analyses

16 vs. historical cohort, 1 prospective observational study;

RCT characteristics

- 5 prospective RCT

- Years of publication: 2003-2018

- Countries: middle – high income countries: US, Canada, Italy, Thailand, Indonesia

- Years of study: 1999-2016

- Single center n= 3 / multicenter n=2

- Population: HM n=5, HSCT n=1 (allo and auto), ST n=1

- Number of patients: 71-624 (mean 212)

RCT: prophylactic regimen (n=number of studies)

- Agents:
  - FQ n=4:
    - ✓ Levofloxacin vs no prophylaxis (n=1) *(not approved for children)*
    - ✓ Ciprofloxacin (n=3; vs placebo 2, no prophylaxis 1) *(approval for children country dependent, but restricted)*
    - ✓ ***Note: March 2019: EMA warning of FQ due to potential permanent AE such as neurotoxicity etc***
    - ✓ Amoxicillin-clavulonate (n=1)
- Period of prophylaxis:
  - ✓ For 2 chemotherapy cycles (n=1)
  - ✓ During induction until its completion, regardless of ANC (n=1)
  - ✓ From chemotherapy onset until ANC 1000/mm3 (n=2)
  - ✓ During chemotherapy, until ANC 500/mm3 for leukemia, 1000/mm3 others (n=1)

Question 1: Does antimicrobial prophylaxis influence mortality?

Author	Patients	Design	N	Prophylaxis	Mortality in controls	Mortality in prophylaxis
Alexander 2018	AML, relapsed ALL , HSCT	Multi--center	624	Levo for 2 chemotherapy cycles	AL: 3/99 (3%); HSCT: 1/208 (0.5%) no bacterial IRM	**No difference.** No bacterial IRM AL: FQP 1/96 (1%); HSCT 0/210.
Laoprasop-wattana 13	ALL, Ly	Single center	71	Cipro from chemotherapy onset until ANC 1000	0/37	**No difference** 1/34 (1.4%)
Widjajanto 2013	ALL	Single center	110	Cipro during induction	3/58 (5.8%, all sepsis)	*Possibly increased*: 9/52 (18.9%; 95% CI: 0.92–13.80; P=0.05) (3.5% due to sepsis)
Castagnola 03	HM, ST	Multi-center	167	amoxi/clav during chemotherapy, until ANC 500 for leukemia, 1000 others	0/84	**No difference** 1/83 (1.2%; *P. aeruginosa* sepsis)

Mortality (total 961 patients): controls 7/486 (1.4%) vs prophylaxis 12/475 (2.5%)

Conclusion:

Antibacterial prophylaxis did not reduce mortality rates in patients with AML, ALL and HSCT; however, mortality rates were very low in controls

Question 2: Does antimicrobial prophylaxis reduce risk of bacterial blood stream infections?

Author	Patients	Design	N	Prophylaxis	BSI in controls	BSI in prophylaxis	Stool FQ-R	Conclusion
Alexander 2018	AML, relapse ALL, HSCT	multi	624	Levo for 2 chemotherapy cycles	Relapse ALL: 18 (50%); AML: 25 (39.7%); total AL 43/99 (43.4%) Auto HSCT: 9 (11.5%); Allo HSCT: 27 (20.8%). Total HSCT 36/208 (17.3%)	ALL 6 (18.8%); AML 15 (23.4%); Total AL 21/96 (21.9%) Auto 3 (3.8%); Allo 20 (15.3%). Total HSCT: 23/210 (11.0%)	9% in AL, ~1% HSCT*	Reduction in relapsed ALL: risk difference (RD), 31.2%, 95%CI, 10.1%-52.5%, P = .007. AML RD 13.6%, p=0.05; Total AL: RD 21.6%; 95%CI, 8.8%-34.4%, P = .001. No reduction in HSCT risk difference, 6.3%; 95%CI, 0.3%-13.0%; P = .06.
Laoprasopwattana 13	ALL, Ly	single	71**	Cipro from chemotherapy onset until ANC 1000	MDI 5/50 (10%)	3/45 (6.7%)	E coli: 17.1% FQP; 22.5% placebo; K. pneumoniae: 26.3% FQP; 36.4% placebo	No reduction
Castagnola 03	HM, ST	multi	167	amoxi/ clav	5/84 (6%)	3/83 (4%)		No reduction

Conclusion (FQ prophylaxis):
1) Prophylaxis reduced BSI rate in acute leukemia patients (mainly in relapsed ALL) in a study with high baseline BSI rate in controls and low FQ resistance rate in colonizing bacteria;
2) Prophylaxis did not reduce BSI rate in HSCT patients;

*Baseline resistance rate not reported, **95 patients total (71 neutropenic)

Question 3: Does antimicrobial prophylaxis reduce risk of febrile neutropenia?

Author	Patients	Design	N	Prophylaxis	FN in controls	FN in prophylaxis	Conclusion
Alexander 2018	AML, relapsed ALL , HSCT	RCT, multi	624	Levo for 2 chemotherapy cycles	252/307 (82.1%)	218/306 (71.2%)	Reduction: risk difference, 10.8%; 95%CI, 4.2%-17.5%; P = .002
Laoprasopwattana 13	ALL, Ly	RCT, single	71	Cipro from chemotherapy onset until ANC 1000	Total: 27/37 [73.0%] ALL 24/30 [80.0%]	Total: 17/34 [50.0%] ALL 13/24 (54.2%);	Reduction: total: absolute risk difference, −23.0%; 95% CI: −45.0% to −0.9%; P = 0.046), NNT = 4. ALL.−25.8% (−50.4 to −1.3) p=0.042 *reduction only in ALL induction; not in consolidation or lymphoma
Widjajanto 2013	ALL ALL (53.6% SR, 46.4% HR)	RCT	110	Cipro during induction	17/52 (32.7%)	29/58 (50.0%; 95% CI: 0.95–4.47; P = 0.07)	No reduction
Castagnola 03	HM, ST	RCT, multi	167	amoxi/clav during chemotherapy, until ANC 500 for leukemia, 1000 others	39/83 (47%); FUO: 38%	29/84 (35%). NS; FUO: 27% NS.	No reduction *Failure rate (FN+MDI+CDI) was lower in patients with HM (45% placebo vs 28% prophylaxis) vs ST (50% vs 45%) p=0.014. NNT to prevent 1 failure = 8 total; 6 in HM

Conclusions:
1) FQ prophylaxis reduced FN rate in patients with acute leukemia and HSCT
2) Amoxicillin clavulanate prophylaxis reduced FN rate in AL (not in solid tumors)

Question 4: Is antimicrobial prophylaxis associated with resistance emergence

Author	Patients	N	Prophylaxis	Resistance in controls	Resistance in prophylaxis
Alexander 2018	AML, relapsed ALL , HSCT	624	Levo for 2 chemo-therapy cycles	Surveillance done: perirectal or stool specimens were collected at baseline and at completion of each infection observation period (study years 2011-2016)	**Stool surveillance: No increase** in proportion with newly detected resistance in colonizing bacteria to levofloxacin (9% in AL, ~1% HSCT), cefepime (GNs and S. mitis), imipenem (GNs) and penicillin (strep mitis) for either patients with AL and HSCT. **BSI: Qualitatively, higher rate** of resistance in prophylaxis compared to control group
Laoprasopwattana 13	ALL, Ly	71	Cipro from chemotherapy onset until ANC 1000	Colonizing bacteria: FQ-R: E coli 17.1% FQP; 22.5% placebo, K pneumoniae 26.3% FQP; 36.4% placebo No difference at baseline in placebo and FQP arms. (years of study 2007-10)	**Increase in FQ-R in colonizing bacteria, no increase in other resistance.** Colonizing bacteria: FQ-R *E coli*: 1st week, 56/59 [94.9%] FQP versus 7/28 [25.0%] placebo, P < 0.001; second week, 34/35 [97.1%] versus 5/22 [22.7%], P < 0.001) and *K. pneumoniae* (first week, 7/7 [100.0%] versus 10/29 [34.5%], P = 0.002; second week, 6/7 [85.7%] versus 2/7 [28.6%], P = 0.103). **No difference** in susceptibility rates to 3d gen cephalosporins, sulperazon, carbapenems, amikacin and ESBL
Tunyapanit 18	ALL, Ly	87	Cipro from chemotherapy onset until ANC 1000	**Rectal surveillance:** baseline *E coli* and *Klebsiella pneumoniae*: Ceftazidime-R: 9.7% FQP vs 26.5% placebo (significant); ceftazidime MIC50: FQP 0.12 vs placebo 0.12. Cipro-R: 16.1% FQP vs 29.4% placebo, MIC 50: 0.02 FQP vs 0.01 placebo (years of study 2007-10)	**Increase in resistance in colonizing bacteria after 3 weeks on FQP/placebo in Cipro (MIC and rate) and ceftazidime (MIC):** **ceftazidime-R** rate: NS difference. MIC 50/90: 0.38/6 in FQP vs 0.09/0.17 placebo (p<0.01). **Cipro-R rate***: increased in weeks 1-3 vs placebo: Week 1: 81.6% vs. 16.7%; week 2: 91.3% vs. 28.9%, and week 3: 95.5% vs. 0%. Cipro MIC 50/90: 33/33 FQP vs 0.01/0.31 placebo (p<0.01).

Stool surveillance

- No increase in FQ-R: (Alexander, baseline rate not reported)/ increase (Laoprasopwattana, Tunyapanit: 16-26% at baseline to 81-100% after 1 week; 86-97% at 2-3 w);

- Other resistances: cephalosporin, carbapenem, sulperazone, amikacin, ESBL no increase (Alexander; Laoprasopwattana) / increase in ceftazidime MIC (Tunyapanit)

BSI isolates

- Qualitatively, higher rate of FQ-R in prophylaxis compared to control group (Alexander)

Question 4: Is antimicrobial prophylaxis associated with resistance emergence

Conclusions:

- FQP possibly leads to increasing FQ-R or resistance to other broad-spectrum beta-lactams in colonizing bacteria; increasing FQ resistance rate in invasive bacteria

- VRE colonization/infection was not analyzed

- NB: adult studies report on correlation between FQ exposure and increase in infections resulting from ESBL+, carbapenem-R (including *Pseudomonas aeruginosa*) and MDR Gram-negatives

- **Studies limited by follow-up time, no institutional resistance level assessed**

Hakki CID 18, Trecarichi AJH 16, Liss Inf 12, Liu BMT 11

**Question 6: Is antimicrobial prophylaxis associated with adverse effects?
(except resistance and collateral damage)**

11 studies (4 RCT and 7 observational studies)

1) FQ monotherapy prophylaxis (n=7):

- ✓ RCT (n=3, 805 patients, 406 on prophylaxis): no difference in musculoskeletal, GI, neurological side effects. 1 patient interrupted FQP due to skin rash

- ✓ Observational studies (n=4, 285 patients and controls*): arthropathy reported (1/23 patients), skin rash leading to discontinuation (1 patient among 64 courses), no SE (2 studies, 81 patients)

2) amoxi-clav – no difference (1 RCT, 84 patients on prophylaxis)

3) <u>Conclusion</u>: FQP, amoxi/clav: no significant increase in toxicity during follow up; but data clearly limited by follow-up time

Meta-analysis

- 6 meta-analysis included pediatric data; years of publication: 2007-2019

- Search for studies published: 1966 – 2018

- Studies: RCT only (3), RCT+quasi-randomized trial with a parallel group design (1), RCT + cohort studies (2)

- Number of studies included: 5 – 113

- *Number of pediatric studies: 1 - 13 exclusively; 3 meta-analysis included 5-18 studies on mixed population*

- Number of patients included: 862 – 13677

- *Number of pediatric patients in exclusively pediatric studies: 97 - 1645*

- Underlying disease: HM (n=6; in one AL only), HSCT (n=5), ST (n=3)

- Intervention:

  - Any prophylaxis vs. placebo/no treatment/other prophylaxis (n=3)

  - Fluoroquinolones prophylaxis (2 - any FQ, 1 - levofloxacin only) vs placebo/no prophylaxis

Meta-analysis: outcomes summary

- Mortality (n=5):
  - ✓ Reduction (Gafter Gvili 2012)
  - ✓ No reduction (Kimura 14, Mikulska 18, Owattanapanich 2019, Egan 2019)

- BSI rate (n=5):
  - ✓ Reduction (n=5)
    Egan 2019:
    - ❖ *Reduction by levofloxacin, but not by ciprofloxacin*
    - ❖ *Pediatric analysis (2 trials, 708 pts): no reduction: RR 0.66 (0.27-1.63), p=0.37*

- FN episodes: reduction (n=5) (Egan 19: *Reduction by levofloxacin, but not by ciprofloxacin*)

- Adverse effects (n=2)
  - ✓ Increase (Gafter Gvili 2012)
  - ✓ No increase in musculosceletal effects (Egan 19)

- *Clostridium difficile*: No increase (n=1)

- Invasive fungal infections: No increase (n=2)

- FQ resistance
  - ✓ No increase in colonization by FQ-R; no increase in MDI by FQ-R among all patients (Gafter Gvili 2012, Gafter Gvili 07)
  - ✓ Increase in proportion of FQ-R among BSI isolates (Egan 19, Gafter Gvili 07)

Recommendations ECIL-8

- Routine antibacterial prophylaxis is **not recommended** for pediatric patients with lymphoma, acute leukemia, relapsed ALL or undergoing HSCT patients during pre-engraftment neutropenia (DI)

Issues in empirical therapy

- Initial therapy

- Later management:
  - De-escalation
  - Early stop
  - Oral treatment

Initial therapy in high risk patients: escalation/de-escalation approach (Previous guidelines including ECIL-4)

❑ Stable patients, no previous infection/colonization with resistant bacteria :

✓ Monotherapy with an antipseudomonal agent (escalation strategy)

- Pediatric guidelines: beta lactam-beta-lactamase inhibitor (BLBLI), 4th-generation cephalosporin, or a carbapenem

Based on pediatric meta-analysis:

- *Antipseudomonal penicillin and fourth-generation cephalosporin monotherapy were associated with similar failure and mortality rates*

- *Aminoglycoside-containing combination therapy vs. monotherapy did not decrease treatment failures and mortality;*

- ECIL guidelines: non-carbapenem beta lactam

❑ Clinically unstable, previous infection/colonization with resistant bacteria, or for centers with a high rate of resistant pathogens (de-escalation strategy):

✓ Carbapenem

✓ Add second Gram-negative agent or anti-resistant Gram-positive agent

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Later management: ECIL recommendations (ECIL-4)

BSI:

- If a pathogen is identified: Whatever was the initial approach – 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 MICs when available, and based on knowledge on drugs with specific activities **AI**.

FUO:

- If a **de-escalation** approach was chosen based on known colonization or previous infection with resistant bacteria and the patient was stable at presentation, streamlining of initial therapy should be considered **BIII**, including:

    (i) discontinuation of any aminoglycoside, quinolone, colistin or any antibiotic directed against resistant Gram-positive pathogens, if given in combination, or

    (ii) for patients with FUO initially treated with a carbapenem, change to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin-tazobactam.

- Empiric antibiotics can be **discontinued** after ≥72 hours of intravenous administration in patients who have been hemodynamically stable since presentation and have been afebrile for ≥48 hours, irrespective of their neutrophil count or expected duration of neutropenia **BII**.

- The patient should be kept hospitalized under close observation for at least a further 24-48 h if (s)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.

Low risk patients: Validated pediatric risk stratification strategies in children

Table 3. Validated Pediatric Risk Stratification Strategies for Low-Risk Patients

Schema-Related Factors	Rackoff[4]	Alexander[5]	Rondinelli[6]	Santolaya[7]	Ammann[8]	Ammann[9]
Patient- and disease-related factors	None	AML, Burkitt lymphoma, induction ALL, progressive disease, relapsed with marrow involvement	2 points for central venous catheter, 1 point for age ≤ 5 years	Relapsed leukemia, chemotherapy within 7 days of episode	Bone marrow involvement, central venous catheter, pre–B-cell leukemia	4 points for chemotherapy more intensive than ALL maintenance
Episode-specific factors	Absolute monocyte count	Hypotension; tachypnea or hypoxia < 94%; new CXR changes; altered mental status; severe mucositis, vomiting, or abdominal pain; focal infection; other clinical reason for inpatient treatment	4.5 points for clinical site of infection, 2.5 points for no URTI, 1 point each for fever > 38.5°C, hemoglobin ≤ 70g/L	CRP ≥ 90 mg/L, hypotension, platelets ≤ 50 g/L	Absence of clinical signs of viral infection, CRP > 50 mg/L, white blood cell count ≤ 500/μL, hemoglobin > 100 g/L	5 points for hemoglobin ≥ 90 g/L, 3 points each for white blood cell count < 300/μL, platelet < 50 g/L
Rule formulation	Absolute monocyte count ≥ 100/μL = low risk of bacteremia; HSCT = high risk	Absence of any risk factor = low risk of serious medical complication; HSCT = high risk	Total score < 6 = low risk of serious infectious complication; HSCT = high risk	Zero risk factors or only low platelets or only < 7 days from chemotherapy = low risk of invasive bacterial infection	Three or fewer risk factors = low-risk of significant infection; HSCT = high risk	Total score < 9 = low risk of adverse FN outcome; HSCT = high risk
Demonstrated to be valid*	USA, Madsen[10]	United Kingdom, Dommett[11], Arif[12]	Brazil, Rondinelli[6]	South America, Santolaya[13]	Europe, Ammann,[9] Macher,[14] Arif[12]	Europe, Miedema[15]

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CRP, C-reactive protein; CXR, chest radiography; HSCT, hematopoietic stem-cell transplantation; URTI, upper respiratory tract infection.
*Valid refers to clinically adequate discrimination of a group at low risk of complications.

Study objective: determination of safety of "reduced" treatment in febrile neutropenic children with hemato-oncological diseases and post-HSCT mainly without microbiologically documented infection.

Definition of "reduced" treatment:

- Withholding antibiotics (no treatment)

- Switch to oral therapy

- Discharge for outpatient management

- De-escalation (narrowing of spectrum)

- Discontinuation of antibiotics
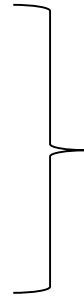
During neutropenia
+/- fever

Outcomes assessed:

- Mortality

- Bacteremia

- Recurrence of fever

- Antibiotic reinitiation

- Recurrence to hospitalization

Relevant studies:

✓RCT n=11, observational studies n=11, metaanalysis n=8

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Part I:

Antibiotic stepdown to outpatient/oral therapy

Step down: Original studies summary - 1 (14 studies)

- 8 RCT, multicenter studies 3; single center 5;

  6 observational studies (OS); 2 multicenter studies; 4 single

- Underlying diagnosis: HM and ST in all studies

  ✓ in 2 RCT: only ALL and ST included;

- Number of patients/episodes:

  ✓ RCT: 37-200 (mean 123.5);

  ✓ OS: 15-551 (mean 124);

- Step down policy following initial inpatient IV:

  ✓ RCT: inpatient vs outpatient (n=4); PO vs IV (n=6);

  ✓ OS: outpatient PO (6 studies)

- Time to "step-down therapy":

  ✓ RCT: 4-96 h; usually 24-72 h;

  ✓ OS: few hours - 48 h;

    - Conditions: 3 OS and 6 RCT – regardless of fever; 5 others - afebrile for 24 - 72h;

Step down: Original studies summary - 2 (14 studies)

- Main **exclusion** criteria: (in addition to allergy to oral AB, inability to tolerate, inappropriate follow up and non-compliance):

- <u>Patients</u>: age restriction (not younger than 1-4 years); weight (restriction of 16 kg);

- <u>Underlying disease</u>**: HSCT (all studies); AML (6); relapse (4); infant ALL (2); ALL and Lymphoma not in maintenance therapy (3);** malignancy not at remission, relapsed/ progressive leukemia, advanced stage of underlying diseases, ie, bone marrow involvement, second tumor, high dose chemotherapy (e.g., high dose cytarabine for AML or Burkitt lymphoma); mature B-ALL/NHL; ST non-responsive/unstable/secondary (2), last chemotherapy < 7 days (2); Down (2); genetic disease (1); HLH (1);

- <u>Episode characteristics</u>: BSI (10 studies); CDI (13 studies); hemodynamic instability, poor clinical condition, severe comorbidity; persistence of fever longer than 48 hours (3 studies);

- <u>Laboratory characteristics</u>: renal insufficiency (n=5), liver dysfunction (n=3), ANC <100 (1), APC (bands+PMN+monocytes)<100 (1), neutropenia predicted to last more than 7 -10 days after the onset of fever (2), platelet count<50,000/mm3 (1), CRP>90 mg/L (1), documentation of *P. aeruginosa* or MRSA in admission surveillance or any recent culture (1), infection with bacteria resistant to step-down therapy;

- <u>Others:</u> no concurrent therapy with ferrous sulfate, antacids or sucralfate, previous recent antibiotic therapy

Step down: Meta-analysis summary

- 7 meta-analyses, 4 pediatric only, 3 include pediatric data

- Years of meta-analysis publication: 2011-2019

- Years of studies publication: 1948 – 2018

- Studies included: RCT only (5), RCT + prospective (2)

- Number of studies included: 4 - 37; pediatric 2 – 37

- Number of patients/episodes included: 934 – 3205; pediatric 268 – 3205

- Step down policy:

- ✓ PO vs IV, n= 6; pediatric only 4

- ✓ Outpatient vs inpatient, n= 5; pediatric only 3

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Step down: outcomes summary - 1

- **Mortality: no increase**
  - ➢8 RCT: **0**/487 in step down vs 2/501 (**0.4%**) in controls (in 2 studies with total 210 episodes)
  - ➢6 OS: no mortality in 869 patients
  - ➢7 Metaanalysis: In-vs Out-patient no difference (n=5);
    IV vs PO no difference (n=3), no mortality (n=3)

- **Bacteremia (total, including since intervention): no increase**
  - ➢8 RCT: no difference (3/487, **0.6%** (0-7.4%) in step down* vs 6/501 (**1.4%**, 0-8.8% controls)
  - ➢5 Observational studies: 3/318, **0.9%** (0-6.7%) (2 patients had initial *Campylobacter* and CONS BSI).
  - ➢1 Metaanalysis: no difference in PO vs IV; in-vs out-patient not reported

- **Recurrence of fever: no increase**
  - ➢ 8 RCT: no difference (23/487, **4.7%** (0-17%) in step down vs 24/467, **5.1%** (0-16%) control)
  - ➢ 4 Observational studies: 8/251, **3.2%** (0-10%)
  - ➢ 3 Metaanalysis: no difference in fever recurrence or duration (In- vs out-patient n=3; IV vs PO n=2)

*3 BSI in controls and 2 in step down were in cultures at admission (not breakthrough)

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Step down: outcomes summary - 2

- **AB modification no increase**
  - 5 RCT: no difference (21/242, **8.7%** (0-31.6%) in step down vs 30/243, **12.3%** (0-21%) control)
  - 2 OS: 7/45 (**15.6%**, 5-20%)

- **Recurrence to hospitalization no increase**
  - 6 RCT: Total re-hospitalization rate in outpatient groups 21/529 **(3.9%)**
    - ✓ 3 RCT: No difference in outpatient IV 9/213, **4.2%** (2.2%-7%) vs outpatient PO 5/211, **2.4%** (0-5%);
    - ✓ 3 RCT: recurrence rate in outpatient arm 7/105, **6.7%** (0-31.6%) (in In- vs Outpatient comparison);
  - 5 OS: 30/318, **9.4%** (7-20%)
  - 5 Metaanalysis:
    - ✓ Tendency to higher readmission rate in children on PO vs IV therapy (n=1)/no difference (n=2);
    - ✓ Hospitalization time (incl. readmission): lower in outpatient (n=2)

<u>Conclusion:</u> step down to oral/outpatient antibiotic therapy in low risk children with FN is not associated with increased risk of mortality, bacteremia rate, recurrent fever, antibiotic modification and re-hospitalization

Part II

Antibiotic de-escalation

Antibiotic de-escalation in BSI

Inclusion: children with ALL and AML either admitted for FN or diagnosed with FN during inpatient stay

Design: retrospective study

Treatment protocol: cefepime as empiric therapy. Addition of an aminoglycoside or glycopeptide antibiotic only for clinically unstable patients, or those patients or institutions with high rates of MDRO infections.

De-escalation was defined as narrowing the spectrum of antibiotic therapy compared with the empiric regimen.

Eligible for de-escalation: BSI once susceptibility results were known and the following clinical criteria were achieved: (1) afebrile for 24 hours, (2) clearance of bacteremia for 48 hours, and (3) normal vital signs for age

Results:

67 pts, 194 FN episodes (ALL=117; AML=77)

19 BSI episodes met de-escalation criteria. 9/19 (47%) de-escalated
De-escalation outcome:
- ✓ No recurrent fever
- ✓ No bacteremia following de-escalation
- ✓ No mortality

De-escalation in neutropenic adult patients

- 7 observational studies in adults

- 52 - 120 Febrile neutropenia courses episodes (median 100 episodes)

- De-escalation = narrowing antibiotic spectrum and/or switch to prophylaxis

- FUO/BSI/CDI; in 2 studies – sepsis in the ICU

- Underlying disease: HSCT (n=5), HM (n=3), cancer (n=2)

- 22% - 58% de-escalation rate

- 0 – 19.5% escalation following de-escalation (mainly due to fever/CDI/MDI)

- Mortality:
  - ✓ 0% in 5 studies
  - ✓ Two studies in the ICU: no difference between de-escalation and not de-escalation group

Petteys JOPP 19, Gustinetti BBMT 18, La Martire EJCMID 18, Snyder, OFID 17, Kroll JOPP 15, Mokart Int Care Med 14, Paskovaty Int Care Med 15

Part III

Antibiotic discontinuation

Antibiotic discontinuation: original studies summary-1

7 studies, 6 in children, 1 in adult

- Design: 3 RCT (2 pediatric, 1 adult), 4 observational

- Multicenter 3; single center 4

- Underlying diagnosis: children: HM (n=6) and ST (n=5); adults: HM and HSCT

- Number of patients/episodes: 73-299, mean 148.4

- Patients who developed FN at the outpatient basis

- Time to discontinuation in FUO:

  48 h (1), 48-120 h (1), 72 h (4 studies, in one of them in MR); 2-10 days since last fever until discharge (1), withheld in LR (1 study)

- At discontinuation: ANC >100 cells/mm3 in significant proportion of patients

Antibiotic discontinuation: original studies summary-2

- Main **exclusion** criteria:
  - ✓ <u>Underlying disease</u> characteristics: HSCT (included in 1 adult study; in 2 studies excluded if within 1 month), relapse leukemia (1 excluded from LR group), AL not in remission (1), AML (1), last chemotherapy < 7 days (1)

  - ✓ <u>Episode characteristics</u>: BSI (n=6); CDI (n=5); clinical sepsis (n=5; in 1 study hypotension at admission allowed if later clinically well); previous antibiotic therapy (3), persistent fever >96 hours after starting IV antibiotics (1); comorbidity necessitating continued inpatient stay (1)

  - ✓ <u>Laboratory characteristics</u>: abnormal CRP and thrombocytopenia (1 study, LR); high IL-8 levels at admission and/or at 12-24 h (1); renal failure (1)

- **High-risk FN included in:**

  - ✓ Santolaya 2017 (n=47 pts): (i) relapse of leukaemia, (ii) hypotension or (iii) CRP ≥90 mg/L, (iv) ≤7 days since last chemotherapy (v) platelet count ≤50 000/mm3;

  - ✓ Aguilar-Guisado: HSCT and hematological malignancies (induction/re-induction AL n=24 pts). Therapy stopped while neutropenic in 41 pts

- Conditions to stop/withheld antibiotics:

  - ✓ Clinical course: afebrile for 24-72 h (n=6); in one study LR patients discharged w/o AB after 12 h of afebrile observation

  - ✓ In one study (Santolaya) only children with "+" respiratory virus sample included

Antibiotic discontinuation: Meta-analysis

Stern 2019 Cochrane

- Studies included: RCT published 1970-2016
- Number of studies: 8, of them pediatric 5
- Number of patients:
  - ✓314 short; 348 long-antibiotic treatment arm
  - ✓Of them 324 children + 83 adults and children

Antibiotic discontinuation: outcomes summary - 1

- **Mortality: no increase**

  ➢ 3 RCT: total 1/198 (0.5%) in placebo vs 3/208 (1.4%) in AB arm

  No mortality (2 pediatric studies, 230 pateints, 249 episodes); 1.3% study vs 3.8% control (adult study).

  ➢ Observational studies: total 1/633 (0.2%)

  No mortalities (3 studies, 443 episodes)

  1/190 episodes in one study (patient discharged with ANC 290, received additional chemotherapy after count recovery and prior to discharge, and was readmitted with *Clostridium tertium* bacteremia.

  ➢ Metaanalysis: total no difference in mortality; no mortality in pediatric RCTs

- **Bacteremia since randomisation/treatment interruption: no increase**

  ➢ 3 RCT: no difference: 6/198 (3.0%, range 0-6.4%) vs 6/208 (2.9%, range 0-5.1%) control

  ➢ Observational studies: 16/633 (2.5%, range 0-7%, 4 studies)*;

  ➢ Metaanalysis: possibly higher BSI rate in the short- compared to the long antibiotic therapy arm

*higher rate at ANC<100 (1 study)

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Antibiotic discontinuation: outcomes summary-2

- **Recurrent fever: no difference**

  ➢ 3 RCT: no difference: 8.5% (5-14%) study vs 9.7% (1-18%) control;

  ➢ Observational studies: 19/334, 5.7% (0-21%) (3 studies*);

  ➢ Metaanalysis: fever duration shorter in short therapy;

- **Antibiotic reinitiation** (1 RCT, 4 observational studies): 40/717, 5.6% (0-14%*)

  ➢ Metaanalysis: total antibiotic days were fewer in the intervention arm by three to seven days compared to the long antibiotic therapy

- **Recurrence to hospitalization: no difference**

  ➢ 1 RCT: No difference (6% study vs 14% control);

  ➢ Observational studies 65/633, 10.3% (0-16.7%) (4 studies*);

Conclusion: antibiotic discontinuation in low risk children with FN developed at the outpatient basis is not associated with increased risk of mortality, BSI rate, recurrent fever and re-hospitalization. Rate of antibiotic re-initiation low

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*higher rate at ANC<100 (1 study)

ECIL-8 recommendations – 1

- Initial antibiotic therapy should follow escalation/de-escalation principles:

  - ✓ monotherapy with an antipseudomonal non-carbapenem b-lactam (penicillin or fourth-generation cephalosporin) is recommended for clinically stable patients at low risk for resistant infections **A IIr** (based on pediatric metaanalysis)

  - ✓ carbapenem +/- a second anti-Gram-negative agent ***+/-*** a glycopeptide is recommended for clinically unstable patients, even when at low risk for resistant infections **A IIt**

  - ✓ empirical treatment should be adjusted based on resistance profile for patients who are colonized/previously infected with resistant Gram-negative bacteria or in centers with a high rate of resistant pathogens **A II tu** (data in adults reports on high rate of BSI in Gram-negative colonized patients)

ECIL-8 recommendations-2

Patients with microbiologically documented infection

- When a pathogen is identified, 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 MICs when available, and based on knowledge of drugs with specific activities **A II tu** (observational studies, mainly in adults, report on successful de-escalation based on susceptibility)

ECIL-8 recommendations-3

Patients with FUO:

- When a patient was initially unstable (e.g., signs of sepsis or septic shock) at presentation, and a de-escalation approach was chosen for this reason, and the patient has stabilized, no change in initial therapy is recommended, even if blood or other cultures remain negative BIII

- When a patient was stable at presentation but a **de-escalation** approach was chosen based on known colonization or previous infection with resistant bacteria, de-escalation of initial therapy should be considered at 72-96 h, including:
  - ✓ discontinuation of any aminoglycoside, quinolone, colistin or any antibiotic directed against resistant Gram-positive pathogens, if given in combination **A II tu in high risk** (observational studies, mainly in adults, report on successful de-escalation (tu)**; AI low risk** patients (pediatric RCT)
  - ✓ change to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin-tazobactam for patients with FUO initially treated with a carbapenem **A II tu** (observational studies, mainly in adults, report on successful de-escalation)

ECIL-8 recommendations-4

- Based on parameters identified in the validated risk prediction rules, each center should define risk groups for the decision to discontinue/step down and to decide the duration of inpatient follow up A IIu (based on uncontrolled studies that performed validation of risk criteria)

  - ✓ Needs analysis of the local epidemiology and definition on patients at low risk for adverse outcome during FN

  - ✓ Depends on local infrastructure and ability to follow and return to hospital

ECIL-8 recommendations-5

- Consider a step-down strategy in patients with FUO (= without clinically or microbiologically documented infection) after ≥72 hours of intravenous antibiotics who have been hemodynamically stable since presentation and have been afebrile for 24-48 hours, even prior to signs of hematological recovery provided careful monitoring is availably.

- Follow-up can be performed on an inpatient or an outpatient basis according to local infrastructure and ability to return quickly to the hospital

- Step-down strategies in patients with FUO

  - Switch to oral antibiotics
    - in low risk BII (moderate recommendation based on pediatric RCT)
    - can be considered in individual high risk patients C II tu

  - Discontinuation of all empiric antibiotics
    - BII in low risk
    - can be considered in individual high risk patients C II u

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