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1 Discontinuation of antimicrobial therapy in adult neutropaenic haematology patients:
2 a prospective cohort

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26

27 **Abstract.**

28 Objectives. Antibiotics for febrile neutropaenia, in acute myeloid leukaemia (AML) patients
29 undergoing intensive chemotherapy, are usually maintained until neutropaenia resolution,
30 because of the risk of uncontrolled sepsis in this vulnerable population. This leads to
31 unnecessarily prolonged antimicrobial therapy.

32

33 Methods. Based on ECIL-4 recommendations, we modified our management strategy and
34 discontinued antibiotics after a pre-established duration, among patients treated for a first
35 episode of febrile neutropaenia between August 2014 and October 2017.

36

37 Results. Antibiotics were stopped during 62 febrile neutropaenia episodes, and maintained in
38 the control group (n=13). Median age was 54 years. 39 (63%) patients received induction and
39 23 (37) consolidation chemotherapy. 36 (58%) patients had fever of unknown origin. Median
40 neutropaenia length was 26 days [IQR 24–30]. Antibiotics were started at day 9 [5–13]. Most
41 patients received piperacillin-tazobactam (56%) or cefepime (32%). Antimicrobial therapy
42 was longer in the control group compared with the policy compliant group, 10 [7–16] vs. 19
43 days [15–23], p=.0001. After antibiotics discontinuation, 20% patients experienced fever
44 recurrence, within 5.5 days [3–7.5]. None of these febrile episodes were severe. 80% patients
45 remained afebrile, with neutrophil recovery occurring within five days [2–8.5]. Overall, 287
46 antibiotics days were spared; this represents 49% of all days with antibiotics. No patient had
47 died at day 30 from intervention; six died during late follow-up, two from Graft-versus-Host
48 disease and four from relapsed or refractory leukaemia.

49

50 Conclusions. Discontinuing antibiotics in neutropaenic AML patients treated for a first
51 episode of febrile neutropaenia is safe, and results in significant antibiotic sparing.

52

53 **Key words:** Acute Myeloblastic Leukaemia; antibiotics discontinuation; febrile neutropaenia;
54 ECIL-4.

55

56 1. Introduction.

57 Acute myeloblastic leukaemia (AML) patients undergoing intensive chemotherapy are
58 considered at high risk for severe infections, because of a deep ($<0.1 \times 10^9/L$) and prolonged
59 (>7 days) neutropaenia. Febrile neutropaenia (FN) will occur in 70 to 80% of these patients
60 [1, 2]. Because of the neutropaenia and the low bacterial inoculum, 60% of patients will
61 present with fever of unexplained origin (FUO), defined by fever with no clinical or
62 microbiological documentation, despite thorough investigations [1, 2].

63

64 Initial treatment of FN should take into account previous documented infections, colonization
65 with resistant bacteria, and hospital ecology. In our centre, according to US and European
66 recommendations, we commonly use an escalation strategy, where initial empirical therapy is
67 based on a beta-lactam covering typical *Enterobacteriaceae* and *Pseudomonas aeruginosa*, but
68 not extended-spectrum beta-lactamase (ESBL), carbapenemase producers, nor multi-resistant
69 non-fermenters. Therapy is escalated, to carbapenems or with adjunction of aminoglycosides,
70 if patient deteriorates, or if a resistant pathogen is isolated. Glycopeptides are used in
71 seriously-ill patients (hemodynamic instability, severe pneumonia), in cases of colonisation
72 with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci,
73 or penicillin-resistant *S. pneumoniae*, skin or soft-tissue or catheter-related infection [1, 3].

74

75 The Infectious Diseases Society of America (IDSA) recommends maintaining antimicrobial
76 therapy (AMT) until resolution of neutropaenia (i.e. absolute neutrophil count $> 0.5 \times 10^9/L$)
77 [1]. This is justified by the risk of uncontrolled sepsis in this vulnerable population. However,
78 it leads to prolonged AMT, which increases the risk of multi-resistant bacteria selection, puts
79 pressure on the colonising microbial flora, leading to colitis with *Clostridium difficile* or
80 colonisation with yeasts, and can be responsible for pharmacological toxicity, including

81 encephalopathy or nephropathy [4-8]. Furthermore, non-bacterial agents, such as viruses or
82 fungi, may cause some of these undocumented febrile episodes. Some may also have a non-
83 infectious origin, such as acute transfusion reactions, or allergic reaction to chemotherapy.

84

85 Early studies addressing the issue of antibiotic discontinuation in neutropaenic patients
86 showed an increased risk of severe infection and mortality [9, 10]. Therefore, antibiotic
87 discontinuation was considered unsafe. However, these conclusions have been challenged by
88 more recent studies. It was shown that fever recurrence can occur whether antibiotics are
89 stopped during neutropaenia or after its resolution, and that, with appropriate AMT and
90 monitoring, non-severe FUO has low mortality, even in high-risk haematology patients [11-
91 14]. Therefore, the 4th European Conference on Infections in Leukaemia (ECIL-4) published
92 guidelines stating that AMT can be discontinued after ≥ 72 hours of intravenous (IV)
93 treatment, in selected patients with non-severe FUO who are afebrile for ≥ 48 hours,
94 irrespective of the absolute neutrophil count (ANC) or expected duration of neutropaenia. If
95 fever recurs, AMT should be started again promptly [3].

96

97 Based on these recommendations, we modified our management strategy among newly
98 diagnosed adult AML patients, receiving intensive chemotherapy, and treated for a first
99 episode of non-severe febrile neutropaenia, and introduced AMT discontinuation after a
100 preestablished duration, whatever the absolute ANC.

101

102 **2. Material and methods.**

103 *2.1 Population.*

104 Our antibiotic policy is reviewed and updated each year in discussions between
105 haematologists, infectious diseases physicians and microbiologists. This antibiotic

106 discontinuation policy was decided and implemented in August 2014. Although this paper
107 reports results of a routine policy change, and not a clinical study, for clarity purpose, we will
108 use the terms “inclusion/included” to define patients concerned by the new policy and
109 “exclusion/excluded” for those unconcerned by the policy.

110

111 We included consecutive patients, admitted to our university hospital between August 2014
112 and October 2017. Inclusion criteria were age ≥ 18 years, new diagnosis of AML or myeloid
113 sarcoma, first-line treatment with intensive chemotherapy, and first non-severe episode of FN,
114 including FUO, primary bacteraemia and focal infections. The policy change also included
115 patients who had an orthopaedic implant, had been admitted in the intensive care unit (ICU)
116 for sepsis or septic shock during a previous hospital stay or were colonized with multi-
117 resistant bacteria. One patient could be included several times in our study, but during a
118 different neutropaenic episode and a different hospital stay (e.g. during induction and
119 consolidation phases).

120

121 Exclusion criteria were Acute Lymphoblastic Leukaemia (ALL) diagnosis, relapse or
122 refractory patients, previous hematopoietic stem-cell transplant (HCST), non-intensive
123 treatment, severe infection (i.e. sepsis or septic shock, according to the recent definition [15]),
124 severe infection such as endocarditis or osteomyelitis, presence of prosthetic heart valve, as
125 these patients were considered too frail and/or at higher risk for severe infectious
126 complications. In these patients, antibiotics were maintained until neutropaenia resolution.

127

128 *2.2 Antimicrobial therapy discontinuation.*

129 Initial empirical therapy was given intravenously (IV) in all cases. It was mostly based on a
130 beta-lactam covering typical *Enterobacteriaceae* and *P. aeruginosa* (e.g. cefepime or

131 piperacillin-tazobactam). Narrower-spectrum beta-lactam (cefotaxime) was used when fever
132 occurred within the first week of hospitalization. Carbapenem or adjunction of an
133 aminoglycoside was used if a resistant pathogen was isolated. Glycopeptides were used in
134 cases of skin, soft-tissue or catheter-related infection.

135

136 AMT was discontinued after at least seven days of intravenous treatment, after resolution of
137 clinical symptoms and at least five days of apyrexia, regardless of the ANC or the predicted
138 duration of neutropaenia. Duration of AMT was determined according to clinical presentation
139 and/or microbiological documentation: seven days for FUO, colitis or pneumonia, ten days
140 for catheter-related infection or bacteraemia, ten days for urinary tract infection in female
141 patients, and 14 days for male patients. Patients were thoroughly monitored. In case of febrile
142 recurrence, the same antibiotics were started again urgently by ward nurses (a standing order
143 allowed for immediate treatment without medical prescription), and maintained until
144 neutrophil recovery. Adjunction of antifungal treatment was discussed according to clinical
145 presentation, duration of neutropaenia, indirect fungal biomarkers (galactomannan antigen),
146 and thoracic CT-scan.

147

148 We do not use antibiotic prophylaxis with fluoroquinolones due to the high level of resistance
149 to fluoroquinolones in our population. All patients received an antifungal prophylaxis with
150 oral posaconazole during neutropaenic period.

151

152 *2.3 Endpoint.*

153 Our primary endpoint was the occurrence of a new febrile episode after AMT discontinuation.
154 Secondary endpoints were number of days without antibiotics, occurrence of severe
155 infections, and 30-days mortality.

156

157 *2.4 Statistics.*

158 Data collected prospectively were analysed retrospectively. Outcomes were compared
159 between the groups with the t test or Mann-Whitney U test for continuous outcomes and with
160 the χ^2 or Fisher's exact test as appropriate for contingency analysis. P values of 0.05 were
161 considered significant. Statistical analysis was performed using Microsoft Excel v.12.2.8 (MS
162 Office 2008) and GraphPad Prism v.7.0.

163

164 *2.5 Ethics.*

165 This study was conducted in accordance with the ethical standards of our hospital committee
166 on human experimentation, and with the Helsinki Declaration of 1975, as revised in 2008. We
167 did not submit this study to a formally constituted review board because the subject of this
168 article was the analysis of a major antibiotic policy change performed to follow European
169 guidelines (ECIL-4) for AML patients. Per French law at the time, review of usual care in
170 monocentric studies did not require submission to an ethical review committee. Patients'
171 usual physicians collected all data analyzed as part of routine diagnosis and treatment.

172

173 **3. Results.**

174 *3.1 Flow-chart.*

175 Between August 2014 and October 2017, 98 patients eligible for intensive treatment were
176 newly diagnosed with AML or myeloid sarcoma in our university hospital. Each patient
177 received at least one intensive treatment course (induction and/or consolidation); number of
178 hospital stays (hence, number of neutropaenic episodes) was 195 overall, as patients could be
179 included more than once, but over different hospital stays. Thirty-five neutropaenic episodes
180 were excluded because of hospitalization in the ICU, due to AML complication or severe

181 infection (sepsis or septic shock). During 45 neutropaenic episodes, patients remained
182 afebrile. Finally, 115 episodes of non-severe FN were included. AMT was not discontinued in
183 66 episodes (58%): neutrophil recovery occurred before the planned end of antibiotic
184 treatment in 35 episodes (30%); apyrexia couldn't be obtained before neutrophil recovery in
185 18 episodes (16%); and in 13 episodes (11%), AMT was not stopped because of physicians'
186 failure to follow the new policy. We chose to use these 13 episodes as a control group. AMT
187 was effectively stopped in 49 non-severe febrile neutropaenic episodes (Figure 1).

188

189 *3.2 Population.*

190 Patients' characteristics are described in Table 1. Overall, 36 patients were included in the
191 policy compliant group and 13 in the control group. Median age was 54 years overall
192 [interquartile range (IQR) 36-63]. Four patients (8%) had previous known ESBL colonization.
193 Overall, 47 patients had AML, including eight Acute Promyelocytic Leukaemia (APL), one
194 had biphenotypic AML treated as an AML, and one had myeloid sarcoma. Induction
195 chemotherapy was based on anthracyclines, either daunorubicin, or idarubicin given during
196 three to five days, in combination with cytarabine (200mg/m²/day) given by continuous
197 intravenous infusion during seven days. One patient received amsacrine combined with
198 cytarabine. Consolidation chemotherapy consisted of cytarabine alone, 1 to 3g/m²/12h over 3
199 days, according to physician judgment. APL patients were treated according to APL2006
200 protocol, or with arsenic trioxide in combination with all-trans retinoic acid.

201

202 *3.3 Control group.*

203 Antibiotics were not stopped in 13 FN episodes (occurring among 13 patients) because of
204 physicians' failure to follow the new policy. These patients were used as a control group.
205 Reasons for maintaining antibiotics were because patients were considered too frail (n=5),

206 uncontrolled infection (n=1); no reasons were identified for the seven remaining patients.
207 Even though there were no statistically significant differences between the two groups,
208 control patients had more aggressive underlying disease, with poor prognosis cytogenetics
209 and higher tumour burden at admission (defined by either leukocyte count >50G/l,
210 intravascular disseminated coagulation, or spontaneous tumour lysis syndrome). This could
211 explain physicians' reluctance to discontinue antibiotics among these patients.

212

213 *3.4 Febrile neutropaenia.*

214 Febrile neutropaenia occurred during induction therapy for 39 (63%) episodes and during
215 consolidation therapy for 23 (37%) episodes. FUO occurred in 36 episodes (58%). Clinical
216 symptoms were upper respiratory tract symptoms (n=4) or pneumonia (n=5), catheter-related
217 infection (n=4), colitis (n=1), dental abscess (n=1), endometritis (n=1). We obtained
218 microbiological documentation in 16 (26%) cases. Blood cultures were positive in eight
219 patients, with gram-negative rods (n=5) or streptococci (n=2), one patient having concomitant
220 *E. coli* and *S. oralis* bacteraemia. Two patients had several positive blood cultures with
221 coagulase-negative staphylococci (*Staphylococcus hominis* and *S. epidermidis*, respectively).
222 One patient had clinical signs of catheter infection, with significant *Staphylococcus*
223 *epidermidis* growth at removal and culture. Three asymptomatic patients had positive urine
224 culture. One female patient presented with *E. coli* endometritis. In four patients with upper
225 respiratory tract symptoms, nasal swab was positive for viruses (Table 2).

226

227 *3.5 Antimicrobial therapy.*

228 Empirical AMT was initiated immediately after the first episode of FN. Four patients (6%)
229 received cefotaxime as monotherapy (100mg/kg/day IV divided in 3 doses). Most patients
230 received antipseudomonal beta-lactam, either piperacillin-tazobactam, 4g/6-8h IV (n=35,

231 56%) or cefepime, 2g/8h IV (n=20, 32%), mostly given as monotherapy (n=41, 66%).
232 Combination therapy with amikacin was given in patients with known ESBL colonization
233 (n=5, 8%), or signs that could suggest severe infection but without sepsis criteria such as
234 mottled skin (n=3, 5%). Anti methicillin-resistant staphylococci therapy (vancomycin or
235 linezolid) was given in case of skin or catheter-related infection (n=6, 10%). One patient with
236 ESBL colonization was given a carbapanem, meropenem. One patient with colitis was treated
237 with cefepime and metronidazole. One patient received vancomycin alone for *S. hominis*
238 bacteremia. The patient diagnosed with *E. coli* endometritis initially received ceftriaxone,
239 metronidazole, and doxycycline (Table 3). AMT was considered adequate, following standard
240 guidelines for FN and according to our center ecology, and when microbiological
241 documentation was available, appropriate, in 46 (94%) patients in the policy compliant group
242 and 12 (92%) in the control group.

243

244 As expected, effective AMT was longer in the control group. In the policy compliant group,
245 antibiotics were discontinued as planned in FUO (n=28; 7.5 days [7-10]) and catheter-related
246 infections and/or bacteraemia (n=10; 10 days [10-17]). However, for other clinical situations,
247 antibiotics were given for a longer time than recommended. Reasons were persistence of
248 clinical symptoms (n=7) and fever recurrence (n=2).

249

250 We observed adverse events in 20 (32%) patients; all were considered mild or moderate
251 (grade 1–2). Most of them are not specific, and might also be caused by anti-leukaemia
252 chemotherapy.

253

254

255

256 3.6 Outcome.

257 Median neutropaenia length was 26 days [IQR 24–30] in the overall population, 27 days [25–
258 34] for patients undergoing induction phase and 24 days [22–27] for patients in consolidation
259 phase (Table 4). One patient never had neutrophil recovery, and was discharged at day 43.

260

261 In the overall population, AMT was started after a median nine days [IQR 5–13] since
262 chemotherapy, and was given for ten days [7–18]. During the induction phase, AMT was
263 started on day six [3–8], and given for 17 days [10–21]; during consolidation, it was started
264 on day 14 [11.5–17], and given for nine days [7–10]. AMT length was significantly higher in
265 the control group compared with the policy compliant group, 10 days [7–16] vs. 19 days [15–
266 23], $p=0.0001$ (Figure 2). This was true for both induction and consolidation phases. There
267 were no differences in neutropaenia length, or antibiotic initiation day between the groups.

268

269 After AMT discontinuation, in the policy compliant group, ten patients (20%) experienced a
270 new febrile episode and 39 (80%) achieved neutrophil recovery without febrile recurrence.
271 Febrile recurrence occurred for nine patients (18%) during induction phase, and for one (2%)
272 during consolidation. Treatment phase was not associated with significantly higher risk of
273 fever recurrence ($p=0.08$). Median duration between AMT interruption and new febrile
274 episode was 5.5 days [3–7.5] in the overall population, six days [3–8] for induction phase, and
275 three days [3–3] for the patient in consolidation phase. None of these ten febrile episodes led
276 to hemodynamic instability, septic shock, or ICU hospitalization. Eight episodes (80%)
277 presented as FUO; febrile recurrence was asymptomatic but microbiologically documented in
278 the two (20%) remaining patients: one had *Escherichia coli* bacteraemia, and another had
279 *Streptococcus mitis* bacteraemia. Interestingly, both of them initially presented as a FUO.

280

281 Use of relatively narrow-spectrum antibiotics such as cefotaxime was associated with higher
282 risk of fever recurrence ($p=0.0009$). However, use of monotherapy vs. combination therapy
283 ($p=0.43$) or use of penicillin vs. cephalosporin ($p=0.9$) had no significant impact on the risk of
284 fever recurrence.

285

286 Patients who achieved neutrophil recovery without fever recurrence were equally distributed
287 between induction ($n=19$, 39%) and consolidation phase ($n=20$, 41%). Median overall
288 duration between AMT discontinuation and neutrophil recovery was five days [IQR 2–8.5],
289 eight days [4.5–12.5] in the induction group and two days [1–6] in the consolidation group.
290 As AMT is usually maintained until neutrophil recovery, this corresponds to the number of
291 days of antibiotics spared. Overall, patients received antibiotics during 845 days, and 586
292 days in the policy-compliant population. Our management strategy allowed us to spare 287
293 days of AMT; this represents 34% of the overall consumption, and 49% for the policy-
294 compliant population.

295

296 *3.7 Mortality.*

297 No patient had died at day 30 from antibiotics discontinuation. Three-year overall survival
298 (OS) was 75%. Median OS was not reached. Median follow-up was 19 months. Overall, six
299 patients (12%) died during follow-up. Two patients underwent allogeneic stem-cell transplant
300 and died of severe GVHD, six and eight months after diagnosis, respectively. Four patients
301 died of AML: three relapsed, and died three years, 19 and 16 months after initial diagnosis,
302 respectively; one had refractory leukaemia and died ten months after diagnosis.

303

304

305 4. Discussion.

306 The main result of our study is that discontinuing AMT, in patients treated for a first episode
307 of FN, is safe, regardless of the ANC. Indeed, 80% patients remained afebrile until neutrophil
308 recovery. Among the 20% patients with a recurrent febrile episode, the outcome was
309 favourable, without any severe sepsis, ICU admission or death. AMT length was significantly
310 higher among patients with compliance failure to the new policy. Implementation of the new
311 strategy resulted in high antibiotic sparing, a mean 6 days per patient, similar in patients with
312 or without a second febrile episode. In the policy compliant population, 49% of all days with
313 antibiotics were spared.

314

315 Most of first and second febrile episodes occurred remotely from each other. Febrile
316 recurrences were diagnosed a median six days and up to 14 days after AMT discontinuation.
317 These episodes are probably independent events, as it seems unlikely that the same
318 microorganism could be incriminated in both episodes. Blood cultures at the time of febrile
319 recurrence were positive in only two patients, who both initially presented as FUO. Previous
320 studies reported that recurrence of fever might occur whether or not AMT is discontinued [9,
321 11, 12]. Patients probably present several infectious episodes during prolonged neutropaenia,
322 with different microorganisms, and that could be another reason to discontinue AMT, as it
323 might allow for better microbiological documentation and lead to de-escalation therapy.

324

325 ECIL-4 guidelines state that AMT can be discontinued after at least three days of IV
326 treatment, in patients with non-severe FUO who are afebrile for ≥ 48 hours. Before these
327 guidelines, standard of care in our unit was to discontinue AMT after neutrophil recovery.
328 Changing clinical practices is challenging, especially in the absence of randomized controlled
329 study to support these paradigm-changing recommendations. We decided to adapt the

330 guidelines to our centre habits, hoping for a better appropriation by our prescribers. We thus
331 chose to discontinue AMT after at least seven days of IV treatment and five days of apyrexia.
332 In contrast, we extended indications of antibiotic discontinuation to cases of documented
333 fever, whereas ECIL-4 recommendations only refer to FUO episodes, which concerned 58%
334 of our population.

335

336 However, in our study, a high number of patients were excluded due to neutrophil recovery
337 before AMT cessation. This accounts for 35 patients (30%) overall, most of them (91%)
338 being in consolidation phase. This could reflect the longer duration of antibiotic therapy used
339 in this study, compared to ECIL-4 guidelines, and indicates that we could probably align our
340 strategy more closely to ECIL-4 guidelines. This is especially true for patients in
341 consolidation phase, who are probably a lower risk group with shorter neutropaenic period. A
342 tighter application of ECIL-4 guidelines could probably save even more AMT days.

343

344 Discontinuation of AMT in neutropaenic patients is not a new topic, but remains
345 controversial. Pizzo *et al.*, in 1979, provided the first study addressing this question. They
346 included 33 patients with FUO after chemotherapy for solid neoplasia or hemopathy,
347 randomized between stopping or continuing treatment after seven days of empirical AMT.
348 Seven patients (41%) in the experimental arm relapsed, with five documented febrile
349 episodes, and two septic deaths due to *E. coli* bacteraemia, vs. only one fever recurrence and
350 no deaths in the standard group. Antibiotic discontinuation was thus considered unsafe in
351 neutropaenic patients. Later, Cherif *et al.*, in 2004, conducted a randomized study among 60
352 high and low-risk haematology patients, in which empirical AMT was stopped after 48 hours
353 of apyrexia. They showed that febrile recurrence occurred both in neutropaenic (9/49, 18%)
354 and non neutropaenic patients (2/11, 18%). One neutropaenic patient died from an invasive

355 fungal infection. Slobbe *et al.* included 169 high-risk haematology patients, receiving
356 fluoroquinolone and fluconazole prophylaxis. Imipenem was stopped after ≤ 72 hours in cases
357 of FUO, or switched to narrower spectrum antimicrobial agents according to microbial
358 documentation. There were no differences between fever recurrence, severe infections or
359 death among the different groups. ECIL-4 guidelines were published in 2013, based on these
360 studies and others [9-14, 16-19].

361

362 To our knowledge, few prospective studies have been published since then. One prospective
363 French study by Micol *et al.* included seven high-risk neutropaenic patients with FUO.
364 Antimicrobial therapy was discontinued after a mean of 15 days, which is longer than the
365 ECIL-4 recommendations; four patients remained afebrile, with neutrophil recovery achieved
366 within two to four days, and three patients had recurrent fever in less than three days, with
367 one septic shock. AMT was spared for a mean of three days, but authors considered that
368 exposing patients to a risk of uncontrolled secondary infections was unethical. However,
369 interpretation of this study is controversial, and was commented by others [20, 21]. It is
370 noteworthy that the patient undergoing septic shock was the only one receiving salvage
371 therapy, underlying the importance of patients' selection.

372

373 Recently, one Spanish team conducted a multicentric randomized study among 157 high-risk
374 neutropaenic haematology patients with FUO [22]. AMT was stopped after ≥ 72 h of apyrexia
375 in the experimental group, or withdrawn at neutrophil recovery. Mean AMT length was 11.9
376 days in the experimental group and 14.4 days in the control group. This allowed a significant
377 spare of 2.5 days of AMT ($p=0.026$). The frequency of recurrent fever was similar in both
378 groups, (11 patients (14%) in the experimental group and 14 (18%) in the control group,
379 $p=0.54$), with only one severe infection; no patient died after AMT withdrawal. However, in

380 our opinion, this study has some limits. First, the overall population is heterogeneous, and
381 includes patients that are at lower risk for FN (81 patients, 52%), such as patients receiving
382 chemotherapy for lymphoid malignancies, including autologous stem cell transplant; these
383 patients are expected to have duration of neutropaenia of 7 days or more, but neutropaenia is
384 usually not as deep as in AML patients or allogeneic stem cell recipients (76 patients, 48%).
385 There are more low-risk patients in the control group, and neutropaenia length is therefore
386 shorter, 11 (8.0–21.3) vs. 14 days (9.5–24) in the experimental group. Secondly, only 41
387 (53%) patients were still neutropaenic at AMT withdrawal in the experimental group; the
388 reason for this is unclear. Although results of this study are encouraging, this may limit
389 extrapolation of these findings. Interestingly, our median antibiotic duration (10 days) was
390 similar to the one reported in this study, despite having a longer afebrile requirement before
391 AMT discontinuation.

392

393 A French observational study included 82 cases of FN; antibiotics were discontinued
394 whatever the ANC, according to ECIL-4 guidelines. Forty-eight (58%) FUO episodes did not
395 relapse during hospital-stay and 14 (17%) had fever recurrence, without excessive in-hospital
396 mortality or intensive care unit admission [23]. Rates of fever recurrence are similar to what
397 we observed in our study, and in others, published before ECIL-4 guidelines [9-14, 16-19].
398 Another study, conducted by la Martire *et al.*, aimed at evaluating the impact of an antibiotic
399 stewardship intervention on antibiotic consumption. Antibiotic discontinuation was performed
400 among 52/100 FN episodes. Surprisingly, no fever recurrence during the same neutropaenic
401 episode was observed. Compared to our population, neutropaenia length was significantly
402 shorter (19 [12–29] vs. 26 [24–31] days); this could explain the higher fever recurrence rates
403 observed in our study [24].

404

405 Management of FN has changed over the past years. The overall tendency to the prudent use
406 of AMT is justified by the global increase in antibiotic resistance in hospitalized patients and
407 in the community. Several studies have shown that antibiotic stewardship leads to improved
408 AMT use, and decreases antibiotic consumption [25, 26]. Antibiotic resistance is a special
409 concern for haematology patients, who undergo several chemotherapy-induced neutropaenia
410 episodes, and are exposed to repeated courses of broad-spectrum AMT [27-29].

411

412 Our study has limitations. First, it is a monocentric cohort based on a small population.
413 Nevertheless, our patients are standard AML patients, included consecutively, who, in our
414 opinion, reflect the overall population of patients with AML. Second, the lack of a control
415 group with patients recruited prospectively limits the impact of our results. However, having
416 observed no adverse effect at all of the new strategy, a control group could not have yielded
417 better results. One of the reasons may be the automatic standing order for readministration of
418 AMT in patients with a new febrile episode. Third, this study, following a policy change,
419 might be biased in patients' selection. However, in our centre, only two haematology
420 physicians manage AML patients, with twice weekly rounds by a consulting infectious
421 disease physician, resulting in a homogenous management of the patients.

422

423 **5. Conclusions.**

424 In conclusion, antibiotic discontinuation in patients newly diagnosed with acute myeloid
425 leukaemia, and presenting a first episode of febrile neutropaenia after receiving intensive
426 chemotherapy, is not only feasible but also safe, provided that appropriate AMT is started
427 again promptly after fever recurrence. This strategy reduces antibiotic use, and does not
428 increase the rate of severe infections or mortality in high-risk haematology patients.

429

430 Declarations

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434

435 Authorship.

436 CBe, HD and SA formulated the research question, and designed the study.

437 CBo, SBo, MN, BC, CL, SBa, PC, AS, AW, JBB, LR, KJW, GE, NB, IA included patients,

438 collected data of tolerance, efficacy and follow-up.

439 ZV included patients, collected and analyzed data, and wrote the manuscript draft.

440 CBe, SA, BQ and MT revised the manuscript.

441 All authors read and approved the final version of this manuscript.

442

443 **References.**

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527

Figure legends and tables (clean version).

Figure 1. Flow chart

AML: acute myeloblastic leukemia. MS: myeloid sarcoma

Numbers correspond to number of neutropaenic episodes (induction phase/consolidation phase).

Figure 2. Antimicrobial therapy length in both groups.

Table 1. Patients' characteristics

Population	Policy compliant group N=36	Control group N=13
Age, years	52 [33-60]	56 [49-66]
Females	17 (47)	3 (23)
Extended-Spectrum Beta-Lactamase colonization	4 (11)	0 (0)
Diagnosis		
Acute Myeloblastic Leukemia	34 (94)	13 (100)
Other	2 (6)	0 (0)
Cytogenetics		
High risk	10 (28)	8 (62)
Intermediate	9 (25)	3 (23)
Favorable	17 (47)	2 (15)
High tumor burden	9 (25)	4 (36)
Datan are N (%) or median [IQR]		

Table 2. Febrile neutropaenia, clinical and microbiological documentation.

Febrile neutropaenia episodes N=62	Policy compliant group N=49	Control group N=13
Treatment phase		
Induction	28 (57)	11 (85)
Consolidation	21 (43)	2 (15)
FUO	28 (56)	8 (62)
Clinical symptoms	12 (24)	4 (31)
Upper respiratory tract infection	3 (6)	1 (8)
Catheter-related infection	3 (6)	1 (8)
Pneumonia	3 (6)	2 (18)
Colitis	1 (2)	0
Dental abscess	1 (2)	0
Endometritis	1 (2)	0
Microbiological documentation	13 (26)	3 (23)
Bacteraemia	7 (14)	1 (8)
<i>Escherichia coli</i>	4 (8)	0
<i>Enterobacter cloacae</i>	1 (2)	0
<i>Streptococcus salivarius</i>	1 (2)	0
<i>Streptococcus oralis</i>	1 (2)	0
<i>Coagulase-negative staphylococci</i> *	1 (2)	1 (8)
Urinary tract infection	2 (4)	1 (8)
Female		
<i>Enterococcus faecalis</i>	1 (2)	0
<i>Escherichia coli</i>	1 (2)	0
Male		
<i>Klebsiella pneumoniae</i>	0	1 (8)
Positive nasal swab	3 (6)	1 (8)
Positive catheter culture	1 (2)	0
*Several blood cultures were positive. Datas are N (%).		

Table 3. Antimicrobial therapy.

Patients were mostly given beta-lactam-based antimicrobial therapy, given as monotherapy or in combination with aminoglycosides and/or anti methicillin-resistant staphylococci therapy, according to clinical presentation, known ESBL colonization or microbiological documentation. Some patients received two or more antibiotics, which is why the sum of each value can exceed the overall number of patients in each group

	Policy compliant group N=49	Control group N=13
Antibiotics used		
Cefotaxime	3 (6)	1 (8)
Monotherapy	3 (6)	1 (8)
Piperacilline-tazobactam	27 (55)	8 (62)
Monotherapy	18 (37)	8 (62)
+ Amikacine	6 (12)	0
+ Vancomycine	2 (4)	0
+ Linezolid	2 (4)	0
Cefepime	16 (33)	4 (31)
Monotherapy	11 (22)	4 (31)
+ Amikacine	3 (6)	0
+ Vancomycine	1 (2)	0
+ Linezolid	1 (2)	0
+ Metrodinazole	1 (2)	0
Meropenem	1 (2)	0
+ Amikacine	1 (2)	0
Others	2 (4)	0
Vancomycine monotherapy	1 (2)	0
Ceftriaxone – Metronidazole – Doxycycline	1 (2)	0
Antimicrobial therapy length, by site		
Fever of Unknown Origin	7.5 [7-10]	18 [14.5-20.5]
Pneumonia / upper respiratory tract infection	13.5 [9-21]	22.5 [19-28]
Catheter-related infection/bacteraemia	10 [10-17.5]	20.5 [19-22]
Male urinary tract infection	10 [10-10]	-
Female urinary tract infection	18 [18-18]	24 [24-24]
Colitis	14 [14-14]	-
Adverse events	16 (33)	4 (31)
Toxidermia	5 (10)	1 (8)
Abnormal liver function tests	5 (10)	1 (8)
<i>C. difficile</i> colitis	2 (4)	0
Diarrhea	2 (4)	1 (8)
Veinitis	1 (2)	0
Acute renal failure	1 (2)	0
Encephalopathy	0	1 (8)
Dadas are N (%) or median [IQR].		

Table 4. Evolution

	Policy compliant group N=49	Control group N=13
Neutropaenia length, days	26 [24–31]	26 [21–27.5]
Induction	27.5 [25–34.25]	26 [22–28.5]
Consolidation	24 [22–27]	23 [21.5–24.5]
Antibiotic therapy initiation, Day	D9 [5.75–14.25]	D5.5 [3–9.25]
Induction	D6 [3–8.5]	D5 [3–6]
Consolidation	D14 [12–18]	D12 [11–13]
Antibiotic therapy length, days	10 [7–16]	19 [15–23]
Induction	15 [8–19.25]	26 [22–28.5]
Consolidation	9 [7–10]	23 [21.5–24.5]
Febrile recurrence after antibiotic discontinuation	10 (20)	-
Induction	9 (18)	-
Consolidation	1 (2)	-
Delay between ATB stop and fever recurrence, days	5.5 [3–7.5]	-
Induction	6 [3–8]	-
Consolidation	3 [3–3]	-
No febrile recurrence after antibiotic discontinuation	39 (80)	-
Induction	19 (39)	-
Consolidation	20 (41)	-
Delay between ATB stop and neutrophil recovery, days	5 [2–8.5]	-
Induction	8 [4.5–12.5]	-
Consolidation	2 [1–6]	-
Datan are N (%) or median [IQR]. ATB: antibiotic therapy.		

Figure legends and tables (highlights version).

Figure 1. Flow chart

AML: acute myeloblastic leukemia. MS: myeloid sarcoma
Numbers correspond to number of neutropaenic episodes (induction phase/consolidation phase).

Figure 2. Antimicrobial therapy length in both groups.

Table 1. Patients' characteristics

	Policy compliant group N=36	Control group N=13
Population (N=49 36)		
Age, years	51 [31-58] 52 [33-60]	56 [49-66]
Sex ratio M/F	24/25 19/17	3 (23)
ESBL colonization	5 (10) 4 (11)	0 (0)
Diagnosis		
AML	37 (76) 26 (73)	13 (100)
APL	10 (24) 8 (21)	0 (0)
Biphenotypic AML	1 (2) 1 (3)	0 (0)
Myeloid sarcoma	1 (2) 1 (3)	0 (0)
Cytogenetics		
High risk	10 (28)	8 (62)
Intermediate	9 (25)	3 (23)
Favorable	17 (47)	2 (15)
High tumor burden	9 (25)	4 (36)
Treatment phase		
Induction	28 (57)	
Consolidation	21 (43)	
Chemotherapy		
AML induction		
Daunorubicin 90 mg/m ²	3 (6)	
Daunorubicin 60 mg/m ²	9 (18)	
Idarubicin 9 mg/m ² , 5 days	4 (8)	
Idarubicin 12 mg/m ² , 3 days	4 (8)	
Amsacrine 100 mg/m ² , 3 days	1 (2)	
APL induction		
Arsenic trioxide	3 (6)	
APL-2006	4 (8)	
Consolidation		
HDAC	14 (29)	
HDAC (1.5 g/m ²)	3 (6)	
HDAC (1 g/m ²)	1 (2)	
APL2006 (IDA 12 mg/m ² + ATRA)	3 (6)	
<p><i>Datas are N (%) or median [IQR]. ESBL: Extended Spectrum Beta Lactamase, AML: Acute Myeloblastic Leukemia, APL: Acute Promyelocytic Leukemia, ATRA: all trans retinoic acid, HDAC: high dose aracytin, IDAC: intermediate dose aracytin.</i></p>		

Table 2. Febrile neutropaenia, clinical and microbiological documentation.

Febrile neutropaenia episodes N=62	Policy compliant group N=49	Control group N=13
Treatment phase		
Induction	28 (57)	11 (85)
Consolidation	21 (43)	2 (15)
FUO	28 (56)	8 (62)
Clinical symptoms	16 (32)	4 (31)
Asymptomatic	32 (65)	
Colitis	3 (6)	0
Dental abcess	1 (2)	0
Upper respiratory tract infection	4 (8)	0
Pneumonia	3 (6)	2 (18)
Catheter-related infection	4 (8)	2 (18)
Endometritis	1 (2)	0
Microbiological documentation	14 (28)	3 (23)
No documentation	35 (71)	
Blood cultures	10 (20)	1 (8)
<i>Escherichia coli</i>	4 (8)	0
<i>Klebsiella pneumoniae</i>	1 (2)	0
<i>Pseudomonas aeruginosa</i>	1 (2)	0
<i>Enterobacter cloacae</i>	1 (2)	0
<i>Streptococcus salivarius</i>	1 (2)	0
<i>Streptococcus oralis</i>	1 (2)	0
Coagulase-negative staphylococci*	1 (2)	1 (8)
Catheter culture	1 (2)	0
<i>Staphylococcus epidermidis</i>	1 (2)	0
Urine culture	2 (4)	1 (8)
<i>Escherichia coli</i>	0	1 (8)
<i>Enterococcus faecalis</i>	1 (2)	0
<i>Klebsiella pneumoniae</i>	1 (2)	0
Nasal swab	3 (6)	1 (8)
Human parainfluenzae virus	1 (2)	0
Coronavirus	1 (2)	0
Influenza A virus	1 (2)	1 (8)
*Several blood cultures were positive. Datas are N (%).		

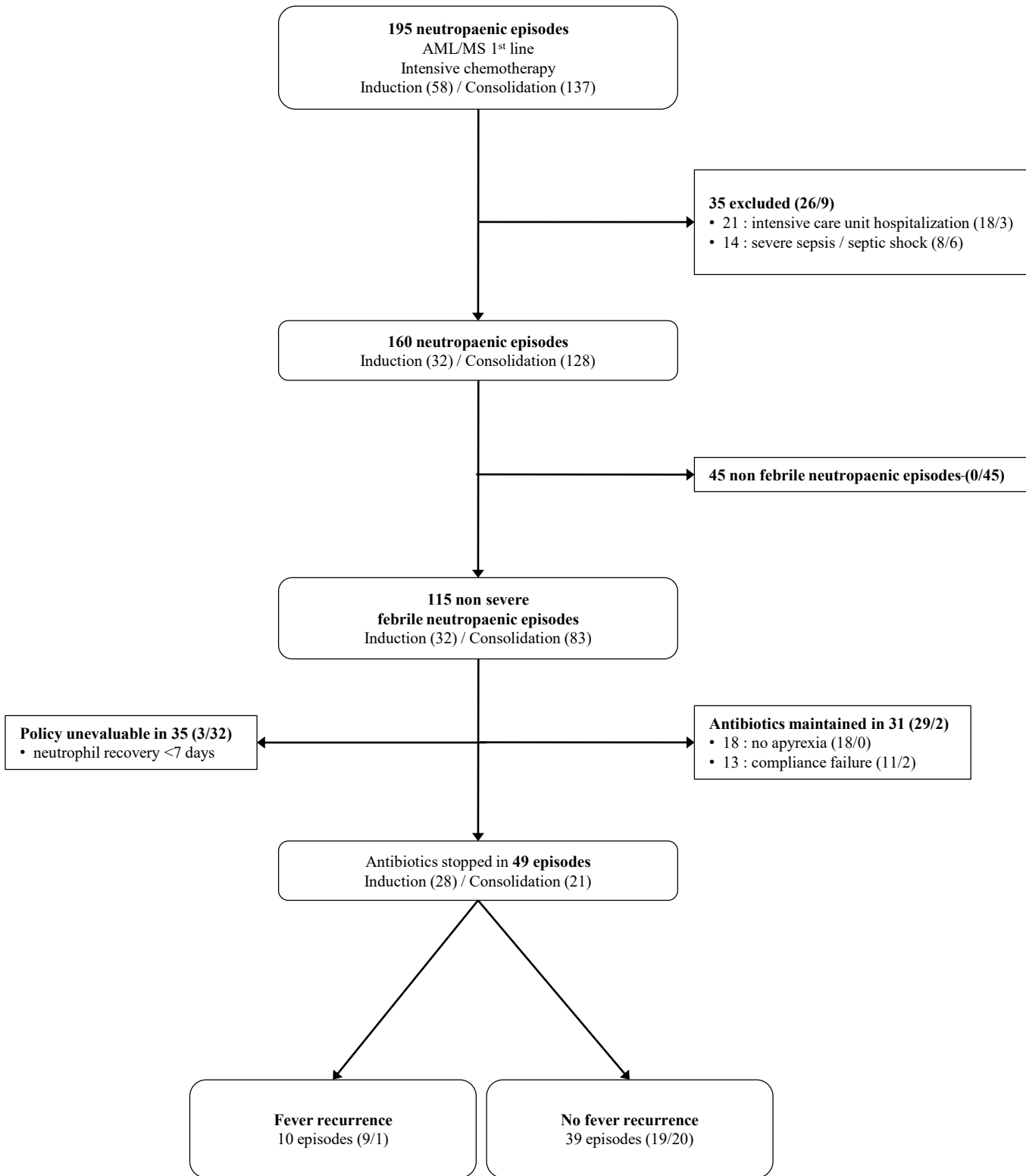
Table 3. Antimicrobial therapy.

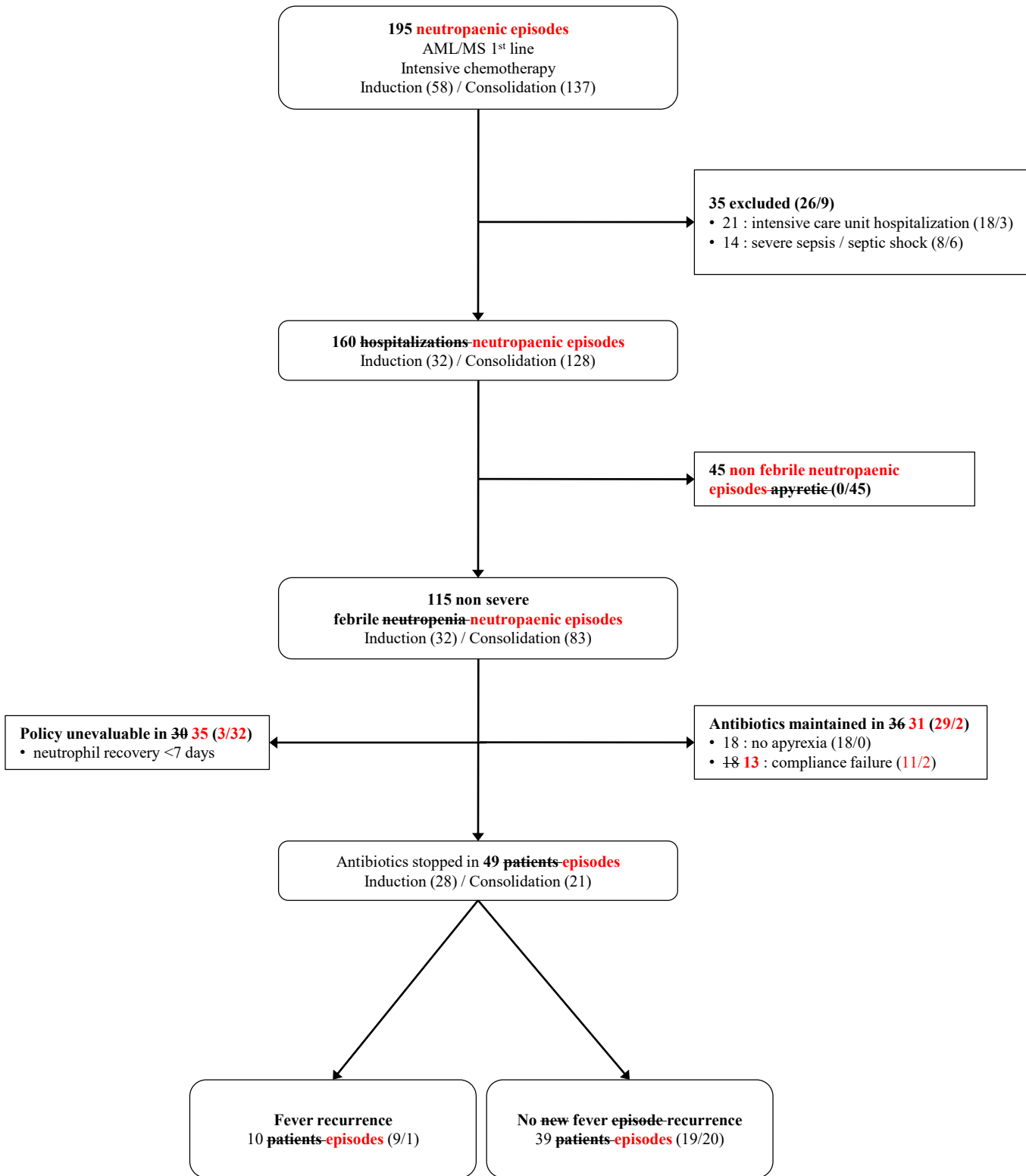
Patients were mostly given beta-lactam-based antimicrobial therapy, given as **monotherapy a single agent** or in combination with aminoglycosides and/or anti methicillin-resistant staphylococci therapy, according to clinical presentation, known ESBL colonization or microbiological documentation. Some patients received two or more antibiotics, which is why the sum of each value can exceed the overall number of patients in each group

<i>Antibiotics used</i>	<i>Policy compliant group N=49</i>	<i>Control group N=13</i>
Cefotaxime	3 (6)	1 (8)
<i>Monotherapy single agent</i>	3 (6)	1 (8)
Piperacilline-tazobactam	27 (55)	8 (62)
<i>Monotherapy single agent</i>	23 (47)	8 (62)
+ Amikacine	6 (12)	0
+ Vancomycine	2 (4)	0
+ Linezolid	2 (4)	0
Cefepime	16 (33)	4 (31)
<i>Monotherapy single agent</i>	13 (27)	4 (31)
+ Amikacine	2 (4)	0
+ Vancomycine	1 (2)	0
+ Linezolid	1 (2)	0
+ Metrodinazole	1 (2)	0
Meropenem	1 (2)	0
+ Amikacine	1 (2)	0
Others	2 (4)	0
Vancomycine	1 (2)	0
Ceftriaxone – Metronidazole – Doxycycline	1 (2)	0
Appropriate / Adequate treatment	46 (94)	12 (92)
Antimicrobial therapy length, by site		
Fever of Unknown Origin	7.5 [7-10]	18 [14.5-20.5]
Pneumonia / upper respiratory tract infection	13.5 [9-21]	22.5 [19-28]
Catheter-related infection	16 [11.5-21]	20.5 [19-22]
Bacteraemia	10 [10-10]	-
Male urinary tract infection	10 [10-10]	-
Female urinary tract infection	18 [18-18]	24 [24-24]
Colitis	14 [12-17.5]	-
Adverse events	16 (33)	4 (31)
Toxidermia	5 (10)	1 (8)
Abnormal liver function tests	5 (10)	1 (8)
Encephalopathy	0	1 (8)
<i>C. difficile colitis</i>	2 (4)	0
Diarrhea	2 (4)	1 (8)
Veinitis	1 (2)	0
Acute renal failure	1 (2)	0
<i>Datas are N (%) or median [IQR].</i>		

Table 4. Evolution

Population (N=49)	Overall	Induction	Consolidation
Febrile neutropaenic episodes	49	28	21
Febrile neutropaenia			
Neutropaenia length, days	26 [24–31]	27.5 [25–34.25]	24 [22–27]
ATB initiation, D	D9 [5.75–14.25]	D6 [3–8.5]	D14 [12–18]
ATB length, days	10 [7–16]	15 [8–19.25]	9 [7–10]
After antibiotic discontinuation			
Febrile recurrence, N (%)	10 (20)	9 (18)	1 (2)
Delay between ATB stop and fever recurrence, days	5.5 [3–7.5]	6 [3–8]	3 [3–3]
No febrile recurrence, N (%)	39 (80)	19 (39)	20 (41)
Delay between ATB stop and neutrophil recovery, days	5 [2–8.5]	8 [4.5–12.5]	2 [1–6]
	Policy compliant group	Control group	
	N=49	N=13	
Neutropaenia length, days	26 [24–31]	26 [21–27.5]	
Induction	27.5 [25–34.25]	26 [22–28.5]	
Consolidation	24 [22–27]	23 [21.5–24.5]	
Antibiotic therapy initiation, Day	D9 [5.75–14.25]	D5.5 [3–9.25]	
Induction	D6 [3–8.5]	D5 [3–6]	
Consolidation	D14 [12–18]	D12 [11–13]	
Antibiotic therapy length, days	10 [7–16]	19 [15–23]	
Induction	15 [8–19.25]	26 [22–28.5]	
Consolidation	9 [7–10]	23 [21.5–24.5]	
Febrile recurrence after antibiotic discontinuation	10 (20)		
Induction	9 (18)		
Consolidation	1 (2)		
Delay between ATB stop and fever recurrence, days	5.5 [3–7.5]		
Induction	6 [3–8]		
Consolidation	3 [3–3]		
Number of recurrent episodes, by site	10 (20)		
Fever of Unknown Origin	7 (14)		
Catheter-related infection / Bacteraemia	2 (4)		
Chemotherapy-induced toxidermia	1 (2)		
No febrile recurrence after antibiotic discontinuation	39 (80)		
Induction	19 (39)		
Consolidation	20 (41)		
Delay between ATB stop and neutrophil recovery, days	5 [2–8.5]		
Induction	8 [4.5–12.5]		
Consolidation	2 [1–6]		
Datas are N (%) or median [IQR]. ATB: antibiotic therapy; D: day.			





Antimicrobial therapy length in both groups

