Conseil en antibiothérapie et neutropénie fébrile

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Maladies Infectieuses et Tropicales – CHU Nantes

Séminaire DES-C – 5 octobre 2021

Q1- Votre équipe d'infectiologie transversale a-t-elle une activité de stewardship en hématologie ?

1. Oui
2. Non
3. NSP

Q2- Quels obstacles identifiez-vous à la mise en œuvre de cette activité en hématologie ?

Situation clinique

- Patiente de 73 ans, bon état général.
- Découverte d'une LAM1 sur asthénie + fièvre

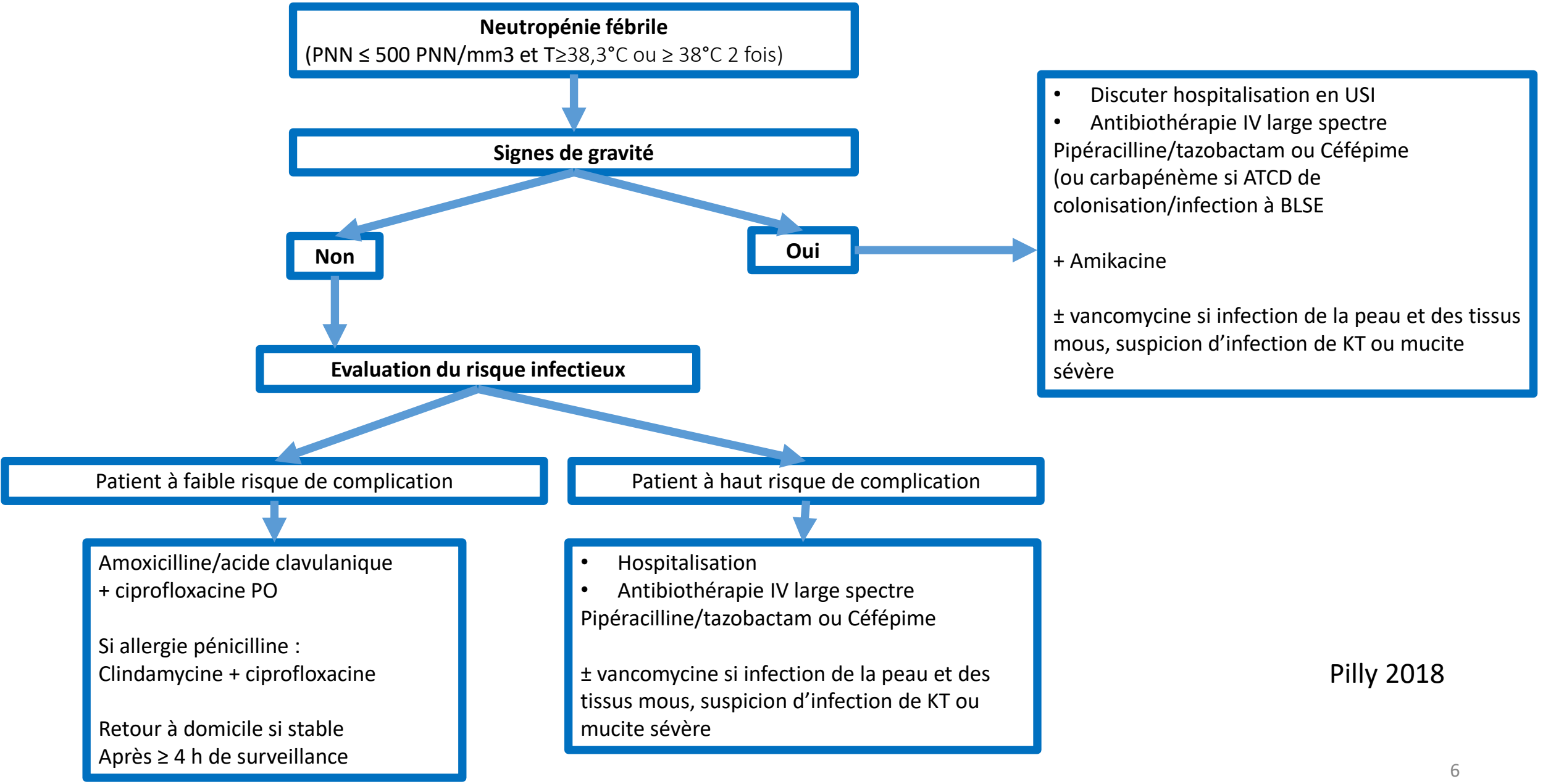
- Fièvre sans point d'appel clinique
- Orifice de picc-line propre
- < 100 neutrophiles

- Pas de défaillance/critère de sévérité
- Pas de colonisation connue par BLSE/BHR

- Elle est hospitalisée en hématologie stérile, dans un service où vous intervenez en infectiologie transversale.

Q3- Quelle antibiothérapie proposez-vous ?

1. Imipénème
2. Pipéracilline-tazobactam
3. Céfépime
4. Pipéracilline-tazobactam + Vancomycine
5. Céfépime + Vancomycine


Neutropénie fébrile
(PNN ≤ 500 PNN/mm3 et T≥38,3°C ou ≥ 38°C 2 fois)
Signes de gravité
Non
Oui
• Discuter hospitalisation en USI
• Antibiothérapie IV large spectre
Pipéracilline/tazobactam ou Céfépime
(ou carbapénème si ATCD de colonisation/infection à BLSE
+ Amikacine
± vancomycine si infection de la peau et des tissus mous, suspicion d'infection de KT ou mucite sévère
Evaluation du risque infectieux
Patient à faible risque de complication
Patient à haut risque de complication
Amoxicilline/acide clavulanique
+ ciprofloxacine PO
Si allergie pénicilline :
Clindamycine + ciprofloxacine
Retour à domicile si stable
Après ≥ 4 h de surveillance
• Hospitalisation
• Antibiothérapie IV large spectre
Pipéracilline/tazobactam ou Céfépime
± vancomycine si infection de la peau et des tissus mous, suspicion d'infection de KT ou mucite sévère

Pilly 2018

European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia

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haematologica | 2013; 98(12)

Indications des carbapénèmes en première ligne

1. Sepsis sévère, choc septique (B-II)

2. Antécédent de colonisation ou infection avec bactérie résistante aux β-lactamines large spectre (dont BLSE) (B-II)

3. Centres avec prévalence élevée de BLSE dans les neutropénies fébriles (B-II) (prévalence élevée si ≥ 10-20 %)

ECIL-4 guidelines, Averbuch et al, Haematologica 2013

Situations d'utilisation d'aminosides en 1ere ligne

1. Sepsis sévère, choc septique (B-III)

2. Risque de bacilles Gram négatif non fermentants (*P. aeruginosa*, *Acinetobacter*) : (B-III)
    1. Épidémiologie locale
    2. Antécédent de colonisation ou d'infection
    3. Carbapénèmes dans le mois précédent

Sensibilité des EBLSE à l'amikacine > 90 % (alternative aux carbapénèmes)

ECIL-4 guidelines, Averbuch et al, Haematologica 2013

Situations où un anti-Gram+ doit être associé

1. Sepsis sévère, choc septique (C-III)

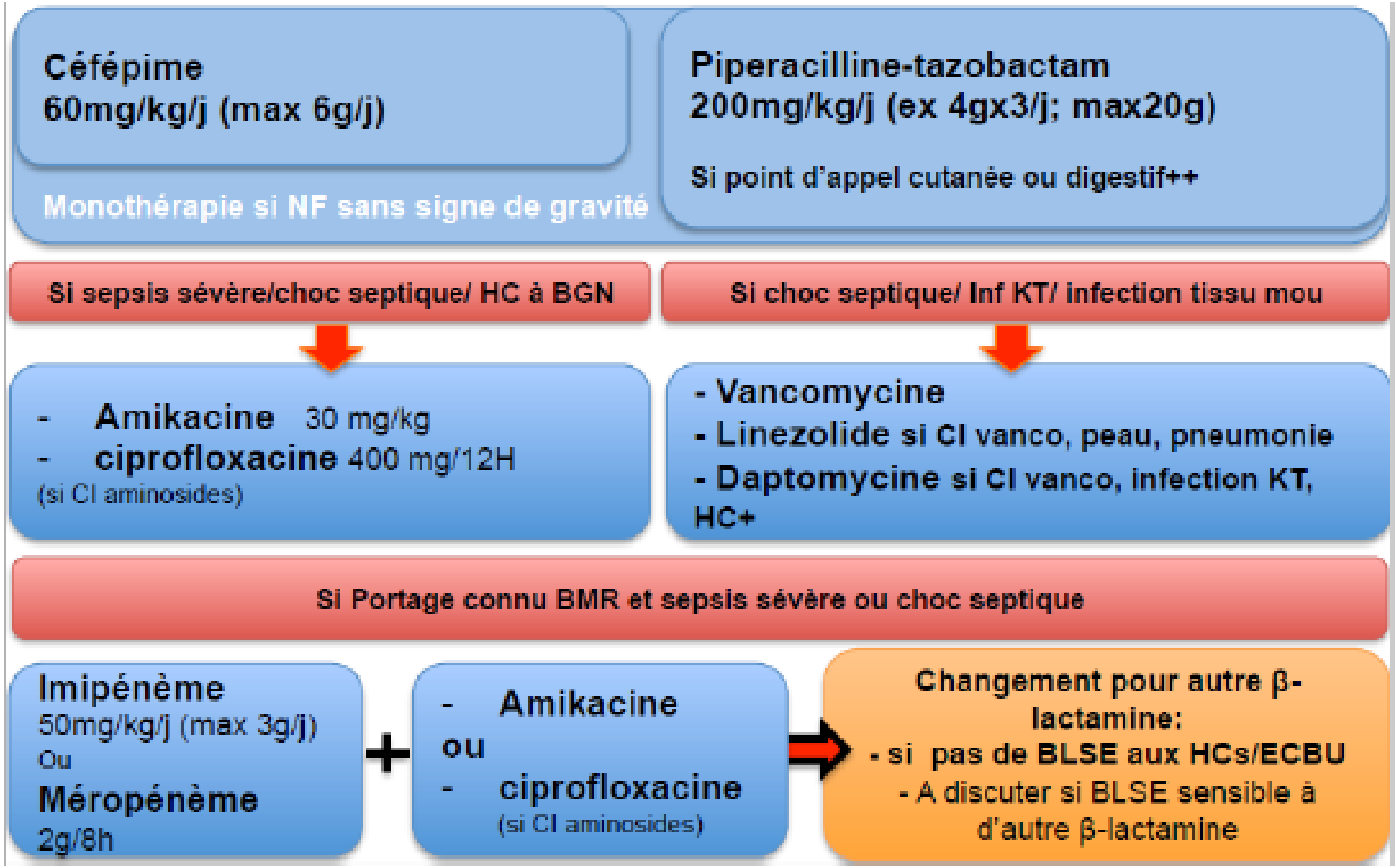
2. Antécédent de colonisation ou infection à SARM ou ERV (C-III)

3. Infection sévère sur KT (cellulite au point d'insertion, frissons à l'utilisation du KT) (C-III)

4. Infection peau et tissus mous (C-III)

ECIL-4 guidelines, Averbuch et al, Haematologica 2013

Stratégie en cas d'aplasie fébrile de haut risque au CHU de Nantes (stratégie écrite et connue de tous…)



- La patiente a été mise sous Céfépime 6 g/24h en monothérapie.
- (+ Posaconazole en prophylaxie)

- Au bout de 48 heures, la patiente reste fébrile
- L'état reste stable, et l'examen clinique reste inchangé.

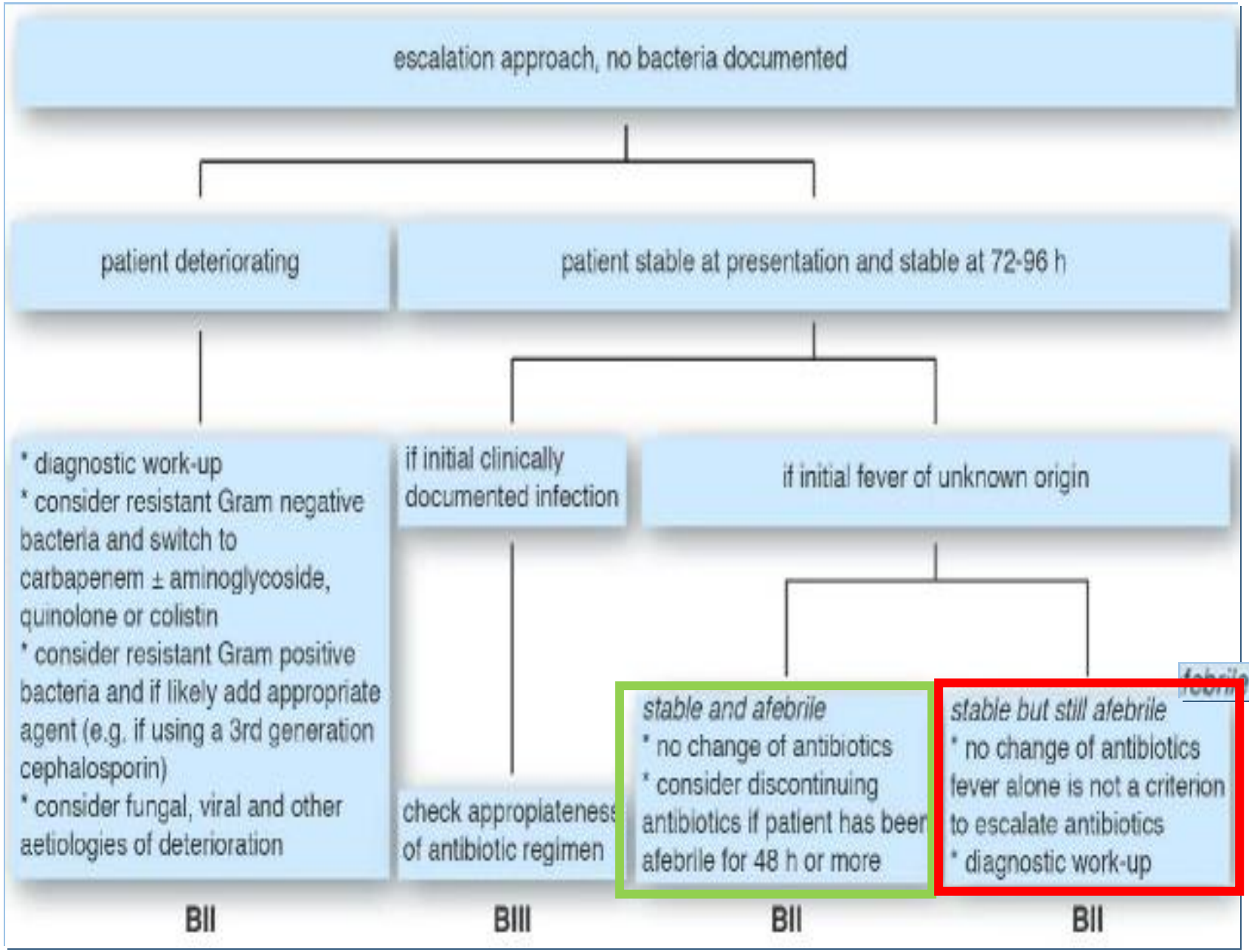
- Les hémocultures et l'ECBU sont négatifs
- Galactomannane sérique et β−D-glucane sont négatifs
- Un TDM thoraco-abdomino-pelvien est réalisé, ne retrouvant pas d'image pulmonaire suspecte, ou de foyer abdomino-pelvien.

Q4- Que préconisez-vous ?

1. Remplacement du céfépime par pipéracilline-tazobactam
2. Remplacement du céfépime par un carbapénème
3. Pas de modification
4. Ajout de vancomycine
5. Ajout d’une échinocandine

La voie du milieu

ECIL-4



Q5- Si le 1er choix a été un carbapénème, que préconisez-vous ?

1. Poursuite du carbapénème

2. Ajout de vancomycine

3. Remplacement par pipéracilline-tazobactam

4. Remplacement par céfépime

Stratégie : escalade ou désescalade

Table 3. ECIL-4 recommendation for initial empirical treatment in high-risk patients (anticipated to have neutropenia for more than 7 days), by indication and escalation or 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 β–lactam + aminoglycoside or quinolone[‖] (with carbapenem as the β–lactam in seriously ill patients) **BIII** 3) Colistin + β–lactam ± rifampicin **BIII**[¶] 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) CIII

ECIL-4 guidelines, Averbuch et al, Haematologica 2013

- Le céfépime a été poursuivi en monothérapie.
- Le bilan microbiologique est resté négatif.
- La patiente devient apyrétique à J5.
- A J8 de céfépime, la patiente reste apyrétique.

Q6- Que proposez-vous à vos collègues ?

1. Poursuite de l’antibiothérapie jusqu’à la sortie d’aplasie

2. Arrêt de l’antibiothérapie

durées de traitement (ecil4)

- Arrêt ATB probabiliste à ≥ 72h BII
  - Si absence de documentation clinico-microbiologique
  - Si apyrexie ≥ 48h et stable

  → Quelque soit profondeur et durée de neutropénie
  Surveillance et reprise des antibiotiques si récidive de la fièvre

- Si infection documentée (microbio ou clinique) AI
  - Jusqu'à éradication microbiologique (i.e., contrôle HC)
  - Jusqu'à résolution de tous les signes d'infection
  - Au moins 7 jours dont 4 d'apyrexie

Averbuch et al ECIL-4. Haematologica 2013

- Les antibiotiques ont été arrêtés à J8.

- 4 jours plus tard, la patiente redevient fébrile.
- Elle a toujours 0 neutrophile.
- Vous n’avez toujours pas de point d’appel clinique.
- La patiente n’a aucun critère de sévérité.

- Un nouveau TDM est réalisé, ne retrouvant pas de foyer ou lésion suspecte d’infection.

Q7- Que proposez-vous ?

1. Reprise du céfépime

2. Tazocilline-tazobactam

3. Carbapénème

- La patiente est mise sous pipéracilline-tazobactam

- Depuis que vous avez proposé cette stratégie d'arrêt des antibiotiques selon les recommandations d'ECIL-4, vous avez été amenés souvent à reprendre précocement les antibiotiques dans les jours suivant l'arrêt (au moins 60 %).

- Vous vous interrogez sur cette stratégie.

Q8- Que décidez-vous ?

1- Vous abandonnez cette stratégie

2- Vous poursuivez cette stratégie

Q9- Vous décidez d’abandonner cette stratégie : pourquoi ?

Q10- Vous décidez de poursuivre cette stratégie : pourquoi ?

Table 1. Guideline recommendations regarding antibiotic usage duration in febrile neutropenia

Guidelines	Recommendation for documented infection	Recommendation for unexplained fever
The Infectious Diseases Society of America (IDSA) clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer (Freifeld 2011)	Duration of antibiotic therapy dictated by the particular organism and site; appropriate antibiotics should continue for at least the duration of neutropenia (until absolute neutrophil count is > 500 cells/mm^3), or longer if clinically necessary.	Initial regimen continued until clear signs of marrow recovery. An option is given, if an appropriate treatment course has been completed and all signs and symptoms of a documented infection have resolved, to resume oral fluoroquinolone prophylaxis until marrow recovery.
European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia (ECIL-4) (Averbuch 2013a; Averbuch 2013b)	Targeted antibiotics should be continued until infection is microbiologically eradicated and all clinical signs of infection are resolved for at least 7 days, of which at least 4 days are afebrile.	Intravenous empirical antibacterial therapy may be discontinued after ≥ 72 h in patients who have been afebrile ≥ 48 h and are stable, irrespective of neutrophil count or expected duration of neutropenia.
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Stern A *et al*. Cochrane Database Syst rev 2019

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Early discontinuation of antibiotic treatment compared to treatment until neutropenia resolution for febrile neutropenia

Patient or population: febrile neutropenia
Setting: hospital
Intervention: early discontinuation of antibiotic treatment
Comparison: treatment until neutropenia resolution

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with treatment until neutropenia resolution	Risk with early discontinuation of antibiotic treatment			
Mortality	Study population 47 per 1000	65 per 1000 (34 to 124)	RR 1.38 (0.73 to 2.62)	603 (8 RCTs)	⊕⊕⊖⊖ LOW [1 2]
Clinical failure	Study population 131 per 1000	161 per 1000 (111 to 231)	RR 1.23 (0.85 to 1.77)	645 (7 RCTs)	⊕⊖⊖⊖ VERY LOW [2 3 4]
Any bacteraemia	Study population 52 per 1000	81 per 1000 (47 to 138)	RR 1.56 (0.91 to 2.66)	662 (8 RCTs)	⊕⊖⊖⊖ VERY LOW [1 2 5]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

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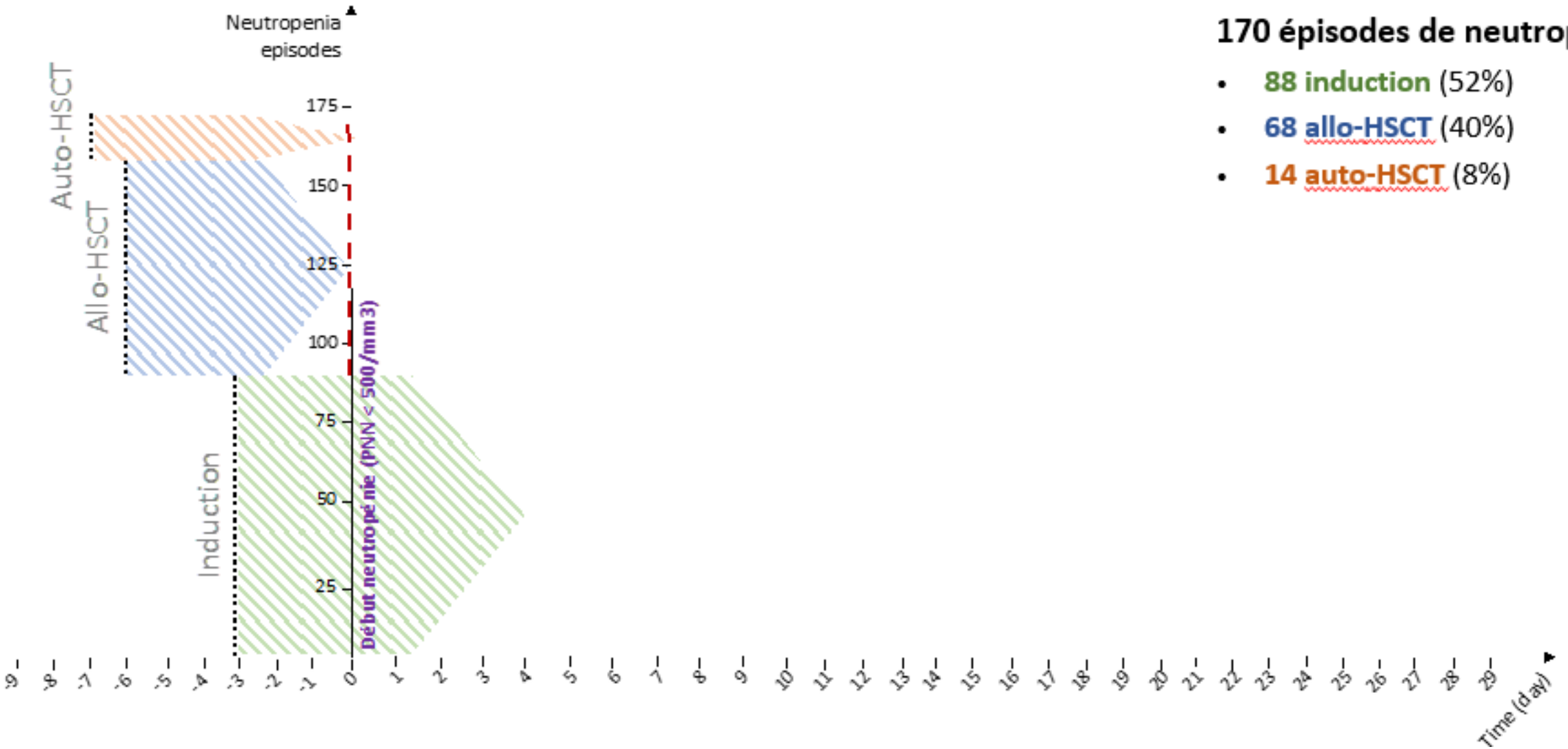
Stratégie d'arrêt CHU Brest et Nantes : travail de thèse Raphaël Paret (période février 2018 – février 2020)

- Etude descriptive **rétrospective**, **observationnelle**
- Centres d'inclusion : Service hématologie CHU Nantes et CHRU Brest
- Stratégie d'arrêt → décidée en staff multidisciplinaire hebdomadaire
- Critères de jugement principaux :
  - **Mortalité** toutes cause à 30 jours
  - **Transfert réanimation** toutes causes à 30 jours
- Critères de jugement secondaires :
  - Nombre de jours moyen sans antibiothérapie
  - **Récidive fébrile**
  - Récidive fébrile avec **bactériémie**

147 patients

Neutropenic episodes



170 épisodes de neutropénie

- **88 induction** (52%)
- **68 allo-HSCT** (40%)
- **14 auto-HSCT** (8%)

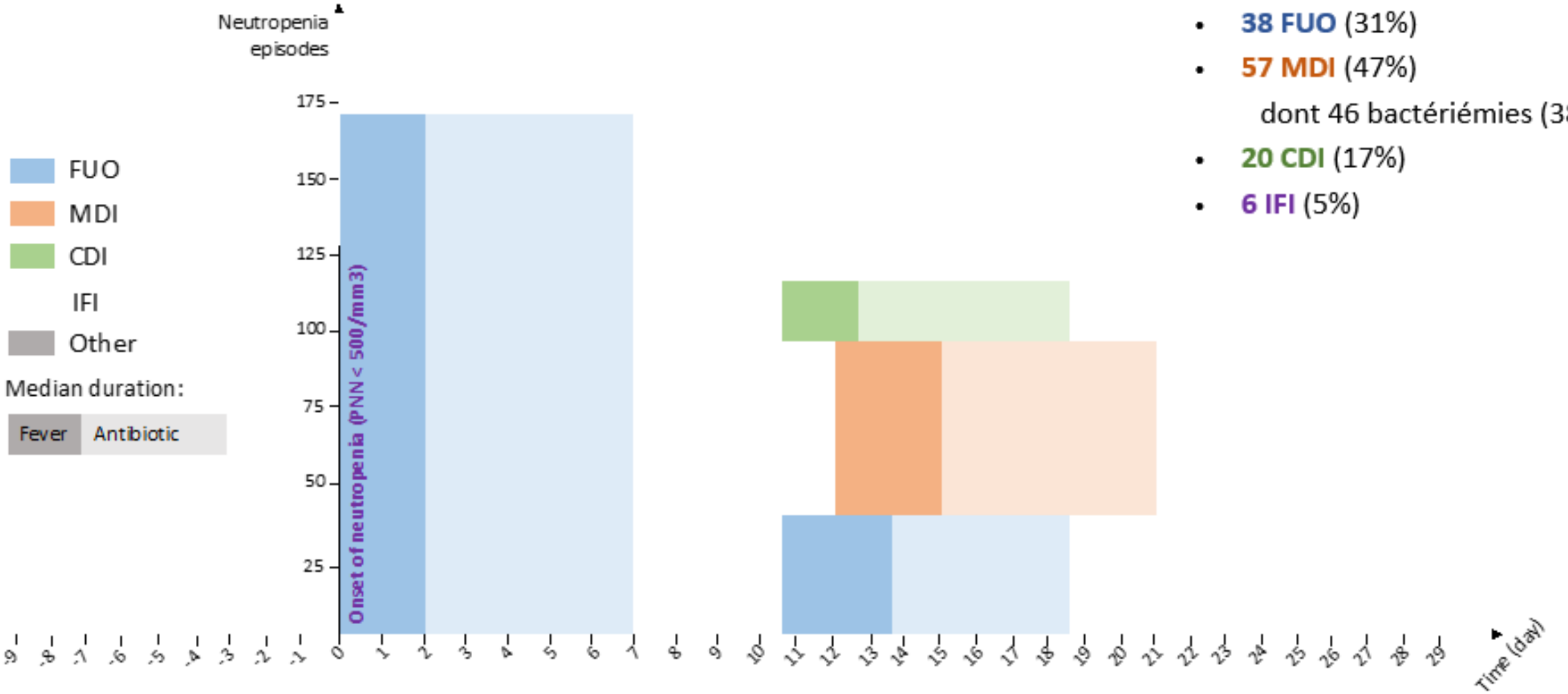
Raphaël Paret. Données personnelles

Febrile episodes

121 récidives fébriles (71%)

- **38 FUO** (31%)
- **57 MDI** (47%)

  dont 46 bactériémies (38%)
- **20 CDI** (17%)
- **6 IFI** (5%)

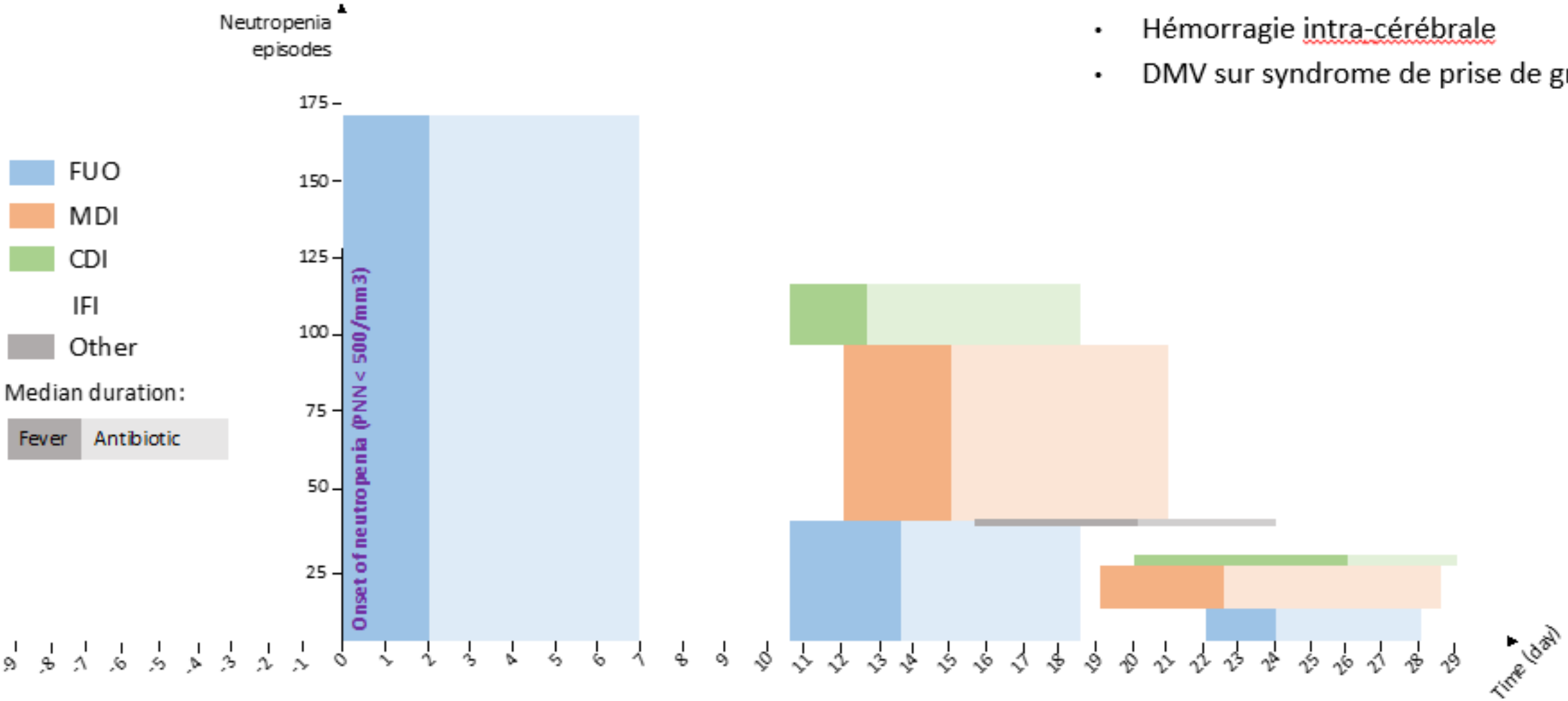


Raphaël Paret. Données personnelles

Febrile episodes

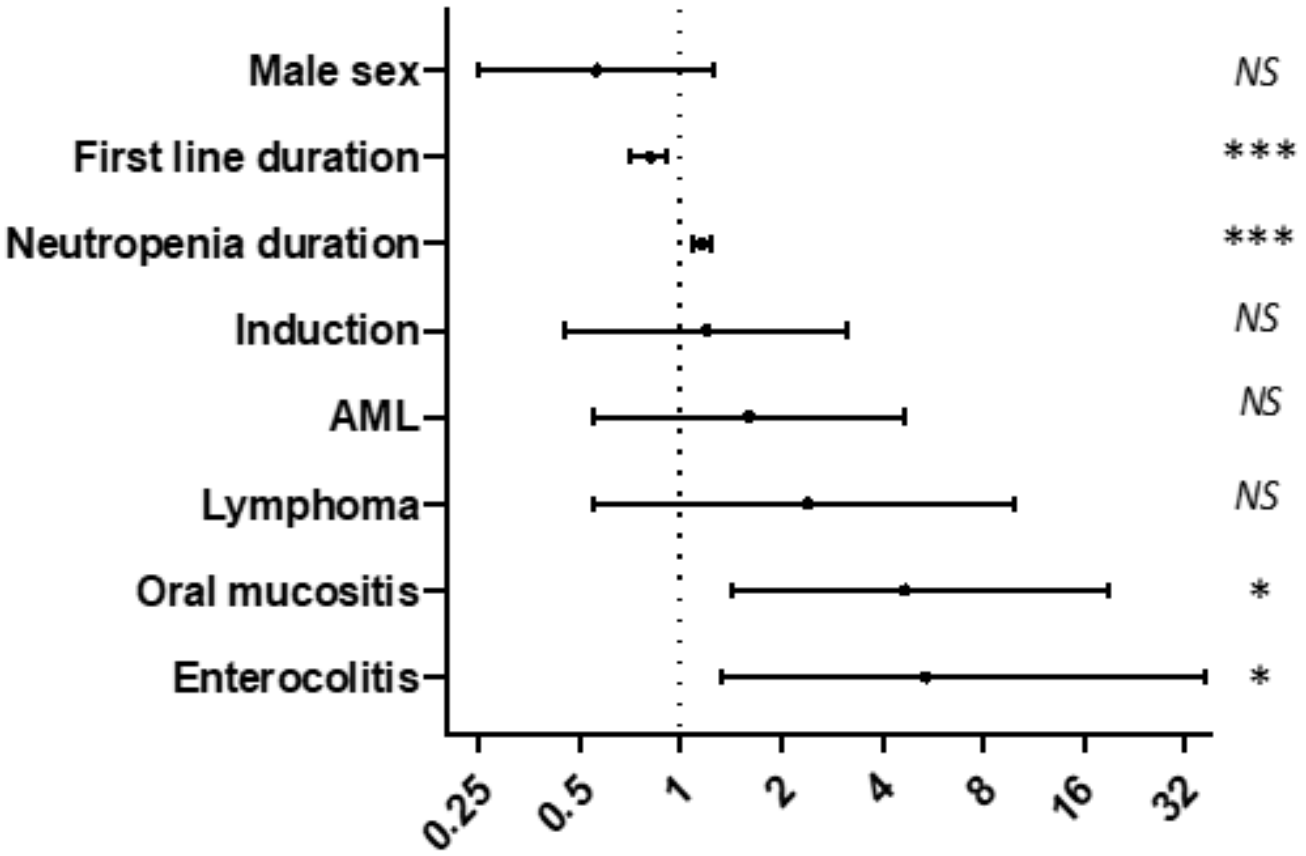
2 décès (1,2%)

- Hémorragie intra-cérébrale
- DMV sur syndrome de prise de greffe



Raphaël Paret. Données personnelles

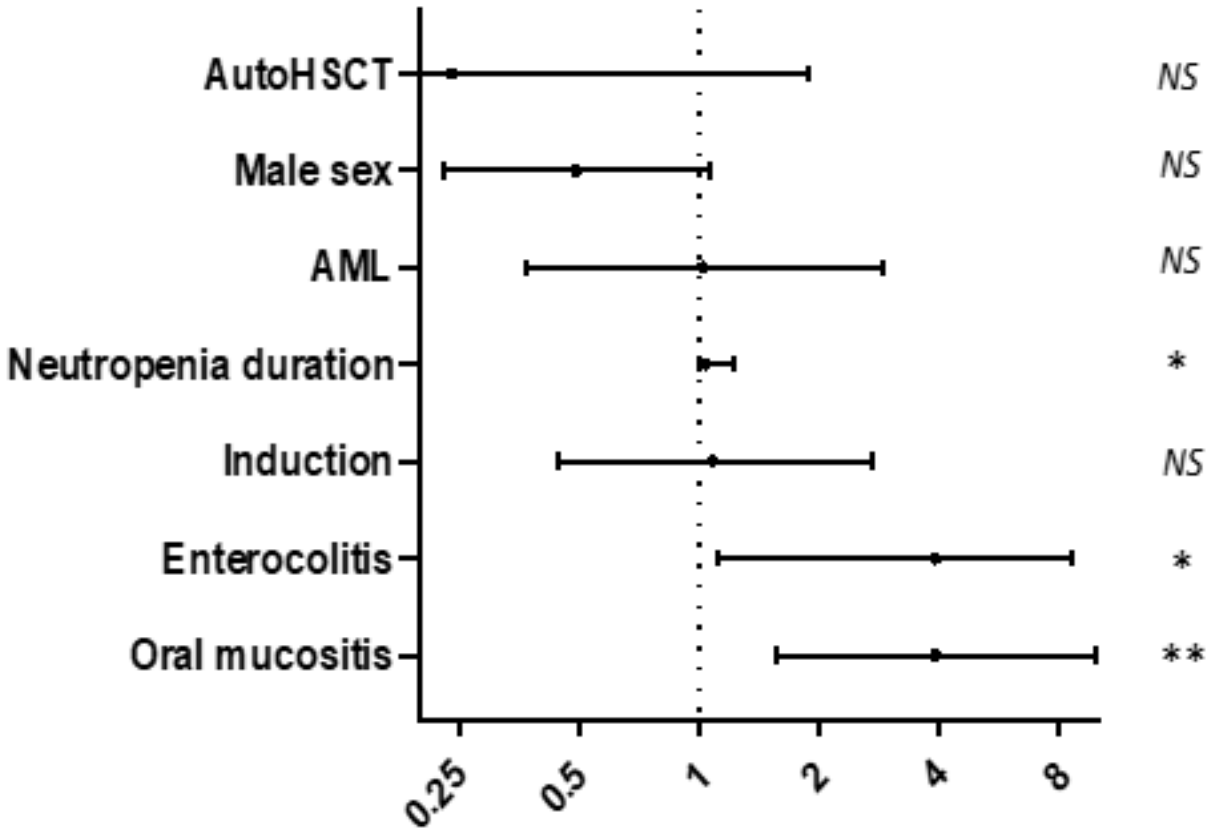
Febrile recurrence



- Durée de la 1ère ligne d'antibiothérapie
  OR=0.81, *P*<.001
- Durée de neutropénie
  OR=1.15, *P*<.001
- Mucite orale stade III-IV
  OR=4.67, *P*=.02
- Entérocolite
  OR=5.40, *P*=.04

Raphaël Paret. Données personnelles

Bacteremia



- Durée de neutropénie
  OR=1.04, *P*=.045
- Entérocolite
  OR=3.07, *P*=.03
- Mucite orale stade III-IV
  OR=3.90, *P*=.004

Raphaël Paret. Données personnelles

Antibiotic saving

Neutropenia episode	Antibiotics duration		EAT-free days	*P value*
	Real	Theorical		
Nonrecurrent febrile episode (n=49)	8.2±4.4	16.8±7.1	8.6±1.6	P<.001
Febrile recurrence episodes (n=121)	18.4±8.3	24.8±10.0	6.4±1.0	P<.001
Total (n=170)	15.5±8.7	22.5±10.0	7.0±0.8	P<.001

Raphaël Paret. Données personnelles

- Sécurité de cette stratégie :
  - Protocole clair
  - Attitudes bien cadrées
  - Patients bien définis
  - Surveillance +++

- 71 % de récidives
- FDR : Mucites, entérocolites => éléments pris en compte depuis dans la stratégie

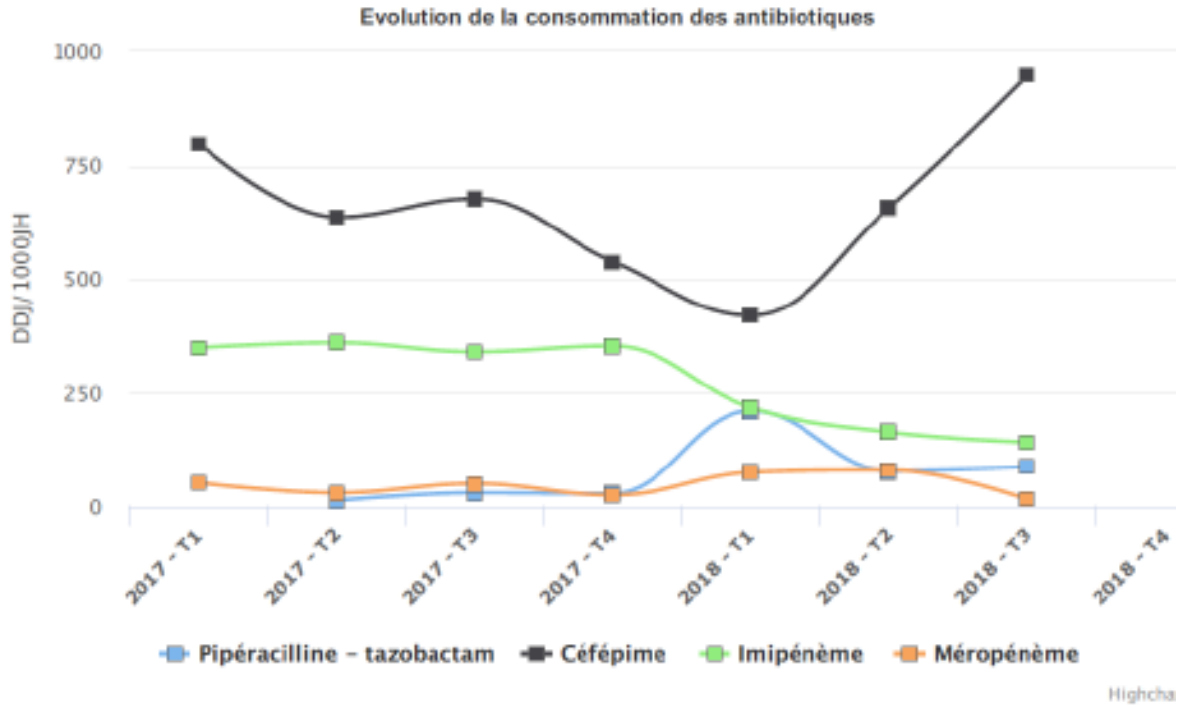
- Epargne conséquente en antibiotiques, notamment en carbapénèmes

Raphaël Paret. Données personnelles

- **l'arrêt d'antibiothérapie chez les patients neutropéniques selon les recommandations de l'ECIL4 est une stratégie réalisable chez les patients d'hématologie, permettant une épargne d'antibiotique.**

Diminution significative de l'usage du tienam pour le secteur stérile avant vs après modification des recommandations de service

Molécule	2017 - T1	2017 - T2	2017 - T3	2017 - T4	2018 - T1	2018 - T2	2018-T3	Cumul
Imipénème	348,9	360,5	340,3	353,3	217,2	163,2	141,5	275,1



Amandine Le Bourgeois. JNI 2019

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ARTICLE

Current antimicrobial practice in febrile neutropenia across Europe and Asia: the EBMT Infectious Disease Working Party survey

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Questionnaire adressé à 567 centres de 57 pays (Europe et Asie)

Désescalade à J3 : 35,3 %

Ajout de glycopeptide si persistance de la fièvre >2-3 j : 60,8 %

Elargissement du spectre si persistance de la fièvre > 3-5 j : 71,4 %

Arrêt des antibiotiques avant sortie d'aplasie :

- Si documentation : 36,6 %
- Si absence de documentation : 49,5 %

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Research Paper

Stopping antibiotic therapy after 72 h in patients with febrile neutropenia following intensive chemotherapy for AML/MDS (safe study): A retrospective comparative cohort study

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Alors que d'autres vont encore plus loin : arrêt des antibiotiques alors que le patient est encore fébrile.

A. Schauwvlieghe et al. / EClinicalMedicine 35 (2021) 100855

	EMC	UHL	
Durée AB large spectre (j)	9	19	P<0,001
Mortalité ou réa J30 (%)	12,5	8,9	P=0,17

Qu'est-ce-qui rend possible un programme de stewardship en hématologie ?

- Adhésion des praticiens (identifier les interlocuteurs +++) :
  - Chefs de service (pour ne pas avoir de veto : diplomatie +++)
  - Praticiens seniors impliqués dans la gestion de ces patients, très sensibilisés à l'antibiorésistance
    - Passés comme internes dans le service de MIT
    - Ou ayant travaillé avec des leaders dans le domaine (CHU Lille)
    - Intégrés à la COMAI
  - Travail régulier des infectiologues avec ces praticiens : relation de confiance

- Protocole clair, écrit et connu, malades bien ciblés
- RCP régulières, discussions respectueuses (pour le praticien en charge du patient, l'objectif principal est de ne pas faire prendre de risque au patient).

- Générer des données +++ : prouver l'innocuité de la démarche.

Antimicrobial Stewardship in Patients With Cancer: The Time Is Now

Table 1. CDC Stewardship Core Elements

Stewardship Core Element	Overview
Leadership commitment	Establish stewardship within the hospital's reporting structure and provide appropriate resources
Accountability	Appoint physician or pharmacist leader responsible for implementing stewardship activities
Drug expertise	Physician or pharmacist should have adequate training in antimicrobial stewardship
Action	Implement processes to promote appropriate antibiotic use
Tracking	Identify and regularly track key stewardship process and outcomes measure
Reporting	Provide key stewardship metrics to physicians, pharmacists, nurses, administrators, and other key stakeholders
Education	Deliver education to healthcare providers that promotes appropriate antibiotic prescribing

Aitken S, et al. J Natl Compr Canc Netw. 2019 Jul 1;17(7):772-775

- Merci pour votre attention